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# Conjugate Addition of 3-Buytn-2-one to Anilines in Ethanol: Alkene Geometric Insights through In Situ FTIR Monitoring

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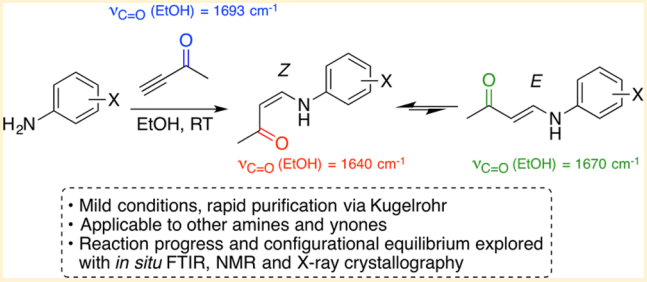
Supporting Information

**ABSTRACT:** A convenient, mild and effective conjugate addition of 3-butyn-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.

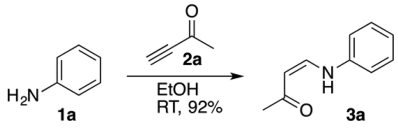



## INTRODUCTION

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 $\alpha,\beta$-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-butyn-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] 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 toward 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-Buytn-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 (ReactIR),[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.

The effect of the solvent on the reaction between aniline, **1a** and 3-butyn-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 h according to $^1$H 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 $^1$H NMR. Only the reactions with the more polar solvents $H_2O$ and DMSO exhibited reasonable conversions to **3a**, although still at a significantly slower rate than the reaction in EtOH.

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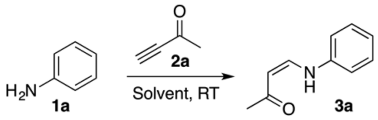
Clearly, at room temperature, EtOH exhibited a substantial rate enhancement compared to the solvents (Table 1).

**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[b]/% |
|---|---|---|
| Toluene | 16 h | 27 |
| DCM | 16 h | 22 |
| THF | 6 h | trace |
| EtOH | 1 h | 100 |
| $H_2O$ | 16 h[c] | 67 |
| DMSO | 24 h | 57 |

[a]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 $H_2O$ and brine, dried ($MgSO_4$), evaporated and then analyzed by $^1H$ NMR. [b]Estimated via analysis of the crude $^1H$ NMR spectra in chloroform-$d_1$ by comparing the relative integrals of the starting **1a** and enaminone **3a**. [c]FTIR monitoring in this case was unreliable due to rapid precipitation of **3a**.

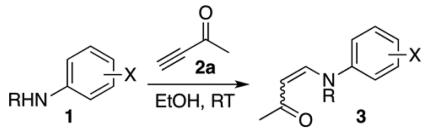
With the ideal solvent identified, the reaction was conducted using a variety of anilines, with monitoring by in situ FTIR. Close monitoring of the reaction between aniline **1a** and **2a** indicated a rapid reaction, with only around 20 min required to effect complete conversion to enaminone **3a**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

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 h 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 h.

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 h.

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

**Table 2. Addition of Anilines 1a−m to 3-Butyn-2-one 2a to Give Enaminones 3a−m**




| aniline | approx. time[a] | enaminone | alkene geometry[b] | yield/% |
|---|---|---|---|---|
| Aniline, **1a** | 20 min | **3a** | *Z* | 92 |
| 2-Methylaniline, **1b** | 20 min | **3b** | *Z* | 93 |
| 4-Methylaniline, **1c** | 20 min | **3c** | *Z* | 87 |
| 3,5-Dimethylaniline, **1d** | 40 min | **3d** | *Z* | 94 |
| 4-Hydroxyaniline, **1e** | 20 min | **3e** | *Z* | 86[d] |
| 4-Methoxyaniline, **1f** | 20 min | **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 min | **3m** | *E* | 93 |

[a]Estimated using FTIR. [b]Assessed by $^1H$ NMR in chloroform-$d_1$. [c]Estimated using TLC. [d]Isolated by chromatography. [e]Isolated by recrystallization.

