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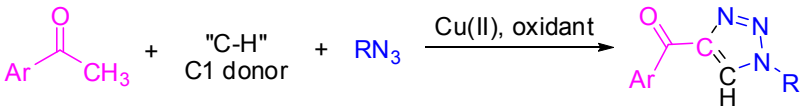
Copper-Catalyzed Oxidative Cross-Dehydrogenative Coupling/Oxidative Cycloaddition: A Synthesis of 4-Acyl-1,2,3-Triazoles

Yi Liu,[†] Gang Nie,[†] Zhongzhen Zhou,[*,‡] Lihui Jia,[†] and Yunfeng Chen[*,†]

[†]School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan 430073, China.

[‡]Department of Neuropharmacology and Novel Drug Discovery, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China.



29 examples
up to 85% yield

ABSTRACT: A copper-catalyzed three-component reaction of methyl ketones, organic azides and various one-carbon (C1) donors has been developed that provides 4-acyl-1,2,3-triazoles in moderate to good yields. While DMF, DMA, TMEDA or DMSO, can serve as the C1 donor, best yields were obtained using DMF. The transformation is proposed to proceed via an oxidative C-H/C-H cross-dehydrogenative coupling followed by an oxidative 1,3-dipolar cycloaddition.

1,2,3-Triazoles are important N-heterocycles, which have shown many applications in various fields.[1] Presently, synthesis of diverse 1,2,3-triazoles is a hot research topic.[2] Among them, 4-acyl-1,2,3-triazoles have drawn particular attention due to their unique biological activities.[3] Some approaches have been disclosed for providing them now, such as CuAAC

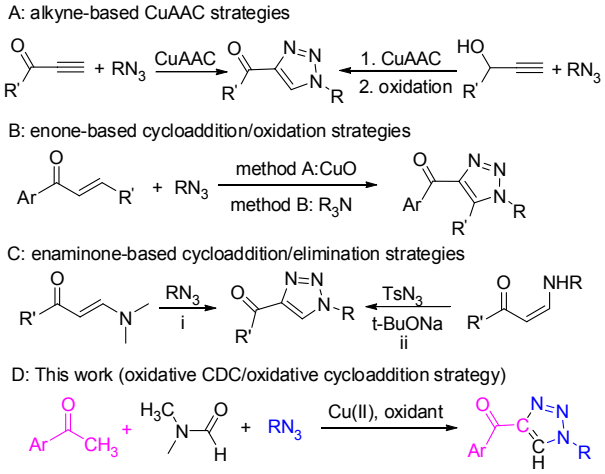
reaction of ynones or acetylenic carbinols with organic azides (Scheme 1A)[4], cyclization/oxidation reaction of enones (Scheme 1B)[5]. Unfortunately, there was the potential polymerization for ynones or enones. Moreover, an enaminone-based cycloaddition/elimination strategy was also developed for the synthesis of 4-acyl-1,2,3-triazoles recently. [6] For example, a metal-free one-pot multi-component reaction between methyl ketones, *N,N*-dimethylformamide dimethyl acetal (DMF dimethyl acetal) and organic azide; this system shows wide substrate scope, but requires a high temperature/microwave step for the formation of the enaminone intermediate (Scheme 1C-i)[6a]. Another approach is a base-promoted cycloaddition of NH-based secondary enaminones and tosyl azide involving a Regitz diazo transfer process (Scheme 1C-ii).[7] Nonetheless, it is desirable for a direct, convenient and efficient method to access 4-acyl-1,2,3-triazoles.

Recently, advances have been made towards direct C-H bond functionalization reactions, especially the C-H/C-H cross-dehydrogenative coupling (CDC) reaction.[8] This approach allows the efficient assembly of N-heterocycles, using, for example, the "Me" in aryl methyl ketones as a carbon source for direct C(sp3)-H bond functionalization.[9,10]

Based on the synthetic analysis of acyl substituted 1,2,3-triazoles， our previous research on 1,2,3-triazoles and related heterocyclic chemistry,[11] we propose that the "Me" group in aryl methyl ketones might serve as a carbon source to construct 1,2,3-triazole ring. Herein, we report a three-component Cu(II)-catalyzed oxidative C-H/C-H CDC/oxidative cycloaddition for the convenient construction of 4-acyl-1,2,3-triazoles, in which aryl methyl ketones,

organic azides and other C1 donor compounds (such as DMF) are used as starting material (Scheme 1D). This three-component one-pot protocol avoids the requirement for purification of reaction intermediates and prevents certain side reactions leading to higher yields.[12]

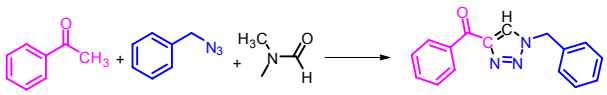
Scheme 1. **Strategies for Synthesis of 4-Acyl-1,2,3-Triazoles**



