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A Metal- and Azide-Free Multicomponent Assembly toward Regioselective Construction of 1,5-Disubstituted 1,2,3-Triazoles

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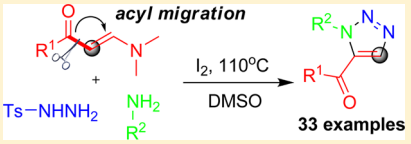
Supporting Information

ABSTRACT: The construction of 1,5-disubstituted 1,2,3-triazoles has been effected through the cascade dual C−N bond formation, N−N bond formation and an acyl migration-based C−C bond formation via the three-component reactions of enaminones, tosylhydrazine and primary amines. This metal- and azide-free, regioselective synthetic method proceeds in the presence of only molecular iodine.



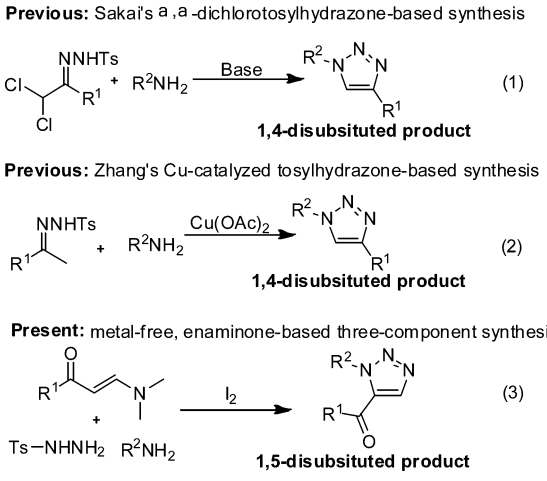
INTRODUCTION

1,2,3-Triazole is a fundamental and fantastic heterocyclic moiety. The extraordinary significance of 1,2,3-triazoles comes from not only their widespread application in cutting edge research of biological and material science,[1] but also their irreplaceable application in important organic synthesis via distinct transformation models such as the transannulation, triazole ring opening, triazole directing group assisted C−H activation and the C−H activation-based triazolation.[2] Because of the exceptional merits of this heterocyclic scaffold, the synthetic research toward 1,2,3-triazoles has been recognized as a strategic issue and attracted tremendous attention. The pioneer work on 1,2,3-triazole synthesis can be dated back to 1960s when Huisgen and co-workers disclose the route to assemble this entity via thermo-induced dipolar cycloaddition between alkynes and azides.[3] Afterward, the independent work from Sharpless[4a] and Meldal[4b] on Cu-catalyzed azide−alkyne cycloaddition (CuAAC) has led to the revolutionary progress in 1,2,3-triazole chemistry owing to the unprecedentedly high efficiency, excellent regioselectivity and general application scope of this "click" transformation.[4] Complementarily, other noble metal-catalyzed protocols such as RuAAC,[5] Ir- and Ag-AAC[6] allowed the click synthesis of 1,2,3-triazol with even broader application scope. The main problem of these metal-catalyzed syntheses, however, lies in the frequent presence of trace metal contaminant following the production of triazoles. This limit critically prevents these click reactions from practical application, especially in the field of biologically relevant investigation.[7,10,11a,12]

To overcome this problem, the organocatalytic 1,2,3-triazole synthesis without using metal catalyst has emerged as another landmark tool.[7] By means of metal-free operation, structurally diverse 1,2,3-triazoles have been readily accessed through the incorporation of azides with a broad array of different reaction partners. Typical protocols are the reaction of azides with enols and enamines,[8] the strain-promoted click cycloaddition of cyclooctyne and aryl azides,[9] the 1,3-dipolar cycloaddition between peptide-functionalized phosphoranes and azides,[10] the *t*-BuOLi promoted, enolate-mediated cascade synthesis,[11a] the nitromethylene-based three-component synthesis[12] and the Lewis based-catalyzed azide-zwitterion reaction using electron deficient olefins,[13] among others.[14]

