

Conjugate addition of 3-butyne-2-one to anilines in ethanol: alkene geometric insights through *in situ* FTIR monitoring

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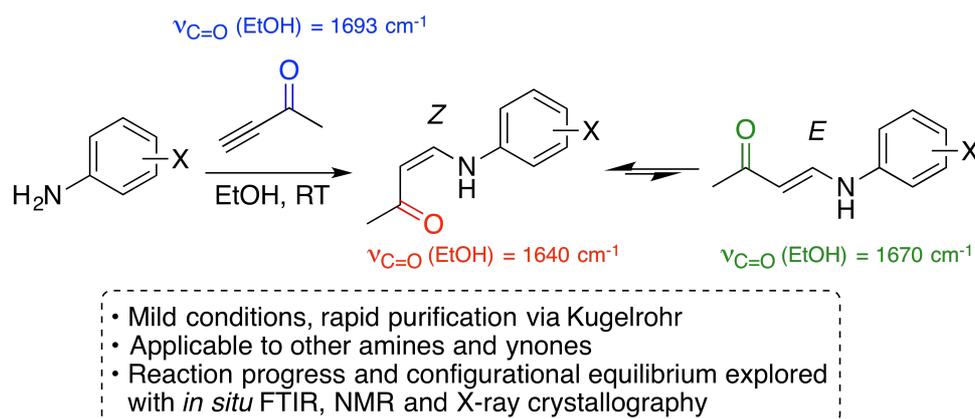
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Abstract

A convenient, mild and effective conjugate addition of 3-butyne-2-one to a variety of anilines in ethanol is reported. The reaction was monitored and characterized through *in situ* FTIR, and the dynamics of the facile *E/Z* alkene geometry interconversion of

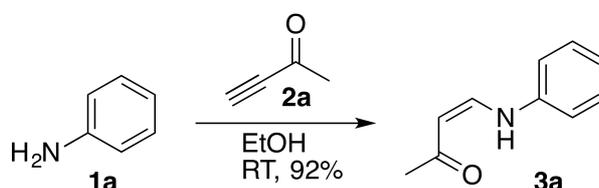
the resultant aniline-derived enaminones was explored through NMR, FTIR and X-ray crystallography. A straightforward purification protocol that employs direct Kugelrohr distillation was identified and the method was further extended to other amines and ynones, allowing rapid access to these interesting compounds.

Introduction

One of the most widely studied methods for forming C-N bonds is the aza-Michael addition.¹ This has classically involved the addition of aliphatic amines to α , β -unsaturated carbonyl compounds, but has been expanded to suit a plethora of acceptors and donors.¹ Due to the reduced nucleophilicity of aromatic amines, methods for conjugate additions to these compounds are less varied, and are often limited to reactive acceptors such as methyl vinyl ketone.²⁻⁴ Activation using Lewis acids,⁵ or high pressures,⁶ are examples of the conditions required for conjugate addition to other acceptors. Clearly, more varied and practical methods are required for these important reactions.

During attempts to assemble enamine functionalities, we noticed that aniline **1a** underwent an efficient conjugate addition to 3-buten-2-one **2a** in EtOH at RT without any activation (Scheme 1). Enaminone **3a** was easily isolated in an excellent yield by Kugelrohr distillation, with high selectivity for the *Z*-isomer, according to NMR. Such a reaction has been reported in water,⁷ and a variety of methods have been developed to synthesize similar compounds,^{8,9} including the use of palladium catalysts,⁹ and silica.¹⁰ In comparison, our protocol was more convenient and effective, and did not require any specialized reagents or catalysts. Accordingly we decided to further investigate the applicability of this convenient method towards anilines and other

amines of varied nucleophilicity, and to explore the structural characteristics of the resultant enaminones using *in situ* FTIR spectroscopy.

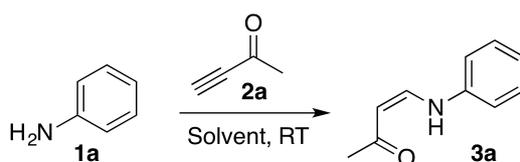


Scheme 1: Facile conjugate addition of aniline **1a** to 3-butyn-2-one **2a** to give the corresponding enaminone **3a**.

Results and Discussion

Previous FTIR studies showed that enaminones exhibit a carbonyl stretch at lower wavenumber than typical ketones due to conjugation with the amine group.¹¹ We therefore anticipated that we could use *in situ* FTIR spectroscopy (ReactIRTM),¹² to explore and follow the conjugate addition reaction in detail by tracking the loss of the ynone carbonyl stretch of **2a** and the rise of the enaminone carbonyl stretch.

Table 1. Comparison of the reaction solvent in the conjugate addition of aniline **1a** to 3-butyn-2-one **2a** to give enaminone **3a**.^a



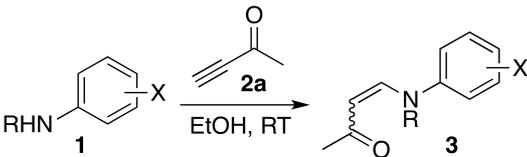
Reaction solvent	Monitoring period	Approx. conversion to 3a ^a /%
Toluene	16 h	27
DCM	16 h	22
THF	6 h	trace
EtOH	1 h	100
H ₂ O	16 h ^b	67
DMSO	24 h	57

Aniline **1a** (0.0910 mL, 1.0 mmol) was stirred with 3-butyn-2-one **2a** (0.0782 mL, 1.0 mmol) in the reaction solvent (4 mL). The disappearance of the ynone carbonyl stretch (around 1680-1690 cm⁻¹) and appearance of the enaminone carbonyl stretch (around 1640-1660 cm⁻¹) was monitored until no further

change was detected. The solution was then diluted with EtOAc, washed with H₂O and brine, dried (MgSO₄), evaporated and then analyzed by ¹H NMR. ^aEstimated via analysis of the crude ¹H NMR spectra in chloroform-*d*₁ by comparing the relative integrals of the starting **1a** and enaminone **3a**. ^bFTIR monitoring in this case was unreliable due to rapid precipitation of **3a**.

The effect of the solvent on the reaction between aniline, **1a** and 3-buten-2-one, **2a** was first assessed, with monitoring by *in situ* FTIR. In all solvents, a clear carbonyl stretch was detected at around 1680-1690 cm⁻¹ upon addition of **2a**. When **1a** was added, in the case of EtOH a rapid decline of the **2a** carbonyl stretch was detected, and was accompanied by the concomitant appearance of the **3a** enaminone carbonyl stretch at around 1640 cm⁻¹. In the nonpolar toluene, a similar spectral effect was observed, although the reaction was found to be significantly slower, and indeed was far from completion after 16 hours according to ¹H NMR. A comparably slow rate was observed in DCM. The more polar THF showed no obvious reaction by *in situ* FTIR and only trace amounts of **3a** were evident by ¹H NMR. Only the reactions with the more polar solvents H₂O and DMSO exhibited reasonable conversions to **3a**, although still at a significantly slower rate than the reaction in EtOH. Clearly, at room temperature, EtOH exhibited a substantial rate enhancement compared to the solvents.

With the ideal solvent identified, the reaction was conducted using a variety of anilines, with monitoring by *in situ* FTIR. Close monitoring of the reaction between aniline **1a** and **2a** indicated a rapid reaction, with only around 20 minutes required to effect complete conversion to enaminone **3a** (Table 2), which allowed straightforward isolation of **3a** in a 92% yield via Kugelrohr distillation.

Table 2. Addition of anilines **1a-m** to 3-butyne-2-one **2a** to give enaminones **3a-m**.

Aniline	Approx. time ^a	Enaminone	Alkene geometry ^b	Yield/%
Aniline, 1a	20 mins	3a	Z	92
2-Methylaniline, 1b	20 mins	3b	Z	93
4-Methylaniline, 1c	20 mins	3c	Z	87
3,5-Dimethylaniline, 1d	40 mins	3d	Z	94
4-Hydroxyaniline, 1e	20 mins	3e	Z	86 ^d
4-Methoxyaniline, 1f	20 mins	3f	Z	88
Ethyl 4-aminobenzoate, 1g	24 h ^c	3g	Z	85
4-Chloroaniline, 1h	6 h	3h	Z	92
4-Bromoaniline, 1i	3.5 h	3i	Z	88
4-Nitroaniline, 1j	>5 days ^c	3j	Z	33 ^e
4-Iodoaniline, 1k	5 h	3k	Z	72 ^e
4-Iodo-2-methylaniline, 1l	5 h	3l	Z	85 ^e
N-Methylaniline, 1m	20 mins	3m	E	93

^aEstimated using FTIR. ^bAssessed by ¹H NMR in chloroform-*d*₁. ^cEstimated using TLC. ^dIsolated by chromatography. ^eIsolated by recrystallization.

Both mildly, and strongly activated anilines (**1b-f**) reacted with **2a** at similar rates compared to **1a**, and the resulting enaminones **3b-f** were isolated in excellent yields by Kugelrohr distillation, which proved to be a quick, easy and highly effective purification method. Reactions of **2a** with electron deficient anilines were much slower. For example, 4-chloroaniline and 4-bromoaniline (**1h-i**) reacted to give enaminones **3h-i** in 6 and 3.5 hours respectively, but with similarly high yields to the activated anilines. Accurate FTIR monitoring of the reaction between **2a** and ethyl 4-aminobenzoate **1g** was difficult due to the overlap of the carbonyl stretch of **2a** with the ester carbonyl stretch of **1g**. TLC indicated conversion to **3g** after 24 hours.