Initially, the reaction of acetophenone (**1a**) and benzyl azide (**2a**) were examined in DMF at 100 ^{o}C in the presence of $CuSO_4$ and $K_2S_2O_8$. To our delight, after 5 hours, the desired 4-acyl substituted 1,2,3-triazole **4a** was isolated in 64% yield (Table 1, entry 1), and the structure of **4a** was also identified by X-ray single crystal analysis (*see supporting information*). Encouraged by this result, we decided to further optimize the reaction conditions by varying the catalysts and oxidants. Firstly, different Cu(I) and Cu(II) salts were investigated (entries 1-6). It was found that Cu(II) salts showed a better catalytic efficiency than Cu(I), and $Cu(NO_3)_2$ produced the best result with 73% yield. The inexpensive iron salt $FeCl_3$, which can promote the cross-dehydrogenative coupling,[13] was examined, but did not give satisfactory result (entry 7). Therefore, $Cu(NO_3)_2$ was selected as

the catalyst for all further reactions. Subsequently, different common oxidants such as benzoyl peroxide (BPO), *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP) were examined, still $K_2S_2O_8$ was the best choice (entries 4, 10-12). The desired product can not be produced without oxidants, even when stoichiometric metal salt was used (entry 13). In order to enhance the catalytic efficiency, some ligands were evaluated (entries 14-17). L-Proline did not promote the efficiency, and 1,10-phenanthroline (phen) inhibited the reaction. Surprisingly, the yield of **4a** was promoted to 82% when *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was used. We also tested the hindered monoamine *N,N*-diisopropyl-ethylamine (DIPEA), but it provided only a small improvement, suggesting that TMEDA serves not only as a base but may also act as a ligand for the metal. Furthermore, the temperature was also evaluated, and the results revealed that the optimal temperature for this reaction was 100 ^{o}C (entry 18).

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 4a

Entry	Catalyst	Oxidant	Additive	Yield(%)[b]
1	$CuSO_4$	$K_2S_2O_8$		64
2[c]	CuX	$K_2S_2O_8$		28/20/22
3	CuO	$K_2S_2O_8$		42
4	$Cu(NO_3)_2$	$K_2S_2O_8$		73
5	$Cu(OAc)_2$	$K_2S_2O_8$		60
6	$Cu(OTf)_2$	$K_2S_2O_8$		55
7	$FeCl_3$	$K_2S_2O_8$		32
8	-	$K_2S_2O_8$		trace
9[d]	$Cu(NO_3)_2$	$K_2S_2O_8$		63
10	$Cu(NO_3)_2$	BPO		65
11	$Cu(NO_3)_2$	TBHP		46
12	$Cu(NO_3)_2$	DTBP		47
13[e]	$Cu(NO_3)_2$	-		0

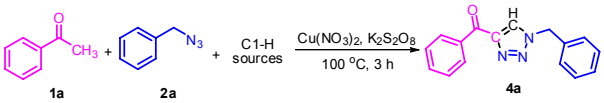
14	$Cu(NO_3)_2$	$K_2S_2O_8$	L-proline	72
15	**$Cu(NO_3)_2$**	**$K_2S_2O_8$**	**TMEDA**	**82**
16	$Cu(NO_3)_2$	$K_2S_2O_8$	phen	45
17	$Cu(NO_3)_2$	$K_2S_2O_8$	DIPEA	70
18[f]	$Cu(NO_3)_2$	$K_2S_2O_8$	TMEDA	trace/74

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), catalyst (0.2 mmol), oxidant (3 mmol), additive (0.2 mmol), DMF (5 mL), reaction time: 3 h, in air. [b]Isolated yields based on **1a**. [c]X = Cl, I, Br. [d]$K_2S_2O_8$ (2 mmol) was used; [e]0.2 mmol or 3 mmol $Cu(NO_3)_2$ were used and both of them without product. [f]80 °C/110 °C were used.

Following the previous investigations, alternative one-carbon sources were employed to test this transformation, especially different N-substituted amides (**Table 2**). The reaction occurred smoothly when DMA was used as solvent, although the yield of **4a** was slightly lower than DMF. When DMSO was employed, the reaction could also occur, albeit in lower yield. When TMEDA served as solvent solely, **4a** could still be generated. However, the conversion was low and prolonging the reaction time did not give the satisfactory result, which suggested that TMEDA served as ligand for the reaction in DMF. In contrast, using *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) as the carbon source resulted in very slow reaction with lower isolated yield (only 24%) after 24 h. **4a** could not be obtained using *N*-methyl amides such as *N*-methylacetamide (MeNHAc), *N*-methyl-*N*-phenylacetamide (PhMeNAc), methylpyrrolidin-2-one (NMP), and *N,N*-dimethylaniline (Me_2NPh) as solvents. In addition, *N,N*-diethylformamide (DEF) also failed to promote this reaction, which suggested that the extended carbon atom originated from the *N,N*-dimethyl moiety rather than the carbonyl carbon in the amides. Therefore,

DMF was chosen as carbon source for this three-component reaction. Indeed, DMF has been reported to serve as a convenient reactant to provide various functional units,[14] especially as one-carbon synthons (CH_3 or CH) in Rh-, Ru- and Cu-catalyzed reactions.[15]

Table 2. Screening of the C1-H Source[a]