With the striking advances of 1,2,3-triazole synthesis, there are still two major challenges remain. The first one is the reliance on the explosive azide as the N1−N3 synthon for the triazole ring construction; the second issue is that most known methods provide the 1,4-disubstituted 1,2,3-triazoles with few examples allowing the selective synthesis of 1,5-disubstituted products.[5,11] In this regard, efforts in devising new synthetic methods providing 1,5-disubstituted 1,2,3-triazoles under metal- and azide-free conditions are currently the most urgent task.[15] In the past few years, a few elegant approaches on azide-free 1,2,3-triazole synthesis have been reported. The presently available examples are the Sakai reaction involving the cyclization reactions of α,α-dichlorohydrazones and primary amines (eq 1, Scheme 1),[16] the copper-catalyzed cyclization

Scheme 1. Typical Azide-Free Synthesis of 1,2,3-Triazoles



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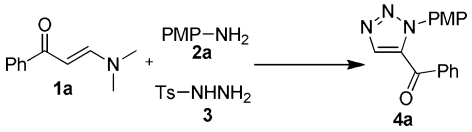
of hydrazones and azides (eq 2, Scheme 1)[17] as well as some related versions with practical modification.[18]

Obviously, each of these prototypes, including the metal-catalyzed AAC, organocatalytic AAC and the azide-free synthesis has individually exhibited unique advantages, however, to our best knowledge, no synthetic method that simultaneously bears the features of metal-free, azide-free operation and selective production of 1,5-disubstituted products is presently available. Herein, upon our continuous research efforts in enaminone-based synthesis, we report a metal- and azide-free, three-component strategy for the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles (eq 3, Scheme 1).

RESULTS AND DISCUSSION

Initially, the reaction of enaminone **1a**, *p*-methoxylaniline **2a** and tosylhydrazine **3** was tentatively run in the presence of a series of different catalysts. It was found that only I_2 could mediate the formation of 1,5-disubstituted 1,2,3-triazole **4a**[19] (entries 1−5, Table 1). Extensive optimization experiments on

Table 1. Optimization on Reaction Conditions[a]



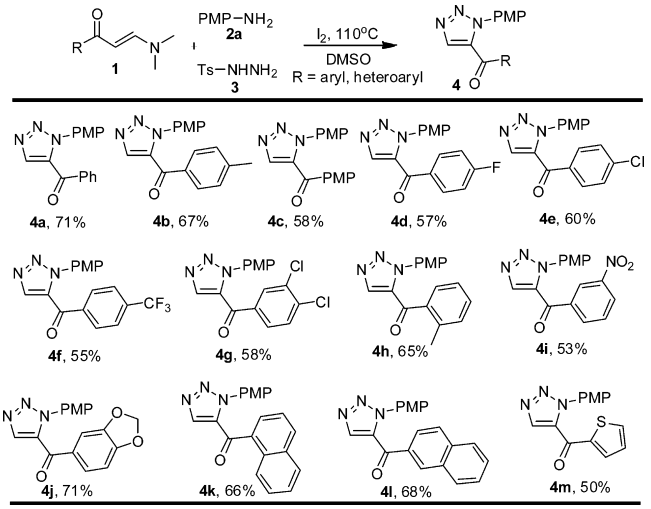
entry	catalyst	additive	T (°C)	solvent	Yield (%)[b]
1	I_2	–	120	DMSO	46
2	TMSCl	–	120	DMSO	NR
3	*p*-TSA	–	120	DMSO	NR
4	$FeCl_3$	–	120	DMSO	trace
5	CAN	–	120	DMSO	NR
6	I_2	$K_2S_2O_8$	120	DMSO	29
7	I_2	TBHP	120	DMSO	trace
8	I_2	DDQ	120	DMSO	44
9	I_2	$PhI(AcO)_2$	120	DMSO	trace
10	I_2	–	110	DMSO	54
11	I_2	–	100	DMSO	37
12	I_2	–	110	toluene	trace
13	I_2	–	reflux	EtOH	trace
14	I_2	–	110	DMF	trace
15[c]	I_2	–	110	DMSO	38
16[d]	I_2	–	110	DMSO	71
17[e]	I_2	–	110	DMSO	42
18[f]	I_2	–	110	DMSO	nr