Addition of **2a** to 4-nitroaniline **1j** was found to be remarkably slow, and precipitation of the product **3j** also caused unreliable FTIR monitoring. After 5 days, **3j** was isolated in a 33% yield by recrystallization. This reduced rate is likely caused by the deactivating nitro-group, though the difference in reactivity to the other

anilines is striking. 4-Iodoaniline and 4-iodo-2-methylaniline **1k-l**, were converted to the corresponding enaminones **3k-l** in good yields over 5 hours.

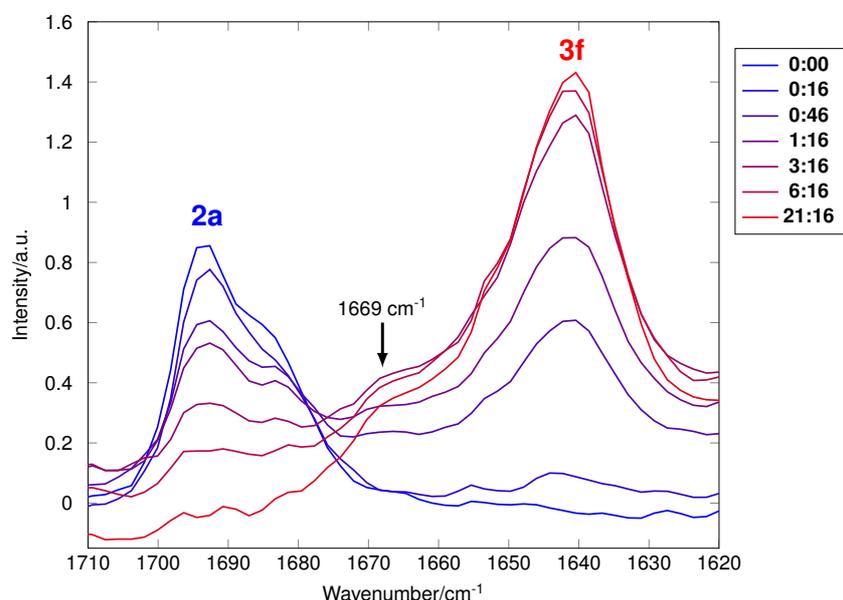
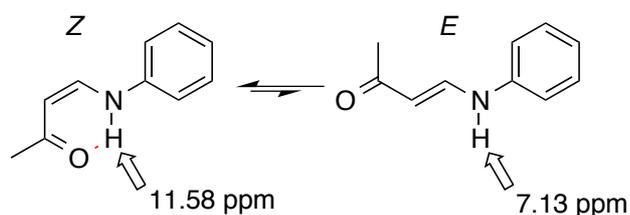


Figure 1. The *in situ* FTIR spectra of the reaction between **1f** and **2a** at selected time points (time proceeds from blue to red). The decline of the carbonyl stretch of **2a** (1693 cm^{-1}) and the consequent rise of the carbonyl stretch of **3f** (1640 cm^{-1}) is shown as the reaction proceeded. The carbonyl stretch of **2a** fell to 50% intensity after approximately 2 minutes. A subtle shoulder is evident at 1669 cm^{-1} that corresponds to the *E*-isomer of **3f**.

Figure 1 shows the FTIR spectra of the reaction between **1f** and **2a** at select time points. After addition of **2a** ($t = 0:00$), the carbonyl stretch of **2a** (1693 cm^{-1}) was visible. When **1f** was added, a rapid appearance of the **3f** carbonyl stretch (1640 cm^{-1}) was observed. This was accompanied by the decline of the carbonyl stretch of **2a**. Clearly the majority of product **3f** was formed after only around 3 minutes, and the reaction rate decreased as the concentration of the reactants declined. At $t = 21:16$, the carbonyl stretch of **2a** was no longer evident, and the carbonyl stretch of **3f** remained constant indicating that the reaction was complete.

The spectra in Figure 1 show that the ketone of **3f** in EtOH exhibited a peak at 1640 cm^{-1} , but a subtle shoulder at 1669 cm^{-1} was also evident. The *E*-isomers of similar enaminones are known to exhibit lower intensity carbonyl stretches at higher wavenumbers compared to the *Z*-isomers, due to the lack of intramolecular hydrogen bonding.^{11,13} This shoulder therefore clearly indicated that both the *Z*- (1640 cm^{-1}) and *E*-isomers (1669 cm^{-1}) were formed during the reaction. Analysis of the full spectra showed that there were no obvious intermediate species, i.e. infrared bands that rose and fell, even when the spectral update frequency was increased to one per second.

Um *et al.* suggested that the corresponding reaction in water was catalyzed by protonation of the ketone of **2a**.⁷ A substantial rate and yield increase was observed in EtOH for the reaction of **1a** and **2a** compared to water, and the other solvents in Table 1, but the $\text{p}K_{\text{a}}$ of the alcoholic proton of EtOH is unlikely to be low enough for the reaction to proceed via acid catalysis. Therefore, although a short-lived, catalytic intermediate such as that suggested for the reaction in water cannot be ruled out, the FTIR monitoring experiments support a direct aza-conjugate addition mechanism in EtOH, perhaps assisted via hydrogen bonding.



Scheme 2. Configurational and conformational equilibrium between *Z,s-cis*- (left) and *E*-isomers (shown in the *s-trans* conformation, right) of **3a** as determined by ^1H NMR in chloroform- d_1 . The intramolecular hydrogen bond evident in the *Z*-isomeric form is shown as a dashed red line.

Analysis of the ^1H NMR spectra of the enaminones in chloroform- d_1 (Scheme 2) highlighted a variety of structural features. Firstly, the N-H proton of **3a** was identified as a low field broad doublet at 11.58 ppm, thus indicating that this proton forms a strong hydrogen bond.¹⁴ Furthermore, the proton of the alkene in the α -keto position presents as a doublet at 5.30 ppm with a 7.7 Hz coupling, indicating the presence of a *Z*-alkene. Both these features indicate the adoption of a *Z,s-cis* geometry of the alkene configuration and N-C=C single bond conformation, which would be maintained by the presence of an intramolecular hydrogen bond between the N-H proton and the carbonyl oxygen.¹³⁻¹⁶ A small amount (3%) of the *E*-isomer was also present, as indicated by a 13.1 Hz coupling of the corresponding α -keto-carbon proton.

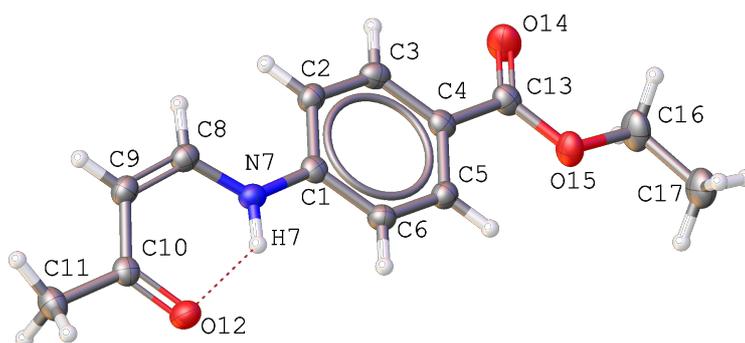


Figure 2. Ball-and-stick representation of the X-ray structure of **3g**, highlighting the *Z*-alkene configuration, *s-cis* C-N bond conformation and intramolecular hydrogen bond (red, dotted line). Figure produced using Olex2.¹⁷

To confirm the assignment of the *Z*-isomer, enaminones **3g** (Figure 2) and **3l** were crystallized and their structures solved by single crystal X-ray diffraction. Both structures showed that in the solid state, the *Z*-configuration is stabilized by a medium length hydrogen bond (**3g**, O--H distance = 1.99 Å, N-H--O angle = 132.9°) consistent with typical values.^{18,19} Comparison of the N7-C8 bond (1.35 Å) with the C8-C9 double bond (1.36 Å) shows that this N-C bond is slightly shorter than the

alkene. This is consistent with this formal single bond possessing a significant degree of imine character.

Interestingly, when the ^1H NMR spectrum of **3a** was recorded in chloroform- d_1 immediately after SiO_2 chromatography, the compound had isomerized to a 1:1 mixture of the *Z*- and *E*-isomers. The broad signal for the N-H proton of the *E*-isomer was evident at much higher field (7.13 ppm) compared to the *Z*-isomer, indicating that this proton was not significantly hydrogen bonded.^{14,21} Furthermore, when the ^1H NMR spectrum of a second fraction of **3a** was recorded one hour after chromatography, the *Z/E*-ratio had returned to 97:3, where it remained indefinitely in chloroform- d_1 . This observation provided clear evidence that enaminones **3a-3l** exist in configurational equilibria that favor the *Z*-isomer, and that the observed *Z/E*-ratio is not governed by the initial conjugate addition reaction.^{11,15} Passing the products through SiO_2 likely causes protonation of **3a**, presumably via the ketone oxygen, which disrupts the internal hydrogen bond required for stabilization of the *Z*-isomer and thus results in the temporary adoption of the sterically, and electronically favored *E*-isomer. However, the thermodynamic stabilization gained from formation of the intramolecular hydrogen bond shifts the equilibrium towards the *Z*-isomer over time.