1a 2a 4a

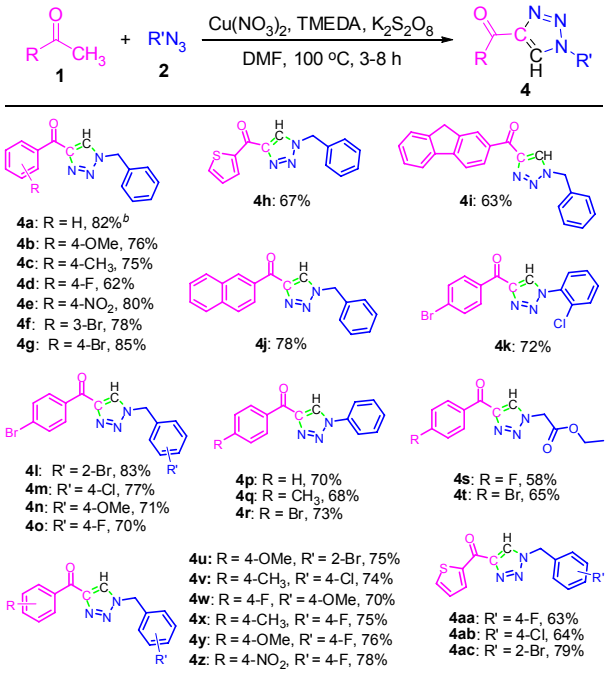
Entry	C1-H source	Yield(%)[b]
1	DMF	73
2	DMA	62
3	DMSO	25
4	TMEDA	30[c]
5	TMEDA	48[d]
6	DMF-DMA	24[e]
7	MeNHAc	trace
8	others[f]	0

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), $Cu(NO_3)_2$ (0.2 mmol), $K_2S_2O_8$ (3 mmol)，C1-H source (5 mL), in air. [b]Isolated yields based on **1a**. [c]65% of **1a** was recovered. [d]Reaction time: 10 h. [e]Reaction time: 24 h. [f]Others: PhMeNAc, NMP, Me_2NPh and DEF.

With the optimal condition established, we then explored the scope of this three-component reaction by employing various methyl ketones and organic azides, and the results are summarized in **Table 3**. Various acetophenones with both electron-withdrawing groups (such as Br, F, NO_2) and electron-donating groups (such as CH_3, OMe) were viable substrates for this reaction. The substrates with electron-withdrawing groups in the acetophenones delivered slightly higher yields. Furthermore, methyl 2-thienyl ketone can also react with different organic azides to generate the 1,2,3-triazoles containing thiophene moiety (**4h**, **4aa-4ac**), however, alkyl methyl ketones, such as acetone, 2-butanone cannot

give the corresponding 1,2,3-triazoles in this reaction system. Pinacolone and benzalacetone with even higher selective reactivity were used, but we still could not obtain the corresponding product. Different organic azides, including aryl aizdes, substituted benzyl azides, and ethyl 2-azidoacetate was all suitable material for this three-component reaction, although ethyl 2-azidoacetate generally produced lower yields than other azides.

Table 3. Synthesis of 4-Acyl-1,2,3-triazoles[a]

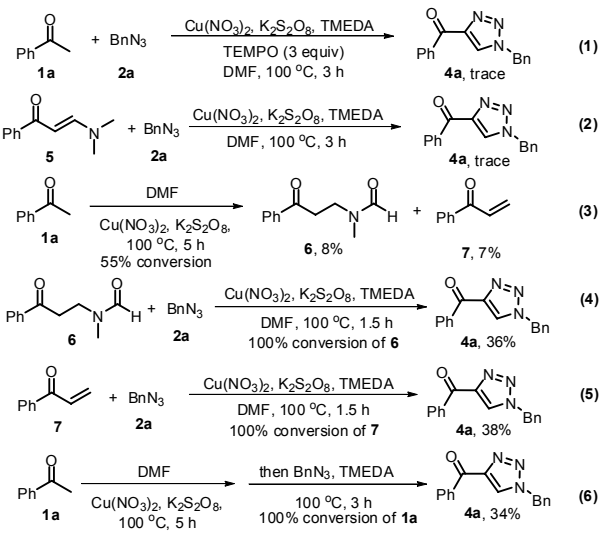


[a]Reaction conditions: **1** (2 mmol), **2** (3 mmol), $Cu(NO_3)_2$ (0.4 mmol), $K_2S_2O_8$ (6 mmol), TMEDA (0.4 mmol), DMF (10 mL), in air. [b]Isolated yields based on **1**.

In order to obtain deeper insight into this reaction, some control experiments were conducted (Scheme 2). Equation 1 shows that this three-component reaction was inhibited by 2,2,6,6- tetramethylpiperidinooxy (TEMPO, 3 equiv), which indicated that the reaction involves a radical process. Equation 2 shows that the enaminone **5** did not react with benzyl

azide to give **4a** under standard reaction conditions, which implies that this reaction may not go via an enaminone intermediate; this key result suggests that this work differs from previous enaminone-azide cyclization processes.[6a] Equation 3 shows that without benzyl azide, acetophenone gave the intermediates **6** and **7** in 8% and 7% yields, respectively, and the conversion of **1a** was only 55%. Reactions between benzyl azide and **6** or **7** were complete in 1.5 h (eqs 4 and 5); however, the yields were only 36% and 38%, respectively, which were lower than the one-pot protocol; it appears that most of reaction materials instead polymerized. These results show that the cycloaddition reactions of intermediates **6** and **7** with benzyl azide are fast, but that the polymerizations of **6** and **7** were fast too. Equation 6 shows that a stepwise reaction in which **1a** was treated with $Cu(NO_3)_2$ and $K_2S_2O_8$ in DMF at 100℃ for 5 h, then benzyl azide **2a** was added to the reaction mixture, followed by an additional 3 h heating afforded triazole **4a** in 34% yield; this low yield is accounted for unreacted acetophenone **1a**.