[a]General conditions: enaminone **1a** (0.2 mmol), amine **2a** (0.2 mmol), tosylhydrazine **3** (0.3 mmol), catalyst/promoter (0.2 mmol) and additive (0.2 mmol) in 2 mL of solvent and stirred for 12 h. PMP = *p*-methoxyphenyl. [b]Yields of isolated products based on **1a**. [c]0.06 mmol I_2. [d]0.1 mmol I_2. [e]0.16 mmol I_2. [f]Phenylhydrazine was employed as alternative reactant of tosylhydrazine **3**.

this model reaction were then conducted. Specifically, employment of different oxidants provided no positive effect (entries 6−9, Table 1). Further optimization in varying reaction temperature, reaction medium and the loading of iodine demonstrated that 110 °C gave the best result in the span of 100−120 °C (entries 1, 10−11, Table 1), and DMSO was the only practical solvent (entries 12−14, Table 1). In addition, the entries with different I_2 loadings suggested that 50 mol % was the proper amount (entries 15−17, Table 1). An additional entry using phenylhydrazine as the alternative substrate of tosylhydrazine did not provide **4a** (entry 18, Table 1).

In the subsequent study, extensive efforts were made to synthesize 1,2,3-triazoles containing different substructures under the standard conditions. First, a variety of enaminones **1** with different substituent were independently employed as reaction partners of **2a** and **3**. According to the representative results from this section (Table 2), functional groups of different

Table 2. Scope of Enaminone for the Synthesis of 5-Aroyl 1,2,3-Triazoles[a]



[a]Yields are calculated with isolated product based on **1**.

properties such as alkyl, alkoxyl, halogen, nitro, trifluoromethyl and heteroaryl all exhibited reliable tolerance to the synthetic protocol and afforded corresponding 1,2,3-triazoles with moderate to good yield. Generally, a strong electron withdrawing group (EWG) (**4f**, **4i**, Table 2) in the aryl ring of the enaminone was found to provide corresponding triazoles with relatively lower yields than their counterparts containing electron donating group (EDG) (**4b**, **4c**, **4h**, **4j**, **4k**, **4l**, Table 2). Notably, hereroaryl (thiophene)-based enaminone also tolerated the synthesis well (**4m**, Table 2).

Subsequently, more comprehensive investigation on the scope of the amine component was examined (entries 1−10, Table 3). When enaminone **1b** was subjected with different aryl amines and **3**, corresponding 1,2,3-triazoles were readily afforded with good generality. The substituent in the aryl ring displayed no evident impact on the efficiency. A notable point was that a heteroaryl primary amine, the 8-aminoquinoline, underwent the transformation to give heteroaryl containing 1,2,3-triazole **4bj** (entry 10, Table 3). Additionally, as expected, the entries composed of both substituted enaminones and aryl amines also displayed satisfactory results in the synthesis of diverse 1,2,3-triazoles (entries 11−18, Table 3). The structure of the products were clearly assigned via full spectroscopic analysis and the X-ray single crystal diffraction on **4l**.[19] Primary alkyl amine, however, failed to react under the present reaction conditions because of their inactivity in generating key intermediate of type **10** via transamination.[20] When alkyl side chain-based enaminone **1i** was employed to the standard reaction condition, the expect transformation did not occur, either (entry 19, Table 3). Extensive efforts in exploring the reactivity of alkyl amine and alkyl-based enmainone for the 1,2,3-triazole synthesis is presently being made.

To further expand the application scope, some examples using particular substrates such as Benzocaine (**5**), a clinical

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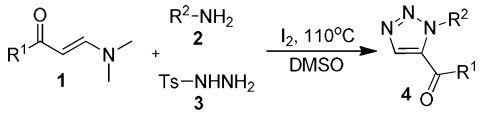
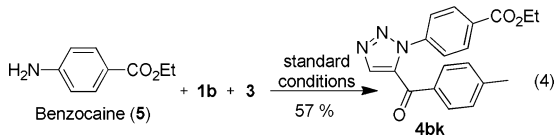
Table 3. Scope of Both Enaminones and Amines