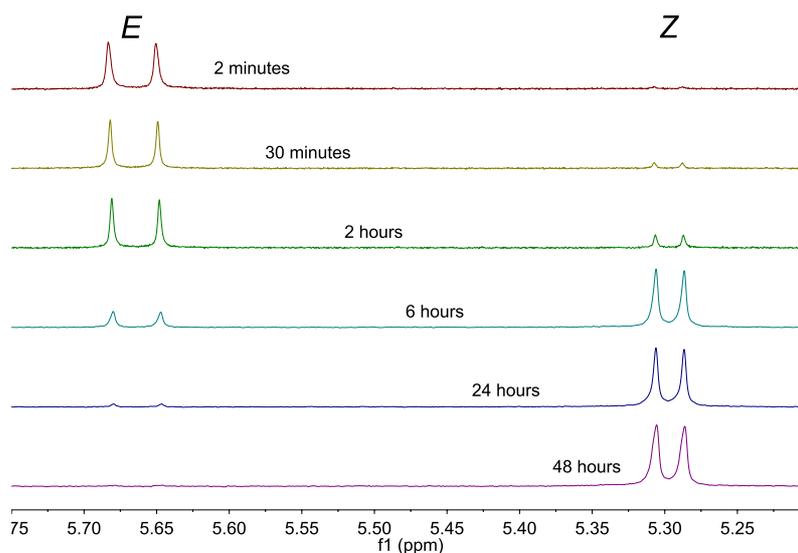


Figure 3. The ¹H NMR spectrum of **3a** in chloroform-*d*₁ monitored over 48 hours after a D₂O shake experiment. The α-carbonyl proton of the *Z*- and *E*-isomers are shown. Immediately after agitation with D₂O the *E*-isomer predominates (2 mins), but over time is found to preferentially isomerize to the thermodynamically favored *Z*-isomer.

This intriguing equilibrium was further probed by a D₂O exchange experiment. When the ¹H NMR spectrum of **3a** in chloroform-*d*₁ was recorded immediately after agitation with D₂O (Figure 3), **3a** was shown to exist in a 7:93 ratio of the *Z*- and *E*-forms, respectively. After 30 minutes, and then after 2 hours, the equilibrium still favored the *E*-form (14:86 and 24:76, respectively), but after 6 hours, the equilibrium shifted towards the *Z*-form (76:24). The equilibrium relaxed over 48 hours to a 97:3 ratio as shown by ¹H NMR. These results indicated that **3a** converts to the *E*-configuration during deuterium exchange, but that the N-D--O deuterium bond interaction in deuterated **3a** is equally as thermodynamically favored as the N-H--O interaction.

In light of the fascinating isomerization behavior observed in chloroform-*d*₁, the effect of the solvent upon the position of the *Z*/*E* equilibrium of **3a** was examined in

acetone- d_6 , methanol- d_4 , DMSO- d_6 , toluene- d_8 and MeCN- d_3 (Figure 4). The ^1H NMR spectra were recorded as quickly as possible after preparation of the samples. After 5 minutes the *E*-isomer was the predominant form in all solvents. After 15 minutes, the equilibrium was found to significantly shift towards the *Z*-isomer in acetone- d_6 , toluene- d_8 and MeCN- d_3 , but exhibited a 1:1 ratio in methanol- d_4 , and favored the *E*-form in DMSO- d_6 . When these equilibria were followed over 6 days, the *Z*-form was favored in the nonpolar aprotic solvent, toluene- d_8 (*Z:E*, 97:3), and polar aprotic solvents; acetone- d_6 (84:16) and MeCN- d_3 (86:14). In polar protic methanol- d_4 the equilibrium was maintained at a 1:1 ratio of the *Z*- and *E*-isomers, and in the dipolar aprotic DMSO- d_6 the *E*-form predominated (30:70).^{14,20,21}

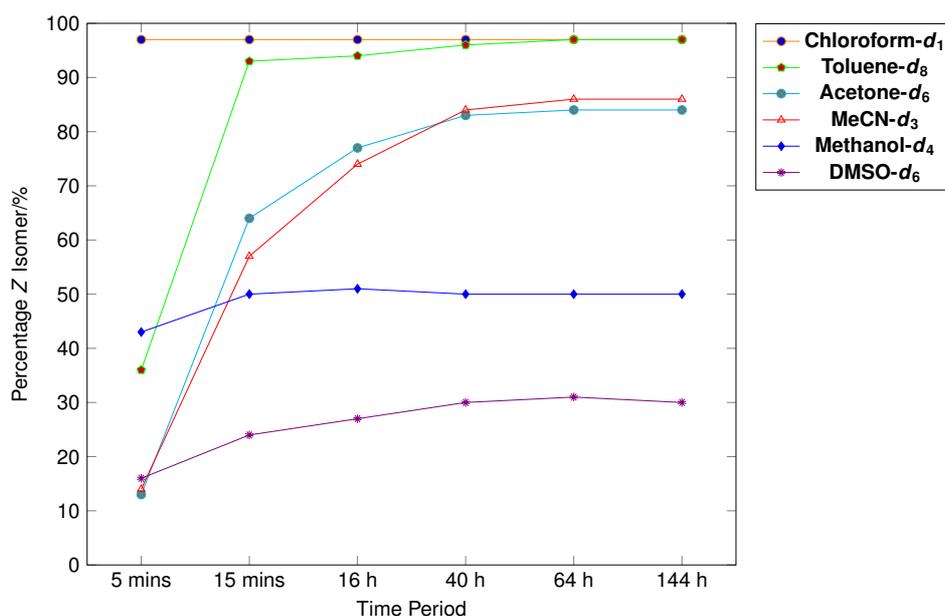


Figure 4. Relative percentage of the *Z*-isomer of **3a** over time in different deuterated solvents.

Percentages were determined from ^1H NMR by comparing the integrals of the α -keto proton of the *Z*- and *E*-isomers.

The fascinating effect of hydrogen bonding is highlighted in Figure 4.^{20,21} After 5 minutes; the *E*-form is favored in all solvents except for chloroform- d_1 , presumably

due to kinetically controlled hydrogen bond formation with the solvent via the ketone oxygen. However, as the system equilibrates, the thermodynamic benefit of the intramolecular hydrogen bond prevails over a reduction in steric hindrance in toluene- d_8 , acetone- d_6 and MeCN- d_3 .¹⁴ In methanol- d_4 and DMSO- d_6 , disruption of the intramolecular hydrogen bond by the solvent results in a significant equilibrium proportion of the *E*-form. In DMSO- d_6 in particular, the *E*-form of **3a** exhibited a lower field N-H proton (9.65 ppm) than in all other solvents; a characteristic that tallies with the low *Z*-isomer proportion in DMSO- d_6 , and indicates significant hydrogen bonding to the solvent.^{16,21}

The equilibrium proportion of the *E* configuration in acetone- d_6 and MeCN- d_3 is around four times greater than that observed in chloroform- d_1 and toluene- d_8 . Given the even higher *E* proportions observed in methanol- d_4 and DMSO- d_6 , we can infer that the position of the configurational equilibrium in the enaminone products **3a-l** can essentially be related to the hydrogen bond accepting ability of the solvent. Indeed, Figure 4 suggests that the solvents fall into three classes, i.e. weak hydrogen bond acceptors (chloroform- d_1 and toluene- d_8), medium hydrogen bond acceptors (acetone- d_6 and MeCN- d_3) and strong hydrogen bond acceptors (methanol- d_4 and DMSO- d_6).^{22,23}

The reaction with **2a** was performed using *N*-methylaniline, **1m** to eliminate the intramolecular hydrogen bond and assess the resulting configurational and conformational effects. The reaction proceeded with equal efficacy to the activated anilines, and FTIR monitoring showed that the carbonyl stretch of enaminone **3m** presented at a higher wavenumber than the other enaminones in EtOH (1658 cm^{-1} , compared to around 1640 cm^{-1}).¹³ After isolation in a 93% yield, ¹H NMR analysis in chloroform- d_1 showed that **3m** exclusively existed in an *E* configuration. While the

addition of the methyl group likely induces a greater steric barrier to the adoption of the *Z*-configuration, it is clear that the removal of the ability to hydrogen bond also has a profound effect on the alkene geometry of **3m**. NOESY NMR experiments indicated that, on the NMR timescale, neither the *E,s-cis* nor *E,s-trans* forms are favored (according to NOE interactions between the ketone methyl and the alkene protons), presumably due to facile rotation of the alkenyl ketone unit around the C-N bond.¹⁴

Differentiation between *Z,s-trans* and *Z,s-cis* forms of enaminones via FTIR is straightforward, whereas conformational assignment of the *E*-isomers has typically been more difficult due to the very subtle differences between the corresponding IR spectra.²² We therefore cannot unequivocally assign the conformation (or suggest that one predominates at all) of the *E*-isomer of **3m**, and by extension, enaminones **3a-l**.²²

Higher wavenumber carbonyl stretches in solid state FTIR, and lower λ_{\max} values have been observed for *E*-enaminones compared to the corresponding *Z*-systems.^{16,23,24} Indeed, the carbonyl stretch of **3m** was also identified at a higher wavenumber (1662 cm⁻¹), and of lower intensity when the solid state FTIR spectrum was compared to those of the other enaminones, **3a-l** (1627-1660 cm⁻¹). Furthermore, The ketone stretches of all the enaminones are also very sharp in the solid state FTIR spectra, with no obvious shoulders in the case of **3a-l** (unlike Figure 1). These findings indicate that enaminones **3a-l** exist exclusively in the *Z*-configuration in the solid state.²¹ UV-Vis analysis also showed that **3a** in chloroform exhibited a significantly longer wavelength, lower intensity absorbance band (343 nm) compared to **3m** (316 nm).¹⁶

These analyses further supported the notion that the subtle shoulder at 1669 cm⁻¹ in Figure 1 originates from the *E*-isomer of **3f**.²² The consistent 1:1 ratio of the

Z/E-isomers of **3a** exhibited in methanol-*d*₄ over 6 days shows that isomerization is likely to be very rapid in alcohols. Therefore, upon formation in the reaction, the enamionones are instantly converted to a 1:1 ratio of *Z/E*-isomers.