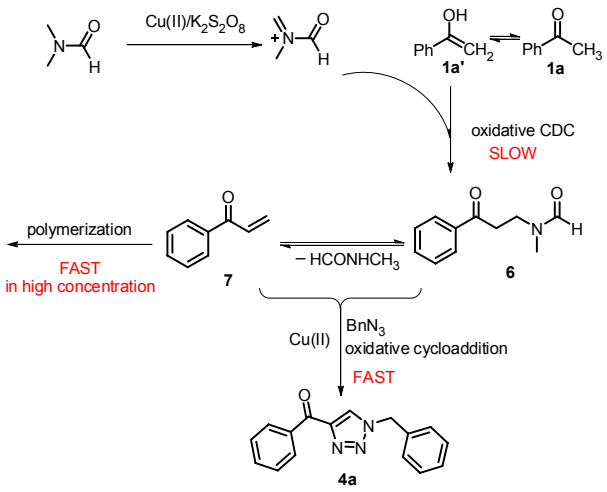
Scheme 2. Control Experiments[a]



[a]General reaction conditions: $Cu(NO_3)_2$ (0.2 mmol), $K_2S_2O_8$ (3 mmol), TMEDA (0.2 mmol), **2a** (1.5 mmol), DMF (5 mL), other reactants (1 mmol), in air.

Based on the results above and previous literature reports,[5] a plausible reaction path is outlined (Scheme 3). Oxidative coupling of acetophenone with DMF in the presence of Cu(II)/$K_2S_2O_8$, forms the intermediate **6**, which can eliminate N-methylformamide to give intermediate **7.** Intermediate **6** and **7** can react with benzyl azide to form 1,2,3-triazole (**4a**) in the presence of copper catalyst and oxidant.[5] The control experiments suggest that the oxidative coupling step is slow, while the second oxidative cycloaddition step is fast. However, polymerization of intermediates can be fast if they accumulate to high concentration. Thus the presence of organic azides in the three-component reaction protocol should consume the intermediate **6** and **7**, preventing their polymerization. This suggests that the rate of polymerization is probably second order or higher, whereas under the conditions of the reaction, the azide cycloaddition is pseudo-first order.

Scheme 3. Plausible Reaction Path



In conclusion, we have developed an efficient copper-catalyzed three-component protocol to synthesize 4-acyl-1,2,3-triazoles in moderate to good yields under operationally convenient conditions. In addition to the readily available materials, mild reaction conditions and shorter reaction time than previous works, this method avoids the isolation of reaction intermediates and inhibits some side reactions as well, which thus improves the overall efficiency. Further investigations on the mechanistic pathway and the synthesis of other heterocycles by using the similar strategy are underway in our laboratory.

EXPERIMENTAL SECTION

General Methods and materials: All of the reactions were carried out in 25mL round-bottom flasks with air condensers. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 600 MHz and 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (TMS) (0.00 ppm) or $CDCl_3$ (7.26 ppm) for ^{1}H, $CDCl_3$ (77.0 ppm) for ^{13}C. Flash column

chromatography was performed on 200-300 mesh silica gel. Analytical thin layer chromatography was performed with precoated glass baked plates (250μ) and visualized by fluorescence. High-resolution mass spectra were recorded on a Solarix XR quadrupole Fourier transform tandem mass spectrometer. Melting points were measured on a melting point tester RY-1G apparatus and uncorrected.

General experimental procedure for synthesis of 4-acyl-1,2,3-triazoles. To a solution of ketone **1** (1mmol) and azide **2** (1.5 mmol, 1.5 equiv) in DMF (5 mL), was added $Cu(NO_3)_2$ (0.2 mmol), $K_2S_2O_8$ (3 mmol, 3.0 equiv) and TMEDA (0.2mmol, 0.2 equiv), the mixture was stirring at 100 ^oC in oil bath under the air atmosphere (1 atm) for 3-8 h. The reaction was checked by TLC (thin layer chromatography). After the completion of the reaction, the mixture was poured into water, and extracted by ethyl acetate, washed with Na_2CO_3(aq), dried with anhydrous Na_2SO_4, then the solvent was removed under reduced pressure to obtain crude product, further purification by column chromatography on silica gel gave the 4-acyl-1,2,3-triazoles.

(1-Benzyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone (4a) Yield: 82% (220 mg). White solid. mp: 116-117 ^oC. Eluent: EtOAc/Pet ether (V/V = 1:30, R_f = 0.1). ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, J = 8.2 Hz, 2H), 8.17 (s, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.40 (d, J = 6.6 Hz, 3H), 7.33 (d, J = 7.8 Hz, 2H), 5.60 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.6, 148.3, 136.4, 133.6, 133.2, 130.5, 129.2, 129.1, 128.3, 128.2, 54.4. Spectral data match those previously reported in the literature.[6a]

(1-Benzyl-1H-1,2,3-triazol-4-yl)(4-methoxyphenyl)methanone (4b) Yield: 76% (223 mg).