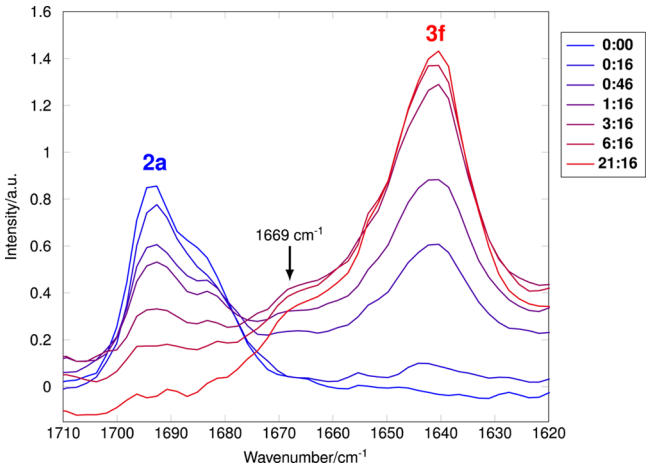



**Figure 1.** In situ FTIR spectra of the reaction between **1f** and **2a** at selected time points (time proceeds from blue to red). The decline of the carbonyl stretch of **2a** (1693 $cm^{-1}$) and the consequent rise of the carbonyl stretch of **3f** (1640 $cm^{-1}$) is shown as the reaction proceeded.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

the carbonyl stretch of **2a**. Clearly the majority of product **3f** was formed after only around 3 min, 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



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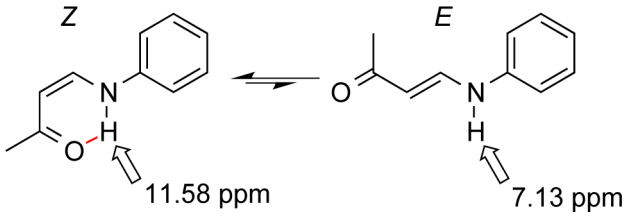
intramolecular hydrogen bonding.[11,13] This shoulder therefore clearly indicated that both the *Z*- (1640 $cm^{-1}$) and *E*-isomers (1669 $cm^{-1}$) were formed during the reaction. Analysis of the full spectra showed that there were no obvious intermediate species, i.e., infrared bands that rose and 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 $pK_a$ 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.

Analysis of the $^1$H NMR spectra of the enaminones in chloroform-$d_1$ (Scheme 2) highlighted a variety of structural

**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 $^1$H NMR in Chloroform-$d_1$**[a]




[a]The intramolecular hydrogen bond evident in the *Z*-isomeric form is shown as a dashed red line.

features. First, 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 $\alpha$-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 $\alpha$-keto-carbon proton.

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 $^1$H 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

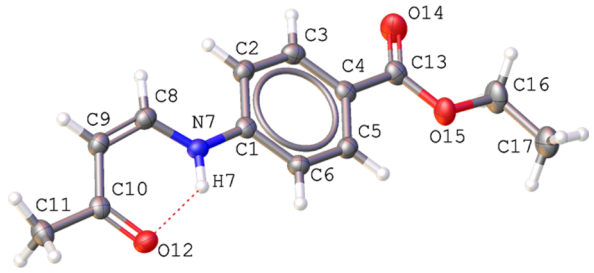



**Figure 2.** Ball-and-stick representation of the X-ray structure of **3g**, highlighting the *Z*-alkene configuration, *s-cis* C−N bond conformation and intramolecular hydrogen bond (red, dotted line). Figure produced using Olex2.[17]

to the Z-isomer, indicating that this proton was not significantly hydrogen bonded.[14,21] Furthermore, when the $^1$H NMR spectrum of a second fraction of **3a** was recorded 1 h 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 toward the *Z*-isomer over time.