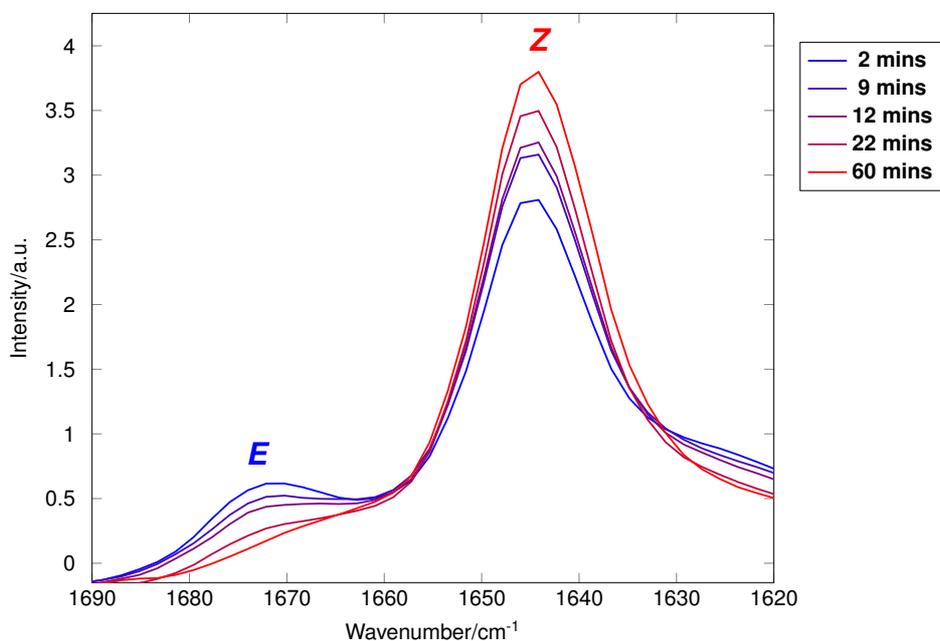
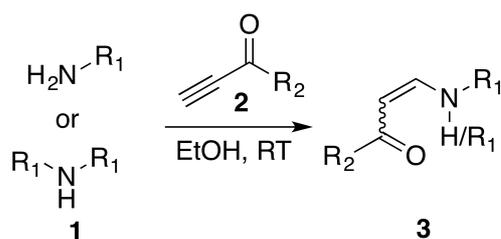


Figure 5. *In situ* FTIR monitoring of the 1620-1690 cm^{-1} region of **3a** in chloroform-*d*₁ immediately after isolation. The relaxation of the *Z/E* equilibrium was followed by monitoring the intensity of the carbonyl stretches of the *E*- and *Z*-isomers over time (time proceeds from blue to red). Initially a small amount of the *E*-isomer (1672 cm^{-1}) is present, but this converts to the *Z*-isomer (1644 cm^{-1}) over 1 hour.²²

To confirm this hypothesis, we utilized *in situ* FTIR monitoring to observe the isomerization equilibrium as it relaxes after isolation of **3a** (Figure 5). A chloroform-*d*₁ solution prepared immediately after Kugelrohr distillation of **3a** was monitored by FTIR. Initially, two well-separated bands corresponding to the *E*- (1672 cm^{-1}) and *Z*-carbonyl (1644 cm^{-1}) stretches were evident.²² Over time, the *E*-stretch quickly diminished and was accompanied by the growth of the *Z*-stretch. After 1 hour, the *Z*-stretch was the major constituent, and remained so indefinitely. This experiment confirmed that the *E*- and *Z*-isomers exhibit distinct carbonyl stretches in solution

state FTIR. Indeed, when enaminones **3a-l** are returned, upon isolation, to EtOH, a low intensity band at around 1670 cm^{-1} is observed *via* FTIR monitoring.^{11,25} When performing the same analysis in DMSO, a higher intensity band at 1670 cm^{-1} is observed, which correlates with the greater proportion of the *E*-isomer observed in ^1H NMR in DMSO-*d*₆ (Figure 4).

In an attempt to understand the mechanism of this facile isomerization process, we prepared separate solutions of **3a** with a conjugate addition acceptor (methyl vinyl ketone), and with a conjugate addition donor (4-methoxyaniline, **1f**), in a range of deuterated solvents. If the isomerization proceeded via rapid elimination, rotation and readdition of the enone unit, one would expect to observe additional conjugate addition products. However, ^1H NMR monitoring of these solutions over one week indicated that there was no perturbation of the *Z/E* equilibrium and no additional conjugate addition products. Therefore, given the significant degree of imine character evident in the X-ray crystal structures of **3g** and **3l**, we can suggest that the enaminone alkene configurations interconvert through a simple rotational process.^{15,23}

Table 3. Addition of amines **1n-w** to ynones **2a-c** to give enaminones **3n-w**.

Amine	R ₂	Approx. time ^a	Enaminone	Alkene geometry ^b	Yield/%
4-Methoxybenzylamine, 1n	Me, 2a	10 mins	3n	<i>Z</i>	93
1-Amino-3,3-diethoxypropane, 1o	Me, 2a	12 mins	3o	<i>Z</i>	99
Diisopropylamine, 1p	Me, 2a	10 mins	3p	<i>E</i>	98
2,2,6,6-Tetramethylpiperidine, 1q	Me, 2a	6 h	3q	<i>E</i>	95
2-Amino-6-methylpyridine, 1r	Me, 2a	>48 h	3r	<i>Z</i>	(<30) ^d
4-Aminoquinoline, 1s	Me, 2a	>48 h	3s	<i>Z</i>	(<15) ^d
2-Aminopyrimidine, 1t	Me, 2a	-	3t	-	0
Morpholine, 1u	Ph, 2b	6 mins	3u	<i>Z</i>	86
Aniline, 1a	Ph, 2b	30 mins ^c	3v	<i>Z</i>	88
Aniline, 1a	OMe, 2c	35 h	3w	<i>E</i>	82

^aEstimated using FTIR. ^bAssessed by ¹H NMR in chloroform-*d*₁. ^cPrecipitated after 5 mins. ^dNot isolated. Enaminones **3n-q** and **3u-w** were all isolated via Kugelrohr distillation. Yields in parentheses were estimated from crude ¹H NMR analysis.

With the conformational preferences of enaminones **3a-l** understood, we assessed the utility of the method towards amines and ynones of varied structure (Table 3). As expected, *in situ* FTIR indicated that unhindered primary alkylamines, **1n** and **1o**, reacted even faster with **2a** than the activated anilines due to their increased nucleophilicity.^{3,4,7} Even the hindered diisopropylamine **1p** reacted at a similar rate, presumably due to the strongly electron donating alkyl groups. However, further increasing steric hindrance (2,2,6,6-tetramethylpiperidine **1q**) caused a significant reduction in rate, though the reaction still provided enaminone **3q** in a convenient timeframe (6 hours). The alkylamine-derived enaminones were all easily isolated in excellent yields via Kugelrohr distillation.

Heteroaromatic amines exhibited a significant decrease in reactivity, due to their reduced nucleophilicity. *In-situ* FTIR analysis of the reactions between **1r-t** and **2a** was much more complex than the other amines, and the solutions swiftly turned a very dark red color. Indeed, all three reactions returned viscous black tars. In contrast

to the exceptionally clean crude reaction mixtures of the other amines, crude ^1H NMR and GCMS analysis of the heteroaromatic amine reactions indicated mainly unreacted amines, an array of unidentified side products and low conversion to the desired enaminone (**3r** and **3s**). Due to these very complex mixtures, we were unable to isolate enaminones **3r-s** chromatographically. Enaminone **3t** was not observed in the case of the reaction between 2-aminopyrimidine **1t** and **2a** and mainly unreacted starting material was evident.

The reaction was conducted with 1-phenyl-2-propyn-1-one **2b** and methyl propiolate **2c** in order to assess the effect of the ynone acceptor.⁷ Morpholine **1u** and aniline **1a** reacted with **2b** at similar rates to the reactions of nucleophilic amines with **2a** due to the similar electrophilicity of the ynone. However, reaction of **1a** with the less electrophilic **2c** exhibited a significant reduction in rate.³⁷ Enaminones **3u-w** were all also isolated in good yields using the Kugelrohr distillation protocol.

Indeed, the rapid reaction time and straightforward purification of most of the enaminones reported herein indicate that this conjugate addition methodology would be ideal for quick generation or diversification of compound libraries for drug screening.

Conclusion

In conclusion, a mild, effective and practical protocol for the synthesis of a range of enaminones has been demonstrated. *In situ* FTIR highlighted the facile *E/Z*-isomerization of the enaminone products during the reaction. Further analytical work explored this isomerization equilibrium, and confirmed the preferential adoption of a *Z*-configuration in the solid state and in solvents with poor hydrogen bonding ability; a characteristic that has occasionally been mistakenly attributed to stereoselective

reaction conditions in the past. Given the high degree of imine character exhibited in the crystal structures of **3g** and **3l**, it can be suggested that the enaminone alkene configurations interconvert through a simple rotational process. The straightforward method and Kugelrohr purification protocol enables rapid access to these interesting compounds.