White solid. mp:129-131 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.47 (m, 2H), 8.14 (s, 1H), 7.43 – 7.29 (m, 5H), 6.99 (d, J = 9.0 Hz, 2H), 5.60 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 163.8, 148.8, 133.7, 133.1, 129.4, 129.3, 129.1, 128.3, 128.1, 113.6, 55.5, 54.4. Spectral data match those previously reported in the literature.[6b]

(1-Benzyl-1H-1,2,3-triazol-4-yl)(p-tolyl)methanone (4c) Yield: 75% (208 mg). White solid. mp: 130-132 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, J = 8.2 Hz, 2H), 8.16 (s, 1H), 7.41 – 7.28 (m, 7H), 5.59 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.1, 148.4, 144.0, 133.9, 133.7, 130.6, 129.2, 129.0, 128.2, 128.1, 54.3, 21.6. Spectral date match those previously reported in the literature.[17]

(1-Benzyl-1H-1,2,3-triazol-4-yl)(4-fluorophenyl)methanone (4d) Yield: 62% (174 mg). White solid. mp: 145-146 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 – 8.50 (m, 2H), 8.18 (s, 1H), 7.45 – 7.31 (m, 5H), 7.21 – 7.14 (m, 2H), 5.61 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.7, 166.7, 165.0, 148.3, 133.6, 133.4 (d, J = 9.0 Hz), 132.7 (d, J = 3.0 Hz), 129.3, 129.1, 128.3, 115.4 (d, J = 21.6 Hz), 54.4. Spectral data match those previously reported in the literature.[6b]

(1-Benzyl-1H-1,2,3-triazol-4-yl)(4-nitrophenyl)methanone (4e) Yield: 80% (246 mg). Light yellow solid. mp:137-139 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 – 8.58 (m, 2H), 8.42 – 8.31 (m, 2H), 8.24 (s, 1H), 7.45 – 7.29 (m, 5H), 5.64 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.7, 150.3, 147.7, 141.0, 133.3, 131.6, 129.4, 129.3, 128.6, 128.4, 123.4, 54.6. Spectral data match those previously

reported in the literature.[6b]

(1-Benzyl-1H-1,2,3-triazol-4-yl)(3-bromophenyl)methanone (4f) Yield: 78% (266 mg). White solid. mp: 95-98 °C. Eluent: EtOAc/Pet ether (V/V = 1:30, R_f = 0.2) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.41 (d, J = 7.8 Hz, 1H), 8.19 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.44 – 7.29 (m, 6H), 5.61 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.9, 147.8, 138.0, 136.0, 133.5, 133.2, 129.8, 129.3, 129.2, 129.1, 128.4, 128.3, 122.5, 122.4, 54.4. HRMS (EI-FTMS) *m/z* [M] calcd. for $C_{16}H_{12}BrN_3O$: 341.0158, found: 341.0152.

(1-Benzyl-1H-1,2,3-triazol-4-yl)(4-bromophenyl)methanone (4g) Yield: 85% (291 mg). White solid. mp: 149-151 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 2H), 8.17 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.43 – 7.31 (m, 5H), 5.61 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.3, 148.1, 135.0, 133.5, 132.1, 131.6, 129.3, 129.2, 128.6, 128.3, 54.5. Spectral data match those previously reported in the literature.[6b]

(1-Benzyl-1H-1,2,3-triazol-4-yl)(thiophen-2-yl)methanone (4h) Yield: 67% (180 mg). White solid. mp: 141-143 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, J = 3.6 Hz, 1H), 8.15 (s, 1H), 7.75 (d, J = 4.8 Hz, 1H), 7.43 – 7.38 (m, 3H), 7.35 – 7.30 (m, 2H), 7.23 (t, J = 4.8 Hz, 1H), 5.61 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 147.9, 142.2, 136.3, 135.0, 133.6, 129.3, 129.2, 128.4, 128.3, 127.6, 54.5. Spectral data match those previously reported in the literature.[4c]

(1-Benzyl-1H-1,2,3-triazol-4-yl)(9H-fluoren-2-yl)methanone (4i) Yield: 63% (221 mg). White solid. mp: 209-210 °C. Eluent: EtOAc/Pet ether (V/V = 1:10, R_f = 0.2). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.51 (d, J = 8.2 Hz, 1H), 8.19 (s, 1H), 7.93 – 7.84 (m, 2H), 7.60 (d, J = 7.2 Hz, 1H), 7.47 – 7.32 (m, 7H), 5.63 (s, 2H), 4.00 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 148.8, 146.7, 144.7, 143.0, 140.6, 134.8, 133.7, 130.0, 129.3, 129.2, 128.4, 128.2, 128.0, 127.4, 127.0, 125.2, 121.0, 119.6, 54.5, 37.0. HRMS (ESI-FTMS) *m/z* $[M + 2H]^+$ calcd. for $C_{23}H_{19}N_3O$: 353.2665, found: 353.2660.