This intriguing equilibrium was further probed by a $D_2O$ exchange experiment. When the $^1$H NMR spectrum of **3a** in chloroform-$d_1$ was recorded immediately after agitation with $D_2O$ (Figure 3), **3a** was shown to exist in a 7:93 ratio of the *Z*- and *E*-forms, respectively. After 30 min, and then after 2 h, the equilibrium still favored the *E*-form (14:86 and 24:76, respectively), but after 6 h, the equilibrium shifted toward the *Z*-form (76:24). The equilibrium relaxed over 48 h to a 97:3 ratio as shown by $^1$H NMR. These results indicated that **3a** converts to the *E*-configuration during deuterium exchange, but

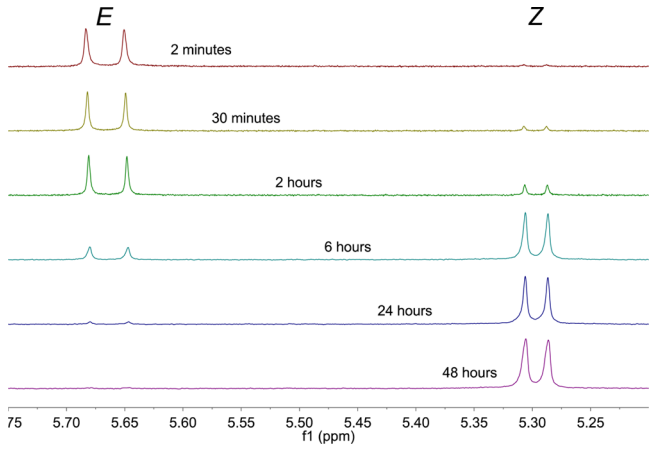



**Figure 3.** $^1$H NMR spectrum of **3a** in chloroform-$d_1$ monitored over 48 h after a $D_2O$ shake experiment. The $\alpha$-carbonyl proton of the *Z*- and *E*-isomers are shown. Immediately after agitation with $D_2O$ the *E*-isomer predominates (2 min), but over time is found to preferentially isomerize to the thermodynamically favored *Z*-isomer.



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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 $^1$H

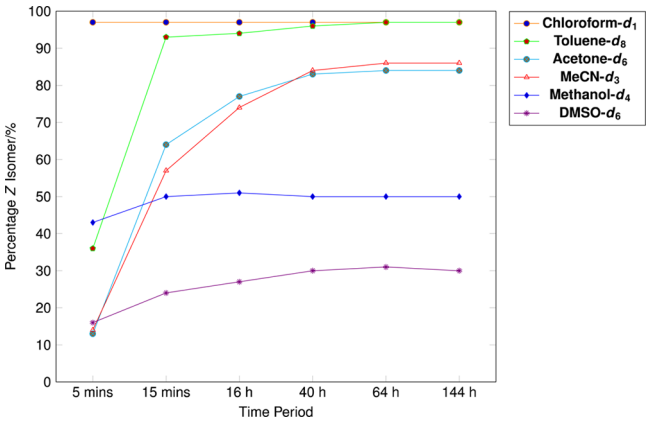


**Figure 4.** Relative percentage of the *Z*-isomer of **3a** over time in different deuterated solvents. Percentages were determined from $^1$H NMR by comparing the integrals of the $\alpha$-keto proton of the *Z*- and *E*-isomers.

NMR spectra were recorded as quickly as possible after preparation of the samples. After 5 min the *E*-isomer was the predominant form in all solvents. After 15 min, the equilibrium was found to significantly shift toward 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]

The fascinating effect of hydrogen bonding is highlighted in Figure 4.[20,21] After 5 min; 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, $^1$H 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 time scale, 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 $\lambda_{max}$ 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 enaminones are instantly converted to a 1:1 ratio of *Z*/*E*-isomers.