Experimental Section

Typical laboratory grade ethanol was used for all reactions. Reagents were purified via Kugelrohr distillation under vacuum, if required. Vacuum distillation/sublimation was performed using a Kugelrohr operating at a pressure of around 0.5-2.0 Torr. NMR peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), combinations thereof, or as a multiplet (m) with reference to the CHCl₃ peak (¹H = 7.26 ppm, ¹³C = 77.23 ppm). ES-MS was performed using a TQD mass spectrometer with a UPLC, and accurate mass measurements were obtained using a QtoF mass spectrometer with a UPLC. Solid state FTIR spectra were recorded using an FT-IR spectrometer. Melting points were uncorrected. All *in situ* FTIR spectroscopy experiments were carried out using an *in situ* FTIR spectrometer with MCT detector, sampling at 2000-650 cm⁻¹. The ¹H NMR spectra of the *Z* enaminones exhibit small amounts (0-3%) of the corresponding *E* isomer due to the observed isomerization equilibrium.

Example synthetic procedure: An amine (1.0 mmol) was added to a solution of 3-butyn-2-one, **2a** (0.078 mL, 1.0 mmol) in EtOH (4 mL) and the resulting solution was stirred at RT until *in situ* FTIR analysis, or TLC, indicated that the reaction was complete. The solution was then diluted with EtOAc, washed with H₂O and brine, dried (MgSO₄), evaporated and then directly distilled under vacuum using a

Kugelrohr apparatus, recrystallized or purified by SiO₂ chromatography to give the enaminone product.

The reactions were monitored by *in situ* FTIR spectroscopy according to the following: (a) EtOH was added to a reaction flask with the FTIR probe inserted. The infrared spectrum of EtOH was then recorded and subtracted from the signal; (b) Acceptor **2** was then added and the ynone carbonyl stretch was identified; (c) Amine **1** was added, and both the reduction of the carbonyl stretch of **2** and the consequent rise of the lower wavenumber carbonyl stretch of the resulting enaminone **3** was examined over time (all reaction progress plots shown in the ESI). The reaction was adjudged to be complete when the carbonyl stretch of **2** was no longer evident, and the carbonyl stretch of enaminone **3** was stable over time. Intensity measurements in reactions plots and spectra were multiplied by a factor of 10 to aid comprehension.

(3Z)-4-(Phenylamino)but-3-en-2-one, 3a: Aniline (0.0910 mL, 1.0 mmol) and 3-butyn-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 20 mins) to give compound **3a** as a white solid (0.149 g, 92%) after purification by Kugelrohr distillation under vacuum (100-120 °C): m.p. = 95-96 °C; ¹H NMR (600 MHz, CDCl₃) δ 2.16 (s, 3H), 5.30 (d, *J* = 7.7 Hz, 1H), 7.00-7.07 (m, 3H), 7.22 (dd, *J* = 12.3, 7.7 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 11.58 (br d, *J* = 13.2 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 29.8, 97.6, 116.3, 123.6, 129.9, 140.6, 143.2, 199.1; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3236m, 3057w, 3036w, 2998w, 1660m, 1600m, 1545s, 1471s, 1260s, 961s; MS (ES): *m/z* = 162.1 [M+H]⁺; HRMS (ES) calcd. for C₁₀H₁₂NO [M+H]⁺: 162.0919, found: 162.0923; Found: C, 74.43; H, 6.85; N, 8.70. Calc. for C₁₀H₁₁NO: C, 74.51; H, 6.88; N, 8.69%.²⁶

(3Z)-4-[(2-Methylphenyl)amino]but-3-en-2-one, 3b: 2-Methylaniline (0.107 mL, 1.0 mmol) and 3-butyn-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 20 mins) to give compound **3b** as an off-white solid (0.160 g, 93%) after purification by Kugelrohr distillation under vacuum (120-130 °C): m.p. = 34-36 °C; ¹H NMR (600 MHz, CDCl₃) δ 2.18 (s, 3H), 2.36 (s, 3H), 5.35 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.17-7.22 (m, 2H), 7.31 (dd, *J* = 12.1, 7.6 Hz, 1H), 11.82 (br d, *J* = 10.5 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 17.8, 29.7, 97.8, 113.7, 123.4, 126.3, 127.3, 131.3, 139.1, 143.6, 199.0; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3200w, 3059w, 2984w, 2910w, 1635m, 1585m, 1563s, 1465s, 1274s, 743s; MS (ES): *m/z* = 176.1 [M+H]⁺; HRMS (ES) calcd. for C₁₁H₁₄NO [M+H]⁺: 176.1075, found: 176.1076; Found: C, 75.27; H, 7.46; N, 7.94. Calc. for C₁₁H₁₃NO: C, 75.40; H, 7.48; N, 7.99%.

(3Z)-4-[(4-Methylphenyl)amino]but-3-en-2-one, 3c: 4-Methylaniline (0.107 g, 1.0 mmol) and 3-butyn-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 20 mins) to give compound **3c** as an off-white solid (0.153 g, 87%) after purification by Kugelrohr distillation under vacuum (100-120 °C): m.p. = 109-110 °C; ¹H NMR (700 MHz; CDCl₃) δ 2.15 (s, 3H), 2.30 (s, 3H), 5.27 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.19 (dd, *J* = 12.4, 7.7 Hz, 1H), 11.57 (br d, *J* = 9.1 Hz, 1H); ¹³C NMR (176 MHz; CDCl₃) δ 20.9, 29.7, 97.1, 116.4, 130.4, 133.3, 138.2, 143.7, 198.8; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3182m, 3033w, 2977w, 2858w, 1634m, 1609m, 1564s, 1475s, 1282s, 812s; MS (ES): *m/z* = 176.1 [M+H]⁺; HRMS (ES) calcd. for C₁₁H₁₄NO [M+H]⁺: 176.1075, found: 176.1085; Found: C, 75.39; H, 7.46; N, 8.04. Calc. for C₁₁H₁₃NO: C, 75.40; H, 7.48; N, 7.99%.²⁷

(3Z)-4-[(3,5-Dimethylphenyl)amino]but-3-en-2-one, 3d: 3,5-Dimethylaniline (0.125 mL, 1.0 mmol) and 3-butyn-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 40 mins) to give compound **3d** as a clear light yellow oil (0.178 g, 94%) after purification by Kugelrohr distillation under vacuum (120-140 °C): ¹H NMR (700 MHz, CDCl₃) δ 2.14 (s, 3H), 2.29 (s, 6H), 5.26 (d, *J* = 7.7 Hz, 1H), 6.65 (s, 2H), 6.69 (s, 1H), 7.21 (dd, *J* = 12.4, 7.7 Hz, 1H), 11.50 (br d, *J* = 10.4 Hz, 1H); ¹³C NMR (176 MHz, CDCl₃) δ 21.5, 29.7, 97.2, 114.1, 125.4, 139.6, 140.5, 143.4, 198.8; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3259w, 3027w, 2918w, 2861w, 1637s, 1571s, 1476m, 1278s, 1171s, 955m, 831m; MS (ES): *m/z* = 190.1 [M+H]⁺; HRMS (ES) calcd. for C₁₂H₁₆NO [M+H]⁺: 190.1232, found: 190.1237; Found: C, 75.55; H, 8.04; N, 6.99. Calc. for C₁₂H₁₅NO: C, 76.16; H, 7.99; N, 7.40%.

(3Z)-4-[(4-Hydroxyphenyl)amino]but-3-en-2-one, 3e: 4-Aminophenol (0.546 g, 5.0 mmol) and 3-butyn-2-one (0.391 mL, 5.0 mmol) were stirred in EtOH (10 mL) (completion indicated after 20 mins) to give compound **3e** as a yellow solid (0.760 g, 86%) after purification by SiO₂ column chromatography (Et₂O, with 1% Et₃N as eluent): m.p. = 138-140 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.15 (s, 3H), 5.25 (d, *J* = 7.6 Hz, 1H), 5.61 (br s, 1H), 6.79-6.87 (m, 2H), 6.87-6.95 (m, 2H), 7.09-7.17 (dd, *J* = 12.4, 7.6 Hz, 1H), 11.60 (br d, *J* = 12.5 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 29.5, 96.7, 116.7, 118.2, 134.1, 144.7, 152.6, 198.8; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3100br, 3080w, 3032w, 2956w, 2813w, 1635m, 1554m, 1489s, 1263s, 1205s, 830s, 747s; MS (ES): *m/z* = 178.1 [M+H]⁺; HRMS (ES) calcd. for C₁₀H₁₂NO₂ [M+H]⁺: 178.0868, found: 178.0873; Found: C, 67.37; H, 6.23; N, 7.79. Calc. for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.90%. Note: **3e** exhibited low solubility in CDCl₃. **3e** was also highly susceptible

to degradation when heated. Mild heating with a heat gun, or in a Kugelrohr caused a rapid colour change to dark red/brown.²⁸

(3Z)-4-[(4-Methoxyphenyl)amino]but-3-en-2-one, 3f: 4-Methoxyaniline (0.123 g, 1.0 mmol) and 3-butyne-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 20 mins) to give compound **3f** as a white solid (0.168 g, 88%) after purification by Kugelrohr distillation under vacuum (100-120 °C): m.p. = 62-64 °C; ¹H NMR (600 MHz, CDCl₃) δ 2.13 (s, 3H), 3.77 (s, 3H), 5.24 (d, *J* = 7.6 Hz, 1H), 6.83-6.88 (m, 2H), 6.94-7.00 (m, 2H), 7.12 (dd, *J* = 12.4, 7.6 Hz, 1H), 11.60 (br d, *J* = 11.4 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 29.6, 55.7, 96.7, 115.1, 117.9, 134.2, 144.3, 156.3, 198.5; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3228w, 3004w, 2956w, 2914w, 2836w, 1634s, 1595m, 1565s, 1477s, 1352m, 1291m, 1201s, 823s; MS (ES): *m/z* = 192.1 [M+H]⁺; HRMS (ES) calcd. for C₁₁H₁₄NO₂ [M+H]⁺: 192.1031, found: 192.1025; Found: C, 69.07; H, 6.85; N, 7.31. Calc. for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32%.²⁹