(1-Benzyl-1H-1,2,3-triazol-4-yl)(naphthalen-2-yl)methanone (4j) Yield: 78% (244 mg). White solid. mp: 155-157 °C. Eluent: EtOAc/Pet ether (V/V = 1:40, R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.98 – 7.82 (m, 2H), 7.71 – 7.29 (m, 7H), 5.62 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 148.7, 135.7, 133.7, 133.5, 132.5, 132.0, 130.1, 129.4, 129.2, 128.7, 128.4, 128.2, 127.7, 126.6, 125.5, 54.5. Spectral data match those previously reported in the literature.[4c]

(4-Bromophenyl)(1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methanone (4k) Yield: 72% (261 mg). White solid. mp: 112-123 °C. Eluent: EtOAc/Pet ether (V/V = 1:40, R_f = 0.3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.44 (d, J = 8.4 Hz, 2H), 7.74 – 7.68 (m, 3H), 7.64 (t, J = 8.4 Hz, 1H), 7.57 – 7.49 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.2, 147.6, 135.1, 134.1, 132.2, 131.8, 131.4, 130.9, 130.5, 128.8, 128.7, 128.1, 127.6. HRMS (ESI-FTMS) *m/z* $[M + Na]^+$ calcd. for $C_{15}H_9BrClN_3ONa$: 383.9509, found: 383.9504.

(1-(2-Bromobenzyl)-1H-1,2,3-triazol-4-yl)(4-bromophenyl)methanone (4l) Yield: 83% (349 mg). White solid. mp: 106-108 °C. Eluent: EtOAc/Pet ether (V/V = 1:40, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 – 8.32 (m, 2H), 8.27 (s, 1H), 7.66 (d, J = 8.4 Hz, 3H), 7.37 (t, J = 7.2 Hz, 1H), 7.34 – 7.27 (m, 2H), 5.75 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.3,

148.0, 135.0, 133.5, 133.1, 132.2, 131.7, 131.0, 130.9, 128.7, 128.7, 128.4, 124.0, 54.2. HRMS (ESI-FTMS) *m/z* $[M + H]^+$ calcd. for $C_{16}H_{12}Br_2N_3O$: 419.9341, found: 419.9326.

(4-Bromophenyl)(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methanone (4m) Yield: 77% (290 mg). White solid. mp: 175-176 °C. Eluent: EtOAc/Pet ether (V/V = 1:30, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 – 8.33 (m, 2H), 8.19 (s, 1H), 7.68 – 7.65 (m, 2H), 7.41 – 7.38 (m, 2H), 7.30 – 7.26 (m, 2H), 5.59 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.2, 148.3, 135.4, 135.0, 132.2, 132.0, 131.7, 129.7, 129.6, 128.8, 128.3, 53.7. HRMS (ESI-FTMS) *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{11}BrClN_3ONa$: 397.9666, found: 397.9658.

(4-Bromophenyl)(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methanone (4n) Yield: 71% (264 mg). White solid. mp: 145-147 °C. Eluent: EtOAc/Pet ether (V/V = 1:30, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 – 8.24 (m, 2H), 8.13 (s, 1H), 7.70 – 7.61 (m, 2H), 7.32 – 7.27 (m, 2H), 6.97 – 6.85 (m, 2H), 5.54 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.3, 160.2, 148.0, 135.1, 132.1, 131.6, 130.0, 128.6, 128.1, 125.4, 114.7, 55.3, 54.0. HRMS (EI-FTMS) *m/z* [M] calcd. for $C_{17}H_{14}BrN_3O_2$: 371.0263, found: 371.0263.

(4-Bromophenyl)(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methanone (4o) Yield: 70% (252 mg). White solid. mp: 134-135 °C. Eluent: EtOAc/Pet ether (V/V = 1:30, R_f = 0.1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 – 8.31 (m, 2H), 8.18 (s, 1H), 7.69 – 7.61 (m, 2H), 7.37 – 7.32 (m, 2H), 7.10 (t, *J* = 8.4 Hz, 2H), 5.58 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.2, 163.1(d, *J* = 249.2 Hz), 148.3, 135.0, 132.1, 131.7, 130.3(d, *J* = 8.4 Hz), 129.4(d, *J* = 3.0 Hz), 128.7, 128.2, 116.4(d, *J* = 22.0 Hz), 53.7. HRMS (EI-FTMS) *m/z* [M] calcd. for $C_{16}H_{11}BrFN_3O$: 359.0064, found: 359.0061.

Phenyl(1-phenyl-1H-1,2,3-triazol-4-yl)methanone (4p) Yield: 70% (174 mg). White solid. mp: 126-127 °C. Eluent: EtOAc/Pet ether (V/V = 1:40, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.47 (m, 3H), 7.38 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 130.2, 129.7, 128.9, 128.7, 128.6, 128.4, 125.8, 120.5, 117.5. Spectral data match those previously reported in the literature.[6a]

(1-Phenyl-1H-1,2,3-triazol-4-yl)(p-tolyl)methanone (4q) Yield: 68% (179 mg). White solid. mp: 152-153 °C. Eluent: EtOAc/Pet ether (V/V = 1:40, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 2H), 7.83 – 7.78 (m, 2H), 7.62 – 7.54 (m, 2H), 7.53 – 7.46 (m, 1H), 7.39 – 7.30 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.0, 148.7, 144.3, 136.4, 133.9, 130.7, 129.9, 129.4, 129.1, 126.2, 120.7, 21.7. Spectral data match those previously reported in the literature.[17]

(4-Bromophenyl)(1-phenyl-1H-1,2,3-triazol-4-yl)methanone (4r) Yield: 73% (239 mg). White solid. mp: 177-178 °C. Eluent: EtOAc/Pet ether (V/V = 1:40, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.71 – 7.67 (m, 2H), 7.60 – 7.56 (m, 2H), 7.54 – 7.49 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.2, 148.4, 136.3, 135.0, 132.2, 131.7, 130.0, 129.6, 128.8, 126.4, 120.8. Spectral data match those previously reported in the literature.[3d]