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 h, 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


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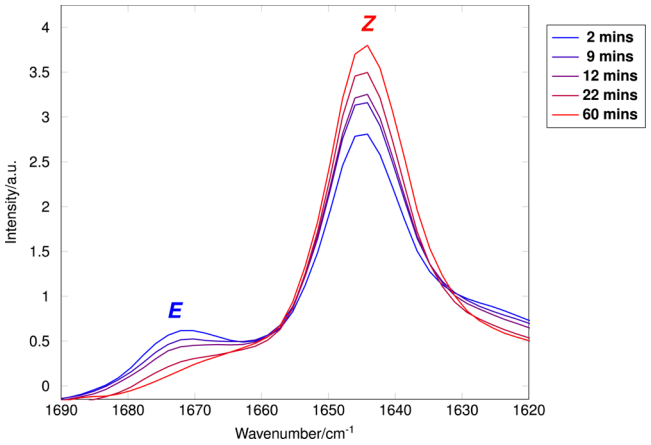



**Figure 5.** In situ FTIR monitoring of the 1620−1690 $cm^{-1}$ region of **3a** in chloroform-$d_1$ immediately after isolation. The relaxation of the *Z*/*E* equilibrium was followed by monitoring the intensity of the carbonyl stretches of the *E*- and *Z*-isomers over time (time proceeds from blue 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 h.[22]

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 $^1$H NMR in DMSO-$d_6$ (Figure 4).

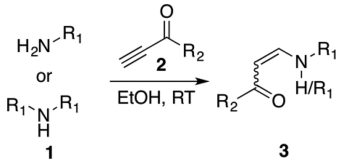
In an attempt to understand the mechanism of this facile isomerization process, we prepared separate solutions of **3a** with a conjugate addition acceptor (methyl vinyl ketone), and with a conjugate addition donor (4-methoxyaniline, **1f**), in a range of deuterated solvents. If the isomerization proceeded via rapid elimination, rotation and readdition of the enone unit, one would expect to observe additional conjugate addition products. However, $^1$H NMR monitoring of these solutions over 1 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]

With the conformational preferences of enaminones **3a**−**l** understood, we assessed the utility of the method toward 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 time frame (6 h). 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 $^1$H 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.

**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 min | **3n** | *Z* | 93 |
| 1-Amino-3,3-diethoxypropane, **1o** | Me, **2a** | 12 min | **3o** | *Z* | 99 |
| Diisopropylamine, **1p** | Me, **2a** | 10 min | **3p** | *E* | 98 |
| 2,2,6,6-Tetramethylpiperidine, **1q** | Me, **2a** | 6 h | **3q** | *E* | 95 |
| 2-Amino-6-methylpyridine, **1r** | Me, **2a** | >48 h | **3r** | *Z* | (<30)[d] |
| 4-Aminoquinaldine, **1s** | Me, **2a** | >48 h | **3s** | *Z* | (<15)[d] |
| 2-Aminopyrimidine, **1t** | Me, **2a** | – | **3t** | – | 0 |
| Morpholine, **1u** | Ph, **2b** | 6 min | **3u** | *Z* | 86 |
| Aniline, **1a** | Ph, **2b** | 30 min[c] | **3v** | *Z* | 88 |
| Aniline, **1a** | OMe, **2c** | 35 h | **3w** | *E* | 82 |

[a]Estimated using FTIR. [b]Assessed by $^1$H NMR in chloroform-$d_1$. [c]Precipitated after 5 min. [d]Not isolated. Enaminones **3n**−**q** and **3u**−**w** were all isolated via Kugelrohr distillation. Yields in parentheses were estimated from crude $^1$H NMR analysis.



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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 $CHCl_3$ peak ($^1H$ = 7.26 ppm, $^{13}C$ = 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 $H_2O$ and brine, dried ($MgSO_4$), evaporated and then directly distilled under vacuum using a Kugelrohr apparatus, recrystallized or purified by $SiO_2$ 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 Supporting Information). 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.