4-[(1Z)-3-Oxobut-1-en-1-yl]aminobenzoate, 3g: Ethyl 4-aminobenzoate (0.165 g, 1.0 mmol) and 3-butyne-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 24 h) to give compound **3g** as a white solid (0.199 g, 85%) after purification by Kugelrohr distillation under vacuum (140-160 °C): m.p. = 75-76 °C; ¹H NMR (700 MHz, CDCl₃) δ 1.38 (t, *J* = 7.1 Hz, 3H), 2.18 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 5.38 (d, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.24 (dd, *J* = 12.1, 7.9 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 11.63 (br d, *J* = 11.8 Hz, 1H); ¹³C NMR (176 MHz, CDCl₃) δ 14.6, 30.0, 61.0, 99.3, 115.2, 125.1, 131.7, 141.7, 144.4, 166.2, 199.8; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3246w, 3036w, 2989w, 2964w, 1703s, 1646m, 1598m, 1558m,

1475m, 1259s, 746s; MS (ES): $m/z = 234.1$ $[M+H]^+$; HRMS (ES) calcd. for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1130, found: 234.1129; Found: C, 66.98; H, 6.50; N, 6.00. Calc. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00%. Note: Overlapping ketone stretches from the starting aniline and enaminone **3g** meant that assessing completion by *in situ* FTIR monitoring was difficult. TLC analysis indicated completion after 24 hours.³⁰

(3Z)-4-[(4-Chlorophenyl)amino]but-3-en-2-one, 3h: 4-Chloroaniline (0.128 g, 1.0 mmol) and 3-buten-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 6 h) to give compound **3h** as a white solid (0.18 g, 92%) after purification by Kugelrohr distillation under vacuum (120-140 °C): m.p. = 111-113 °C; ¹H NMR (600 MHz, CDCl₃) δ 2.15 (s, 3H), 5.31 (d, $J = 7.8$ Hz, 1H), 6.92-6.97 (m, 2H), 7.14 (dd, $J = 12.2, 7.8$ Hz, 1H), 7.24-7.29 (m, 2H), 11.57 (br d, $J = 9.3$ Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 29.8, 98.2, 117.4, 128.5, 129.9, 139.3, 142.8, 199.4; IR (neat) ν_{max}/cm^{-1} 3175w, 3093w, 3002w, 2960w, 1643s, 1594s, 1569s, 1472s, 1291s, 1220s, 1090m, 818s; MS (ES): $m/z = 196.0$ $[M+H]^+$; HRMS (ES) calcd. for $C_{10}H_{11}NOCl$ $[M+H]^+$: 196.0529, found: 196.0521; Found: C, 61.51; H, 5.17; N, 7.14. Calc. for $C_{10}H_{10}NOCl$: C, 61.39; H, 5.15; N, 7.16%.³¹

(3Z)-4-[(4-Bromophenyl)amino]but-3-en-2-one, 3i: 4-Bromoaniline (0.172 g, 1.0 mmol) and 3-buten-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 3.5 h) to give compound **3i** as a yellow solid (0.21 g, 88%) after purification by Kugelrohr distillation under vacuum (115-140 °C): m.p. = 121-124 °C; ¹H NMR (700 MHz, CDCl₃) δ 2.16 (s, 3H), 5.32 (d, $J = 7.8$ Hz, 1H), 6.87-6.92 (m, 2H), 7.14 (dd, $J = 12.2, 7.8$ Hz, 1H), 7.38-7.43 (m, 2H), 11.56 (br d, $J =$

12.1 Hz, 1H); ^{13}C NMR (176 MHz, CDCl_3) δ 29.9, 98.3, 115.9, 117.7, 132.8, 139.7, 142.6, 199.4; IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3177w, 3073w, 2994w, 2908w, 1634m, 1591s, 1566s, 1471s, 1289m, 1180m, 814s, 752s; MS (ES): $m/z = 240.0$ $[\text{M}+\text{H}]^+$; HRMS (ES) calcd. for $\text{C}_{10}\text{H}_{11}\text{NOBr}$ $[\text{M}+\text{H}]^+$: 240.0024, found: 240.0039; Found: C, 50.09; H, 4.19; N, 5.81. Calc. for $\text{C}_{10}\text{H}_{10}\text{NOBr}$: C, 50.02; H, 4.20; N, 5.83%.

(3Z)-4-[(4-Nitrophenyl)amino]but-3-en-2-one, 3j: 4-Nitroaniline (0.691 g, 5.0 mmol) and 3-butyn-2-one (0.39 mL, 5.0 mmol) were stirred in EtOH (10 mL) for 5 days to give compound **3j** as a yellow/orange solid (0.34 g, 33%) after recrystallization from EtOH: m.p. = 178-180 °C; ^1H NMR (700 MHz, CDCl_3) δ 2.21 (s, 3H), 5.48 (d, $J = 8.0$ Hz, 1H), 7.04-7.09 (m, 2H), 7.22 (dd, $J = 11.8, 8.0$ Hz, 1H), 8.18-8.23 (m, 2H), 11.73 (br d, $J = 11.9$ Hz, 1H); ^{13}C NMR (176 MHz, CDCl_3) δ 30.3, 101.0, 115.2, 126.2, 140.6, 142.9, 146.1, 200.4; IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3201w, 3094w, 3003w, 1647m, 1575s, 1496s, 1473s, 1377m, 1325s, 1274s, 838s; MS (ES): $m/z = 207.0$ $[\text{M}+\text{H}]^+$; HRMS (ES) calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 207.0770, found: 207.0772; Found: C, 57.80; H, 4.82; N, 13.50. Calc. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_3$: C, 58.25; H, 4.89; N, 13.59%. Note: Precipitation of **3j** caused unreliable *in situ* FTIR monitoring. The reaction was therefore halted after 5 days according to TLC analysis.^{14a}

(3Z)-4-[(4-Iodophenyl)amino]but-3-en-2-one, 3k: 4-Iodoaniline (1.10 g, 5.0 mmol) and 3-butyn-2-one (0.39 mL, 5.0 mmol) were stirred in EtOH (10 mL) (completion indicated after 5 h) to give compound **3k** as a beige solid (1.04 g, 72%) after recrystallization from EtOH: m.p. = 128-130 °C; ^1H NMR (700 MHz, CDCl_3) δ 2.15 (s, 3H), 5.32 (d, $J = 7.8$ Hz, 1H), 6.76-6.81 (m, 2H), 7.14 (dd, $J = 12.2, 7.8$ Hz, 1H), 7.56-7.61 (m, 2H), 11.54 (br d, $J = 11.8$ Hz, 1H); ^{13}C NMR (176 MHz, CDCl_3) δ

29.9, 86.0, 98.4, 118.1, 138.7, 140.4, 142.4, 199.4; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3174w, 3075w, 2990w, 2915w, 1633m, 1588s, 1561s, 1465s, 1366m, 1280m, 1120w, 812s; MS (ES): $m/z = 288.0$ $[\text{M}+\text{H}]^+$; HRMS (ES) calcd. for $\text{C}_{10}\text{H}_{11}\text{INO}$ $[\text{M}+\text{H}]^+$: 287.9885, found: 287.9892. Note: **3k** was susceptible to degradation when heated above 120 °C in a Kugelrohr under vacuum. Precipitation of **3k** caused unreliable *in situ* FTIR monitoring.

(3Z)-4-[(4-Iodo-2-methylphenyl)amino]but-3-en-2-one, 3l: 4-Iodo-2-methylaniline (1.17 g, 5.0 mmol) and 3-butyne-2-one (0.39 mL, 5.0 mmol) were stirred in EtOH (10 mL) (completion indicated after 5 h) to give compound **3l** as a beige solid (1.28 g, 85%) after recrystallization from EtOH: m.p. = 106-107 °C; ^1H NMR (700 MHz, CDCl_3) δ 2.18 (s, 3H), 2.30 (s, 3H), 5.38 (d, $J = 7.6$ Hz, 1H), 6.85 (d, $J = 8.5$ Hz, 1H), 7.23 (dd, $J = 11.9, 7.7$ Hz, 1H), 7.48 (d, $J = 9.2$ Hz, 1H), 7.50 (s, 1H), 11.75 (br d, $J = 11.3$ Hz, 1H); ^{13}C NMR (176 MHz, CDCl_3) δ 17.4, 29.8, 86.1, 98.6, 115.3, 128.6, 136.1, 139.0, 139.8, 142.7, 199.4; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3331m, 3030w, 3010w, 2964w, 1630m, 1577m, 1393m, 1255s, 760s, 669m; MS (ES): $m/z = 302.0$ $[\text{M}+\text{H}]^+$; HRMS (ES) calcd. for $\text{C}_{11}\text{H}_{13}\text{INO}$ $[\text{M}+\text{H}]^+$: 302.0042, found: 302.0052; Found: C, 43.95; H, 3.96; N, 4.65. Calc. for $\text{C}_{11}\text{H}_{12}\text{INO}$: C, 43.88; H, 4.02; N, 4.65%. Note: **3l** was susceptible to degradation when heated above 120 °C in a Kugelrohr. Precipitation of **3l** caused unreliable *in situ* FTIR monitoring.