Ethyl 2-(4-(4-fluorobenzoyl)-1H-1,2,3-triazol-1-yl)acetate (4s) Yield: 58% (161 mg). White solid. mp: 160-161 °C. Eluent: EtOAc/Pet ether (V/V = 1:50, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 – 8.48 (m, 2H), 8.42 (s, 1H), 7.20 (t, *J* = 8.4 Hz, 2H), 5.25 (s, 2H),

4.31 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.6, 166.8, 165.5, 165.1, 148.3, 133.4 (d, J = 9.6 Hz), 129.9, 115.5 (d, J = 21.9 Hz), 62.8, 50.9, 14.0. HRMS (EI-FTMS): *m/z* [M] calcd. for $C_{13}H_{12}FN_3O_3$: 277.0857, found: 277.0856.

Ethyl 2-(4-(4-bromobenzoyl)-1H-1,2,3-triazol-1-yl)acetate (4t) Yield: 65% (219 mg). White solid. mp: 162-164 °C. Eluent: EtOAc/Pet ether (V/V = 1:10, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.39 – 8.31 (m, 2H), 7.72 – 7.63 (m, 2H), 7.26 (s, 1H), 5.26 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.2, 165.5, 148.2, 135.0, 132.1, 131.7, 129.9, 128.7, 62.8, 51.0, 14.0. HRMS (ESI-FTMS) *m/z* $[M + H]^+$ calcd. for $C_{13}H_{13}BrN_3O_3$: 338.0134, found: 338.0129.

(1-(2-Bromobenzyl)-1H-1,2,3-triazol-4-yl)(4-methoxyphenyl)methanone (4u) Yield: 75% (279 mg). White solid. mp: 125-127 °C. Eluent: EtOAc/Pet ether (V/V = 1:10, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 – 8.42 (m, 2H), 8.24 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.42 – 7.10 (m, 3H), 7.09 – 6.84 (m, 2H), 5.74 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.7, 163.8, 148.6, 133.4, 133.3, 133.1, 130.8, 130.7, 129.3, 128.4, 128.3, 128.3, 123.8, 113.6, 55.4, 54.0. HRMS (EI-FTMS) *m/z* [M] calcd. for $C_{17}H_{14}BrN_3O_2$: 371.0263, found: 371.0260.

(1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)(p-tolyl)methanone (4v) Yield: 74% (231 mg). White solid. mp: 178-180 °C. Eluent: EtOAc/Pet ether (V/V = 1:15, R_f = 0.3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 2H), 8.16 (s, 1H), 7.40 – 7.35 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.29 – 7.25 (m, 2H), 5.58 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.0, 148.7, 144.3, 135.3, 133.9, 132.3, 130.7, 129.6, 129.5, 129.1, 128.1, 53.7, 21.7.

HRMS (EI-FTMS) *m/z* [M] calcd. for $C_{17}H_{14}ClN_3O$: 311.0819, found: 311.0819.

(4-Fluorophenyl)(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methanone (4w) Yield: 70% (218 mg). White solid. mp: 144-145 °C. Eluent: EtOAc/Pet ether (V/V = 1:40, R_f = 0.1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 – 8.50 (m, 2H), 8.13 (s, 1H), 7.31 – 7.27 (m, 2H), 7.21 – 7.14 (m, 2H), 6.95 – 6.89 (m, 2H), 5.54 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.8, 165.9 (d, J = 255.0 Hz), 160.2, 148.2, 133.4 (d, J = 9.3 Hz), 132.7 (d, J = 3.0 Hz), 130.0, 128.1, 125.4, 115.5 (d, J = 21.9 Hz), 114.7, 55.3, 54.0. HRMS (ESI-FTMS) *m/z* $[M + H]^+$ calcd. for $C_{17}H_{15}FN_3O_2$: 312.1142, found: 312.1132.

(1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)(p-tolyl)methanone (4x) Yield: 75% (221 mg). White solid. mp: 145-147 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 – 8.24 (m, 2H), 8.22 – 8.04 (m, 1H), 7.37 – 7.05 (m, 6H), 5.57 (d, J = 5.4 Hz, 2H), 2.43 (d, J = 5.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.1, 163.0 (d, J = 249.0 Hz), 148.6, 144.2, 133.8, 130.7, 130.2 (d, J = 8.4 Hz), 129.6 (d, J = 3.3 Hz), 129.0, 128.0, 116.3 (d, J = 21.9 Hz), 53.6, 21.7. HRMS (EI-FTMS) *m/z* [M] calcd. for $C_{17}H_{14}FN_3O$: 295.1115, found: 295.1112.

(1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-methoxyphenyl)methanone (4y) Yield: 76% (237 mg). White solid. mp: 131-132 °C. Eluent: EtOAc/Pet ether (V/V = 1:15, R_f = 0.3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 – 8.38 (m, 2H), 8.15 (s, 1H), 7.38 – 7.30 (m, 2H), 7.10 (t, J = 8.4 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 5.58 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.7, 163.8 (d, J = 2.4 Hz), 162.2, 148.8, 133.0, 130.2 (d, J = 8.4 Hz), 129.6, 129.2, 127.9, 116.3 (d, J = 21.9 Hz), 113.6, 55.4, 53.6. HRMS (ESI-FTMS) *m/z* [M +

H]$^+$ calcd. for $C_{17}H_{15}FN_3O_2$: 312.1142, found: 312.1134.