**(3*Z*)-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 min) to give compound **3a** as a white solid (0.149 g, 92%) after purification by Kugelrohr distillation under vacuum (100−120 °C): mp = 95−96 °C; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 29.8, 97.6, 116.3, 123.6, 129.9, 140.6, 143.2, 199.1; IR (neat) $\nu_{max}/cm^{-1}$ 3236m, 3057w, 3036w, 2998w, 1660m, 1600m, 1545s, 1471s, 1260s, 961s; MS (ES) $m/z$ = 162.1 $[M + H]^+$; HRMS (ES) calcd. for $C_{10}H_{12}NO$ $[M + H]^+$: 162.0919, found 162.0923. Found: C, 74.43; H, 6.85; N, 8.70. Calc. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%.[26]

**(3*Z*)-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 min) to give compound **3b** as an off-white solid (0.160 g, 93%) after purification by Kugelrohr distillation under vacuum (120−130 °C): mp = 34−36 °C; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 17.8, 29.7, 97.8, 113.7, 123.4, 126.3, 127.3, 131.3, 139.1, 143.6, 199.0; IR (neat) $\nu_{max}/cm^{-1}$ 3200w, 3059w, 2984w, 2910w, 1635m, 1585m, 1563s, 1465s, 1274s, 743s; MS (ES) $m/z$ = 176.1 $[M + H]^+$; HRMS (ES) calcd. for $C_{11}H_{14}NO$ $[M + H]^+$: 176.1075, found 176.1076. Found: C, 75.27; H, 7.46; N, 7.94. Calc. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%.

**(3*Z*)-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 min) to give compound **3c** as an off-white solid (0.153 g, 87%) after purification by Kugelrohr distillation under vacuum (100−120 °C): mp = 109−110 °C; $^1H$ NMR (700 MHz; $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (176 MHz; $CDCl_3$) $\delta$ 20.9, 29.7, 97.1, 116.4, 130.4, 133.3, 138.2, 143.7, 198.8; IR (neat) $\nu_{max}/cm^{-1}$ 3182m, 3033w, 2977w, 2858w, 1634m, 1609m, 1564s, 1475s, 1282s, 812s; MS (ES) $m/z$ = 176.1 $[M + H]^+$; HRMS (ES) calcd. for $C_{11}H_{14}NO$ $[M + H]^+$: 176.1075, found 176.1085. Found: C, 75.39; H, 7.46; N, 8.04. Calc. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%.[27]

**(3*Z*)-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 min) 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, $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (176 MHz, $CDCl_3$) $\delta$ 21.5, 29.7, 97.2, 114.1, 125.4, 139.6, 140.5, 143.4, 198.8; IR (neat) $\nu_{max}/cm^{-1}$ 3259w, 3027w, 2918w, 2861w, 1637s, 1571s, 1476m, 1278s, 1171s, 955m, 831m; MS (ES) $m/z$ = 190.1 $[M + H]^+$; HRMS (ES) calcd. for $C_{12}H_{16}NO$ $[M + H]^+$: 190.1232, found 190.1237. Found: C, 75.55; H, 8.04; N, 6.99. Calc. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40%.

**(3*Z*)-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 min) to give compound **3e** as a yellow solid (0.760 g, 86%) after purification by $SiO_2$ column chromatography ($Et_2O$, with 1% $Et_3N$ as eluent): mp = 138−140 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 29.5, 96.7, 116.7, 118.2, 134.1, 144.7, 152.6, 198.8; IR (neat) $\nu_{max}/cm^{-1}$ 3100br, 3080w, 3032w, 2956w, 2813w, 1635m, 1554m, 1489s, 1263s, 1205s, 830s, 747s; MS (ES) $m/z$ = 178.1 $[M + H]^+$; HRMS (ES) calcd. for $C_{10}H_{12}NO_2$ $[M + H]^+$: 178.0868, found 178.0873. Found: C, 67.37; H, 6.23; N, 7.79. Calc. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90%. Note: **3e** exhibited low solubility in $CDCl_3$. **3e** was also highly susceptible to degradation when heated. Mild heating with a heat gun, or in a Kugelrohr caused a rapid color change to dark red/brown.[28]