(3E)-4-[Methyl(phenyl)amino]but-3-en-2-one, 3m: *N*-Methylaniline (0.107 mL, 1.0 mmol) and 3-butyne-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 20 mins) to give compound **3m** as a yellow oil (0.164 g, 93%) after purification by Kugelrohr distillation (125-145 °C) under vacuum: ^1H

NMR (700 MHz, CDCl₃) δ 2.18 (s, 3H), 3.27 (s, 3H), 5.41 (d, $J = 13.1$ Hz, 1H), 7.12-7.18 (m, 3H), 7.33-7.39 (m, 2H), 7.89 (d, $J = 13.1$ Hz, 1H); ¹³C NMR (176 MHz, CDCl₃) δ 28.4, 37.1, 102.0, 120.5, 124.9, 129.7, 146.7, 148.6, 196.4; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3061w, 2909w, 2828w, 1662m, 1612m, 1583s, 1544s, 1494s, 1427m, 1251s, 950s, 756s; MS (ES): $m/z = 176.1$ [M+H]⁺; HRMS (ES) calcd. for C₁₁H₁₄NO [M+H]⁺: 176.1078, found: 176.1075.³²

(3Z)-4-[(2-Methoxyphenyl)methyl]amino}but-3-en-2-one, 3n: 2-

Methoxybenzylamine (0.131 mL, 1.0 mmol) and 3-butyne-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 10 mins) to give compound **3n** as a light yellow oil (0.190 g, 93%) after purification by Kugelrohr distillation under vacuum (180-190 °C): ¹H NMR (700 MHz; CDCl₃) δ 2.04 (s, 3H), 3.86 (s, 3H), 4.33 (d, $J = 6.3$ Hz, 2H), 4.99 (d, $J = 7.4$ Hz, 1H), 6.72 (dd, $J = 12.8, 7.4$ Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 6.92 (td, $J = 7.4, 1.1$ Hz, 1H), 7.17 (d, $J = 7.4$ Hz, 1H), 7.27 (td, $J = 8.1, 1.7$ Hz, 1H), 10.06 (br s, 1H); ¹³C NMR (176 MHz; CDCl₃) δ 29.2, 48.8, 55.5, 94.0, 110.6, 120.8, 126.6, 128.7, 129.3, 152.8, 157.4, 197.5; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3261br, 3042w, 2939w, 2838w, 1637m, 1601m, 1557m, 1489m, 1354m, 1240s; MS(ES): $m/z = 206.4$ [M+H]⁺; HRMS (ES) calcd. for C₁₂H₁₆NO₂ [M+H]⁺: 206.1181, found 206.1187.

(3Z)-4-[(3,3-Diethoxypropyl)amino]but-3-en-2-one, 3o: 1-Amino-3,3-

diethoxypropane (0.162 mL, 1.0 mmol) and 3-butyne-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 12 mins) to give compound **3o** as a yellow oil (0.213 g, 99%) after purification by Kugelrohr distillation under vacuum (155-160 °C): ¹H NMR (700 MHz; CDCl₃) δ 1.19 (t, $J = 7.1$ Hz, 6H), 1.84

(td, $J = 6.8, 5.6$ Hz, 2H), 2.02 (s, 3H), 3.26 (q, $J = 6.6$ Hz, 2H), 3.46-3.50 (m, 2H), 3.61-3.65 (m, 2H), 4.53 (t, $J = 5.6$ Hz, 1H), 4.95 (d, $J = 7.3$ Hz, 1H), 6.60 (dd, $J = 12.8, 7.3$ Hz, 1H), 9.75 (br s, 1H); ^{13}C NMR (176 MHz; CDCl_3) δ 15.5, 29.1, 35.1, 45.2, 61.9, 93.9, 100.8, 152.6, 197.5; $\nu_{\text{max}}/\text{cm}^{-1}$ 3267br, 2975w, 2930w, 2886w, 1639m, 1557m, 1486m, 1373w, 1254m, 1122s; MS(ES): $m/z = 216.5$ $[\text{M}+\text{H}]^+$; HRMS (ES) calcd. for $\text{C}_{11}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 216.1600, found 216.1606.

(3E)-4-[Bis(propan-2-yl)amino]but-3-en-2-one, 3p: Diisopropylamine (0.140 mL, 1.0 mmol) and 3-butyne-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 10 mins) to give compound **3p** as a yellow oil (0.166 g, 98%) after purification by Kugelrohr distillation under vacuum (120-125 °C): ^1H NMR (400 MHz, CDCl_3) δ 1.20 (d, $J = 6.8$ Hz, 12H), 2.07 (s, 3H), 3.56 (br, 1H), 3.81 (br, 1H), 5.20 (d, $J = 12.9$ Hz, 1H), 7.61 (br, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 19.8, 23.7, 29.1, 48.1, 49.0, 95.7, 147.4, 195.2; IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2975w, 2934w, 2879w, 1649m, 1597m, 1545m, 1456m, 1297s; MS (ES): $m/z = 170.1$ $[\text{M}+\text{H}]^+$; HRMS (ES) calcd. for $\text{C}_{10}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 170.1545, found 170.1543.³³

(3E)-4-(2,2,6,6-Tetramethylpiperidin-1-yl)but-3-en-2-one, 3q: 2,2,6,6-Tetramethylpiperidine (0.169 mL, 1.0 mmol) and 3-butyne-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 6 h) to give compound **3q** as a colourless crystalline solid (0.197 g, 95%) after purification by Kugelrohr distillation under vacuum (145-155 °C): m.p. = 92-94 °C; ^1H NMR (600 MHz; CDCl_3) δ 1.38 (s, 12H), 1.58-1.66 (m, 6H), 2.10 (s, 3H), 5.42 (d, $J = 13.8$ Hz, 1H), 7.79 (br d, $J = 13.6$ Hz, 1H); ^{13}C NMR (151 MHz; CDCl_3) δ 16.4, 29.3, 41.1, 58.0, 102.8, 148.3, 195.4; IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2971w, 2939w, 2863w, 1653m, 1534m,

1465m, 1344s, 1245s, 1163s; MS (ES): $m/z = 210.5 [M+H]^+$; HRMS (ES) calcd. for $C_{13}H_{24}NO [M+H]^+$: 210.1858, found 210.1859; Found: C, 74.58; H, 10.99; N, 6.64. Calc. for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69%. Note: ^{13}C NMR signal for the ketone methyl group was not observed.

1-Phenylprop-2-yn-1-one, 2b: Ethynyl magnesium bromide (0.5 M in THF, 36 mL, 18.0 mmol) was added dropwise under Ar to a solution of benzaldehyde (1.53 mL, 15.0 mmol) in anhydrous THF (10 mL) at $-78\text{ }^{\circ}C$. The resultant solution was allowed to warm to RT and stirred for 2.5 h. The solution was quenched with sat. NH_4Cl , diluted with DCM, and the organics washed with H_2O , dried ($MgSO_4$) and evaporated to give a crude yellow oil. This was purified by SiO_2 chromatography (DCM:hexane, 4:1 as eluent) to give 1-phenylprop-2-yn-1-ol as a yellow oil (1.79 g, 90%). 1-Phenylprop-2-yn-1-ol (1.79 g, 13.5 mmol) was then dissolved in acetone (10 mL), and a solution of CrO_3 (0.9 g, 9.00 mmol) in a mixture of H_2O (7 mL) and conc. H_2SO_4 (3 mL) was added dropwise over 20 mins at $0\text{ }^{\circ}C$. The resultant suspension was stirred at $0\text{ }^{\circ}C$ for 5 h, before being diluted with H_2O and extracted with $CHCl_3$ (3x). The organics were washed with H_2O , dried ($MgSO_4$), and evaporated to give a crude yellow solid. This was distilled under vacuum using a Kugelrohr ($105\text{-}115\text{ }^{\circ}C$) to give 1-phenylprop-2-yn-1-one, **2b**, as a white solid (1.18 g, 67%): m.p. = $41\text{-}44\text{ }^{\circ}C$; 1H NMR (700 MHz, $CDCl_3$) δ 3.46 (s, 1H), 7.46 (t, $J = 7.7$ Hz, 2H), 7.59 (t, $J = 7.4$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 80.4, 81.1, 128.8, 129.8, 134.6, 136.2, 177.5; IR (neat) ν_{max}/cm^{-1} 3232s, 3099w, 3067w, 2091s, 1637s, 1595m, 1580m, 1452m, 1247s, 692s; MS (EI): $m/z = 130.1 [M]^+$.^{34,35}

(2E)-3-(Morpholin-4-yl)-1-phenylprop-2-en-1-one, 3u: Morpholine (0.0874 mL, 1.0 mmol) and 1-phenylprop-2-yn-1-one (0.13 g, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 6 mins) to give compound **3u** as a yellow oil (0.187 g, 86%) after purification by Kugelrohr distillation under vacuum (210-220 °C): ¹H NMR (700 MHz; CDCl₃) δ 3.38 (t, *J* = 4.9 Hz, 4H), 3.73-3.76 (m, 4H), 5.87 (d, *J* = 12.6 Hz, 1H), 7.38-7.42 (m, 2H), 7.43-7.47 (m, 1H), 7.72 (d, *J* = 12.6 Hz, 1H), 7.85-7.88 (m, 2H); ¹³C NMR (176 MHz; CDCl₃) δ 66.5, 92.7, 127.7, 128.4, 131.4, 140.4, 152.9, 189.4; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3005w, 2965w, 2908w, 2854w, 1636m, 1580m, 1531s, 1439m, 1203s; MS (ES): *m/z* = 218.8 [M+H]⁺; HRMS (ES) calcd. for C₁₃H₁₆NO₂ [M+H]⁺: 218.1181, found 218.1187.³⁶