(1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)(4-nitrophenyl)methanone (4z) Yield: 78% (184 mg). White solid. mp: 127-128 °C. Eluent: EtOAc/Pet ether (V/V = 1:20, R_f = 0.2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 – 8.55 (m, 2H), 8.38 – 8.29 (m, 2H), 8.25 (s, 1H), 7.39 – 7.32 (m, 2H), 7.12 (t, J = 8.4 Hz, 2H), 5.62 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.6, 163.9, 162.2, 149.0 (d, J = 377.2 Hz), 140.9, 131.6, 130.3 (d, J = 8.4 Hz), 129.2 (d, J = 3.3 Hz), 128.5, 123.4, 116.4 (d, J = 21.9 Hz), 53.8. HRMS (EI-FTMS) *m/z* [M] calcd. for $C_{16}H_{11}FN_4O_3$: 326.0809, found: 326.0808.

(1-(4-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)(thiophen-2-yl)methanone (4aa) Yield: 63% (181 mg). White solid. mp: 152-154 °C. Eluent: EtOAc/Pet ether (V/V = 1:10, R_f = 0.3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 – 8.69 (m, 1H), 8.16 (s, 1H), 7.81 – 7.65 (m, 1H), 7.37 – 7.30 (m, 2H), 7.24 – 7.21 (m, 1H), 7.10 (t, J = 8.4 Hz, 2H), 5.58 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 147.9, 142.1, 136.3, 135.1, 130.2 (d, J = 8.7 Hz), 128.44, 127.49, 116.39 (d, J = 21.9 Hz), 53.74. HRMS (ESI-FTMS) *m/z* [M + H]$^+$ calcd. for $C_{14}H_{11}FN_3OS$: 288.0601, found: 288.0600.

(1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)(thiophen-2-yl)methanone (4ab) Yield: 64% (194 mg). White solid. mp:193-195 °C. Eluent: EtOAc/Pet ether (V/V = 1:10, R_f = 0.3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, J = 3.6 Hz, 1H), 8.17 (s, 1H), 7.76 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 10.2 Hz, 2H), 7.23 (t, J = 4.8 Hz, 1H), 5.58 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 147.7, 142.2, 136.3, 135.1, 133.5, 133.1, 130.9, 130.8, 128.4, 128.4, 127.9, 123.9, 54.2. HRMS (ESI-FTMS) *m/z* [M + H]$^+$ calcd. for

$C_{14}H_{11}ClN_3OS$: 304.0305, found: 304.0300.

(1-(2-Bromobenzyl)-1H-1,2,3-triazol-4-yl)(thiophen-2-yl)methanone (4ac) Yield: 79% (275 mg). White solid. mp: 121-123 °C. Eluent: EtOAc/Pet ether (V/V = 1:10, R_f = 0.3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (d, *J* = 3.6 Hz, 1H), 8.25 (s, 1H), 7.75 (d, *J* = 4.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.23 (t, *J* = 4.2 Hz, 1H), 5.75 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 147.7, 142.2, 136.3, 135.1, 133.5, 133.1, 130.9, 130.8, 128.5, 128.4, 127.9, 123.9, 54.2. HRMS (ESI-FTMS) *m/z* $[M + H]^+$ calcd. for $C_{14}H_{11}BrN_3OS$: 347.9800, found: 347.9797.

(E)-3-(Dimethylamino)-1-phenylprop-2-en-1-one (5) According to the reported procedure[16], yield: 81% (70 mg). Eluent: EtOAc/Pet ether (V/V = 3:2, R_f = 0.3). Light yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H), 7.79 (d, *J* = 12.4 Hz, 1H), 7.49 – 7.30 (m, 3H), 5.71 (d, *J* = 12.4 Hz, 1H), 3.01 (d, *J* = 71.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 154.2, 140.6, 130.8, 128.1, 127.5, 92.2, 44.9, 37.2..

N-Methyl-N-(3-oxo-3-phenylpropyl)formamide (6) Yield: 8% (15 mg). Yellow liquid. Eluent: EtOAc/Pet ether (V/V = 1:3, R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 0.5H), 8.02 (s, 0.5H), 7.98 – 7.89 (m, 2H), 7.65 – 7.54 (m, 1H), 7.48 (q, *J* = 7.2 Hz, 2H), 3.74 (t, *J* = 6.8 Hz, 2H), 3.34 – 3.21 (m, 2H), 3.03 (s, 1.5H), 2.89 (s, 1.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 197.2, 163.1, 162.8, 136.5, 136.3, 133.6, 133.4, 128.8, 128.7, 128.1, 127.9, 44.5, 40.5, 36.7, 36.2, 35.7, 29.6. Spectral data match those previously reported in the literature.[17]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/ x0xx00000x. Scanned copies of ^{1}H, ^{13}C NMR and HRMS spectra of the synthesized compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: yfchen@wit.edu.cn

*E-mail: zhouzz@smu.edu.cn

ORCID

Yunfeng Chen: 0000-0002-6220-5015

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