**(3*Z*)-4-[(4-Methoxyphenyl)amino]but-3-en-2-one, 3f.** 4-Methoxyaniline (0.123 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



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min) to give compound **3f** as a white solid (0.168 g, 88%) after purification by Kugelrohr distillation under vacuum (100−120 °C): mp = 62−64 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 29.6, 55.7, 96.7, 115.1, 117.9, 134.2, 144.3, 156.3, 198.5; IR (neat) $\nu_{max}$/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 $C_{11}H_{14}NO_2$ [M + H]$^+$: 192.1031, found 192.1025. Found: C, 69.07; H, 6.85; N, 7.31. Calc. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.[29]

**4-[(1*Z*)-3-Oxobut-1-en-1-yl]aminobenzoate, 3g.** Ethyl 4-aminobenzoate (0.165 g, 1.0 mmol) and 3-butyn-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): mp = 75−76 °C; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 14.6, 30.0, 61.0, 99.3, 115.2, 125.1, 131.7, 141.7, 144.4, 166.2, 199.8; IR (neat) $\nu_{max}$/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 h.[30]

**(3*Z*)-4-[(4-Chlorophenyl)amino]but-3-en-2-one, 3h.** 4-Chloroaniline (0.128 g, 1.0 mmol) and 3-butyn-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): mp = 111−113 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 29.8, 98.2, 117.4, 128.5, 129.9, 139.3, 142.8, 199.4; IR (neat) $\nu_{max}$/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]

**(3*Z*)-4-[(4-Bromophenyl)amino]but-3-en-2-one, 3i.** 4-Bromoaniline (0.172 g, 1.0 mmol) and 3-butyn-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): mp = 121−124 °C; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 29.9, 98.3, 115.9, 117.7, 132.8, 139.7, 142.6, 199.4; IR (neat) $\nu_{max}$/cm$^{-1}$ 3177w, 3073w, 2994w, 2908w, 1634m, 1591s, 1566s, 1471s, 1289m, 1180m, 814s, 752s; MS (ES) $m/z$ = 240.0 [M + H]$^+$; HRMS (ES) calcd. for $C_{10}H_{11}NOBr$ [M + H]$^+$: 240.0024, found 240.0039. Found: C, 50.09; H, 4.19; N, 5.81. Calc. for $C_{10}H_{10}NOBr$: C, 50.02; H, 4.20; N, 5.83%.

**(3*Z*)-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: mp = 178−180 °C; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 30.3, 101.0, 115.2, 126.2, 140.6, 142.9, 146.1, 200.4; IR (neat) $\nu_{max}$/cm$^{-1}$ 3201w, 3094w, 3003w, 1647m, 1575s, 1496s, 1473s, 1377m, 1325s, 1274s, 838s; MS (ES) $m/z$ = 207.0 [M + H]$^+$; HRMS (ES) calcd. for $C_{10}H_{11}N_2O_3$ [M + H]$^+$: 207.0770, found 207.0772. Found: C, 57.80; H, 4.82; N, 13.50. Calc. for $C_{10}H_{10}N_2O_3$: 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]

**(3*Z*)-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: mp = 128−130 °C; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 29.9, 86.0, 98.4, 118.1, 138.7, 140.4, 142.4, 199.4; IR (neat) $\nu_{max}$/cm$^{-1}$ 3174w, 3075w, 2990w, 2915w, 1633m, 1588s, 1561s, 1465s, 1366m, 1280m, 1120w, 812s; MS (ES) $m/z$ = 288.0 [M + H]$^+$; HRMS (ES) calcd. for $C_{10}H_{11}INO$ [M + 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.