(2Z)-1-Phenyl-3-(phenylamino)prop-2-en-1-one, 3v: Aniline (0.0910 mL, 1.0 mmol) and 1-phenylprop-2-yn-1-one (0.13 g, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 30 mins) to give compound **3v** as a yellow crystalline solid (0.196 g, 88%) after purification by Kugelrohr distillation under vacuum (205-215 °C): m.p. = 128-130 °C; ¹H NMR (600 MHz; CDCl₃) δ 6.03 (d, *J* = 7.8 Hz, 1H), 7.06-7.14 (m, 3H), 7.32-7.38 (m, 2H), 7.43-7.49 (m, 2H), 7.47-7.56 (m, 2H), 7.92-7.98 (m, 2H), 12.16 (d, *J* = 12.7 Hz, 1H); ¹³C NMR (151 MHz; CDCl₃) δ 93.9, 116.5, 123.9, 127.5, 128.6, 129.9, 131.8, 139.4, 140.4, 145.1, 191.2; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3260br, 3058w, 3033w, 1623m, 1593m, 1549m, 1508m, 1451m, 1238s, 741s; MS (ES): *m/z* = 224.4 [M+H]⁺; HRMS (ES) calcd. for C₁₅H₁₄NO [M+H]⁺: 224.1075, found 224.1072.³⁷

Methyl (2Z)-3-(phenylamino)prop-2-enoate, 3w: Aniline (0.0910 mL, 1.0 mmol) and methyl propiolate (0.0890 mL, 1.0 mmol) were stirred in EtOH (4 mL)

(completion indicated after 35 h) to give compound **3w** as a white crystalline solid (0.146 g, 82%) after purification by Kugelrohr distillation under vacuum (150-160 °C): m.p. = 147-149 °C; ¹H NMR (400 MHz; CDCl₃) δ 3.72 (s, 3H), 4.85 (d, *J* = 8.3 Hz, 1H), 6.91-7.06 (m, 3H), 7.19-7.38 (m, 3H), 9.88 (br d, *J* = 10.5 Hz, 1H); ¹³C NMR (101 MHz; CDCl₃) δ 50.9, 87.2, 115.6, 115.7, 122.8, 122.8, 129.9, 129.9, 140.9, 143.4, 170.9; IR (neat) $\nu_{\max}/\text{cm}^{-1}$ 3269br, 3111w, 3019w, 2949w, 1686m, 1613m, 1582m, 1494m, 1448m, 1260s, 1147s; MS (ES): *m/z* = 178.3 [M+H]⁺; HRMS (ES) calcd. for C₁₀H₁₂NO₂ [M+H]⁺: 178.0868, found 178.0862.^{8b}

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Supporting Information

Supporting information: photos of experimental setup, *in situ* FTIR reaction progress plots, UV-Vis analysis, further FTIR spectra, copies of ¹H and ¹³C NMR spectra, X-ray crystallographic data including pictures, crystallographic information files (.cif).

References

- [1] a) *Conjugate Addition Reactions in Organic Synthesis*; Perlmutter, P.; Pergamon: Oxford, 1992.
b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058-11076.
- [2] a) Phippen, C. B. W.; Beattie, J. K.; McErlean, C. S. P. *Chem. Commun.* **2010**, *46*, 8234–8236.
b) De, K.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *J. Org. Chem.* **2009**, *74*, 6260–6265.
- [3] Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679–3688.

- [4] Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 6379–6385.
- [5] Fetterly, B. M.; Jana, N. K.; Verkade, J. G. *Tetrahedron* **2006**, *62*, 440–456.
- [6] Fedotova, A.; Crousse, B.; Chataigner, I.; Maddaluno, J.; Rulev, A. Y.; Legros, J. *J. Org. Chem.* **2015**, *80*, 10375–10379.
- [7] a) Um, I. H.; Lee, E. J.; Min, J. S. *Tetrahedron* **2001**, *57*, 9585–9589. b) Um, I. H.; Lee, J. S.; Yuk, S. M. *J. Org. Chem.* **1998**, *63*, 9152–9153. c) Um, I. H.; Lee, E. J.; Seok, J. A.; Kim, K. H. *J. Org. Chem.* **2005**, *70*, 7530–7536.
- [8] a) Sun, J.; Sun, Y.; Xia, E.-Y.; Yan, C.-G. *ACS Comb. Sci* **2011**, *13*, 436–441. b) Matsumoto, S.; Mori, T.; Akazome, M. *Synthesis* **2010**, 3615–3622. c) Price, C. C.; Leonard, N. J.; Reitsema, R. H. *J. Am. Chem. Soc.* **1946**, *68*, 1256–1259. d) Bartsch, H.; Schwarz, O. *J. Heterocyclic Chem.* **1983**, *20*, 45–48. e) Gray, F. W.; Mosher, H. S.; Whitmore, F. C.; Oakwood, T. S. *J. Am. Chem. Soc.* **1951**, *73*, 3577–3578. f) Heindel, N. D.; Kennewel, P. D.; Fish, V. B. *J. Heterocyclic Chem.* **1969**, *6*, 77–81. g) Yang, J.; Wang, C.; Xie, X.; Li, H.; Li, Y. *Eur. J. Org. Chem.* **2010**, 4189–4193. h) Choudhary, G.; Peddinti, R. K. *Green Chem.* **2011**, *13*, 3290–3299.
- [9] Ji, X.; Huang, H.; Wu, W.; Li, X.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 11155–11162.
- [10] Thorwirth, R.; Stolle, A. *Synlett* **2011**, 2200–2202.
- [11] Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294.
- [12] a) Calow, A. D. J.; Batsanov, A. S.; Fernández, E.; Solé, C.; Whiting, A. *Chem. Commun.* **2012**, 48, 11401–11403. b) Foley, D. A.; Doecke, C. W.; Buser, J. Y.; Merritt, J. M.; Murphy, L.; Kissane, M.; Collins, S. G.; Maguire, A. R.; Kaerner, A. *J. Org. Chem.* **2011**, *76*, 9630–9640.
- [13] Vdovenko, S. I.; Gerus, I. I.; Gorbunova, M. G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 559–562.
- [14] a) Kashima, C.; Aoyama, H.; Yamamoto, Y.; Nishio, T.; Yamada, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 665–670. b) Chiara, J. L.; Gómez-Sánchez, A.; Bellanato, J. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1797–1806.
- [15] Dabrowski, J.; Kozerski, L. *J. Chem. Soc. B* **1971**, 345–348.

- [16] a) Dabrowski, J.; Kamienska-Trela, K. *J. Am. Chem. Soc.* **1976**, *98*, 2826–2834. b) Ostercamp, D. L. *J. Org. Chem.* **1970**, *35*, 1632–1641. c) Kashima, C.; Yamamoto, M.; Sugiyama, N. *J. Chem. Soc. C* **1970**, 111–114.
- [17] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339–341.
- [18] Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 49–76.
- [19] Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997.
- [20] a) Vdovenko, S. I.; Gerus, I. I.; Kukhar, V. P. *Vib. Spectrosc.* **2010**, *52*, 144–153. b) Vdovenko, S. I.; Gerus, I. I.; Fedorenko, H. A.; Kukhar, V. P. *Spectrochim. Acta Mol. Biomol. Spectrosc.* **2013**, *103*, 368–377.
- [21] Zheglova, D. K.; Genov, D. G.; Griбанov, A. V.; Kol'tsov, A. I.; Smirnov, S. N. *Monatsh. Chem.* **1994**, *125*, 1443–1446.
- [22] a) Dudek, G. O. *J. Org. Chem.* **1965**, *30*, 548–552. b) Dabrowski, J.; Kamińska-Trela, K. *Spectrochim. Acta* **1966**, *22*, 211–220. c) Dabrowski, J. *Spectrochim. Acta* **1963**, *19*, 475–496.
- [23] Greenhill, J. V. *J. Chem. Soc. B* **1969**, 299–300.
- [24] Greenhill, J. V. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2207–2210.
- [25] Gómez Sánchez, A.; Tena Aldave, M.; Scheidegger, U. *J. Chem. Soc., Ser. C* **1968**, 2570–2573.
- [26] Girling, P. R.; Batsanov, A. S.; Shen, H. C.; Whiting, A. *Chem. Commun.* **2012**, *48*, 4893–4895.
- [27] Shaw, G. *J. Chem. Soc.* **1952**, 3428–3432.
- [28] Hohenlohe-Oehringen, K.; Rhomberg, A.; Bretschneider, H. *Monatsh. Chem. Verw. TL* **1966**, *97*, 135–144.
- [29] LARGERON, M.; Fleury, M.-B. *Chem. Eur. J.* **2015**, *21*, 3815–3820.
- [30] DeGraw, J. I.; Marsh, J. P.; Acton, E. M.; Crews, O. P.; Mosher, C. W.; Fujiwara, A. N.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 3404–3409.
- [31] Bohme, H.; Berg, G.; Schneider, H. *Arch. Pharm.* **1964**, *297*, 321–325.
- [32] Bozell, J. J.; Hegedus, L. S. *J. Org. Chem.* **1981**, *46*, 2561–2563.

- [33] Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039–3052.
- [34] Caliendo, G.; Fiorino, F.; Grieco, P.; Perissutti, E.; Santagada, V.; Albrizio, S.; Spadola, L.; Bruni, G.; Rosaria, M. R. *Eur. J. Med. Chem.* **1999**, *34*, 719–727.
- [35] Aulakh, V. S.; Ciufolini, M. A. *J. Org. Chem.* **2009**, *74*, 5750–5753.
- [36] Kang, Y.-W.; Cho, Y. J.; Han, S. J.; Jang, H.-Y. *Org. Lett.* **2016**, *18*, 272–275.
- [37] Al-Saleh, B.; El-Asery, M. A.; Abdel-Aziz, R. S.; Elnagdi, M. H. *J. Heterocyclic Chem.* **2005**, *42*, 563–566.