**(3*Z*)-4-[(4-Iodo-2-methylphenyl)amino]but-3-en-2-one, 3l.** 4-Iodo-2-methylaniline (1.17 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 **3l** as a beige solid (1.28 g, 85%) after recrystallization from EtOH: mp = 106−107 °C; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 17.4, 29.8, 86.1, 98.6, 115.3, 128.6, 136.1, 139.0, 139.8, 142.7, 199.4; IR (neat) $\nu_{max}$/cm$^{-1}$ 3331m, 3030w, 3010w, 2964w, 1630m, 1577m, 1393m, 1255s, 760s, 669m; MS (ES) $m/z$ = 302.0 [M + H]$^+$; HRMS (ES) calcd. for $C_{11}H_{13}INO$ [M + H]$^+$: 302.0042, found 302.0052. Found: C, 43.95; H, 3.96; N, 4.65. Calc. for $C_{11}H_{12}INO$: 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.

**(3*E*)-4-[Methyl(phenyl)amino]but-3-en-2-one, 3m.** *N*-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 min) to give compound **3m** as a yellow oil (0.164 g, 93%) after purification by Kugelrohr distillation (125−145 °C) under vacuum: $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 28.4, 37.1, 102.0, 120.5, 124.9, 129.7, 146.7, 148.6, 196.4; IR (neat) $\nu_{max}$/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 $C_{11}H_{14}NO$ [M + H]$^+$: 176.1078, found 176.1075.[32]

**(3*Z*)-4-{[(2-Methoxyphenyl)methyl]amino}but-3-en-2-one, 3n.** 2-Methoxybenzylamine (0.131 mL, 1.0 mmol) and 3-butyn-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 10 min) to give compound **3n** as a light yellow oil (0.190 g, 93%) after purification by Kugelrohr distillation under vacuum (180−190 °C): $^1$H NMR (700 MHz; $CDCl_3$) $\delta$ 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); $^{13}$C NMR (176 MHz; $CDCl_3$) $\delta$ 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) $\nu_{max}$/cm$^{-1}$ 3261br, 3042w, 2939w, 2838w, 1637m, 1601m, 1557m, 1489m, 1354m, 1240s; MS(ES) $m/z$ = 206.4 [M + H]$^+$; HRMS (ES) calcd. for $C_{12}H_{16}NO_2$ [M + H]$^+$: 206.1181, found 206.1187.

**(3*Z*)-4-[(3,3-Diethoxypropyl)amino]but-3-en-2-one, 3o.** 1-Amino-3,3-diethoxypropane (0.162 mL, 1.0 mmol) and 3-butyn-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 12 min) to give compound **3o** as a yellow oil (0.213 g, 99%) after purification by Kugelrohr distillation under vacuum (155−160 °C): $^1$H NMR (700 MHz; $CDCl_3$) $\delta$ 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; $CDCl_3$) $\delta$ 15.5, 29.1, 35.1, 45.2, 61.9, 93.9, 100.8, 152.6, 197.5; $\nu_{max}$/cm$^{-1}$ 3267br, 2975w, 2930w, 2886w, 1639m, 1557m, 1486m, 1373w, 1254m, 1122s; MS(ES) $m/z$ = 216.5 [M +



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H]$^+$; HRMS (ES) calcd. for $C_{11}H_{22}NO_3$ [M + H]$^+$: 216.1600, found 216.1606.

**(3*E*)-4-[Bis(propan-2-yl)amino]but-3-en-2-one, 3p.** Diisopropylamine (0.140 mL, 1.0 mmol) and 3-butyn-2-one (0.0782 mL, 1.0 mmol) were stirred in EtOH (4 mL) (completion indicated after 10 min) to give compound **3p** as a yellow oil (0.166 g, 98%) after purification by Kugelrohr distillation under vacuum (120−125 °C): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 19.8, 23.7, 29.1, 48.1, 49.0, 95.7, 147.4, 195.2; IR (neat) $\nu_{max}$/cm$^{-1}$ 2975w, 2934w, 2879w, 1649m, 1597m, 1545m, 1456m, 1297s; MS (ES) $m/z$ = 170.1 [M + H]$^+$; HRMS (ES) calcd. for $C_{10}H_{20}NO$ [M + H]$^+$: 170.1545, found 170.1543.[33]

**(3*E*)-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-butyn-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 colorless crystalline solid (0.197 g, 95%) after purification by Kugelrohr distillation under vacuum (145−155 °C): mp = 92−94 °C; $^1$H NMR (600 MHz; $CDCl_3$) $\delta$ 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; $CDCl_3$) $\delta$ 16.4, 29.3, 41.1, 58.0, 102.8, 148.3, 195.4; IR (neat) $\nu_{max}$/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 °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 min at 0 °C. The resultant suspension was stirred at 0 °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 (105−115 °C) to give 1-phenylprop-2-yn-1-one, **2b**, as a white solid (1.18 g, 67%): mp = 41−44 °C; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 80.4, 81.1, 128.8, 129.8, 134.6, 136.2, 177.5; IR (neat) $\nu_{max}$/cm$^{-1}$ 3232s, 3099w, 3067w, 2091s, 1637s, 1595m, 1580m, 1452m, 1247s, 692s; MS (EI) $m/z$ = 130.1 [M]$^+$.[34,35]

**(2*E*)-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 min) to give compound **3u** as a yellow oil (0.187 g, 86%) after purification by Kugelrohr distillation under vacuum (210−220 °C): $^1$H NMR (700 MHz; $CDCl_3$) $\delta$ 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); $^{13}$C NMR (176 MHz; $CDCl_3$) $\delta$ 66.5, 92.7, 127.7, 128.4, 131.4, 140.4, 152.9, 189.4; IR (neat) $\nu_{max}$/cm$^{-1}$ 3005w, 2965w, 2908w, 2854w, 1636m, 1580m, 1531s, 1439m, 1203s; MS (ES) $m/z$ = 218.8 [M + H]$^+$; HRMS (ES) calcd. for $C_{13}H_{16}NO_2$ [M + H]$^+$: 218.1181, found 218.1187.[36]

**(2*Z*)-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 min) to give compound **3v** as a yellow crystalline solid (0.196 g, 88%) after purification by Kugelrohr distillation under vacuum (205−215 °C): mp = 128−130 °C; $^1$H NMR (600 MHz; $CDCl_3$) $\delta$ 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); $^{13}$C NMR (151 MHz; $CDCl_3$) $\delta$ 93.9, 116.5, 123.9, 127.5, 128.6, 129.9, 131.8, 139.4, 140.4, 145.1, 191.2; IR (neat) $\nu_{max}$/cm$^{-1}$ 3260br, 3058w, 3033w, 1623m, 1593m, 1549m, 1508m, 1451m, 1238s, 741s; MS (ES) $m/z$ = 224.4 [M + H]$^+$; HRMS (ES) calcd. for $C_{15}H_{14}NO$ [M + H]$^+$: 224.1075, found 224.1072.[37]

**Methyl (2*Z*)-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): mp = 147−149 °C; $^1$H NMR (400 MHz; $CDCl_3$) $\delta$ 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); $^{13}$C NMR (101 MHz; $CDCl_3$) $\delta$ 50.9, 87.2, 115.6, 115.7, 122.8, 122.8, 129.9, 129.9, 140.9, 143.4, 170.9; IR (neat) $\nu_{max}$/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 $C_{10}H_{12}NO_2$ [M + H]$^+$: 178.0868, found 178.0862.[8b]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01110.

Photos of experimental setup, in situ FTIR reaction progress plots, UV−vis analysis, further FTIR spectra, copies of $^1$H and $^{13}$C NMR spectra, X-ray crystallographic data including pictures (PDF)

Crystal data (CIF)

Crystal data (CIF)

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### Notes

The authors declare no competing financial interest.

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