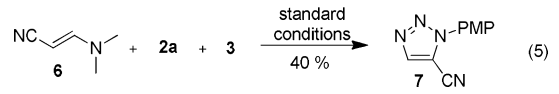


entry	R^1/**1**	R^2	product	yield (%)[a]
1	4-MeC_6H_4 (**1b**)	Ph	**4ba**	54
2	**1b**	4-MeC_6H_4	**4bb**	71
3	**1b**	4-ClC_6H_4	**4bc**	59
4	**1b**	4-BrC_6H_4	**4bd**	61
5	**1b**	2-MeC_6H_4	**4be**	65
6	**1b**	2-ClC_6H_4	**4bf**	61
7	**1b**	3-ClC_6H_4	**4bg**	63
8	**1b**	3-$NO_2C_6H_4$	**4bh**	53
9	**1b**	2,4-$Me_2C_6H_3$	**4bi**	64
10	**1b**	Qu-8-yl[b]	**4bj**	60
11	Ph(**1a**)	4-MeC_6H_4	**4aa**	66
12	4-$MeOC_6H_4$ (**1c**)	4-BrC_6H_4	**4ca**	60
13	4-ClC_6H_4 (**1d**)	4-ClC_6H_4	**4da**	57
14	**1d**	4-BrC_6H_4	**4db**	58
15	4-$CF_3C_6H_4$ (**1e**)	4-BrC_6H_4	**4ea**	56
16	3,4-$(MeO)_2C_6H_3$ (**1f**)	4-ClC_6H_4	**4fa**	61
17	naphtha-2-yl (**1g**)	4-ClC_6H_4	**4ga**	62
18	3,4-$(OCH_2O)C_6H_3$ (**1h**)	4-BrC_6H_4	**4ha**	59
19	Me (**1i**)	PMP	–	nr
20	Ph	4-OHC_6H_4	–	nr

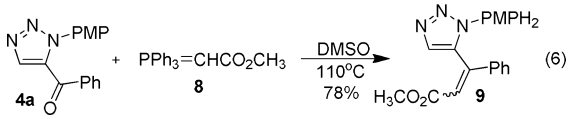
[a]Yields are calculated with isolated product based on **1**. [b]Qu = quinoline.

drug and cyanoenamine **6** were then investigated, respectively. To our delight, both triazole modified benzocain **4bk** (eq 4)

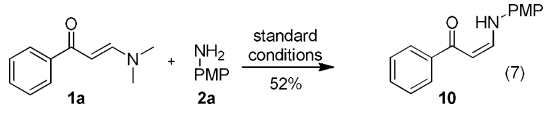


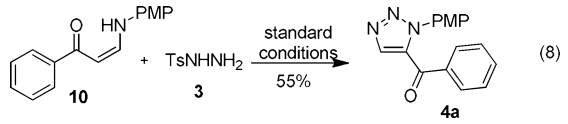


and 5-cyano 1,2,3-triazole **7** (eq 5) were readily synthesized using this azide-freeapproach. In addition, primary attempt also proved that other 1,2,3-triazole derivatives such as 5-vinyl 1,2,3-triaozle **9** could be easily obtained via simple elaboration on triazole products **4** (eq 6).



In order to probe the possible pathway in the formation of 1,5-disubstituted product, the stepwise control experiments were performed. Under the standard conditions, enaminone **1a** and amine **2a** incorporated smoothly to afforded *NH*-containing enaminone **10** (eq 7). Subsequent employment of **10** with tolsylhydrazine was found to yield triazole **4a** with





reasonable yield (eq 8). Although clear mechanism of the three-component reaction was not yet known, the production of **4a** from **10** confirmed that an acyl migration occurred during the reaction to enable the formation of the 1,5-disubstituted products.[21] Investigation on the detailed reaction mechanism is present in progress along with the research on the extended synthesis involving cleavage of enaminone C═C bond.

CONCLUSION

In conclusion, through the three-component assembly of enaminones, primary amines and tosylhydrazine, a novel synthetic protocol toward 1,5-disubstituted 1,2,3-trizoles has been established. Besides the desirable regioselectivity, the present method possesses significant advantages for the benign metal-, azide-free conditions. This method will reasonable be useful complement to those classical approaches such as CuAAC for the synthesis of 1,2,3-triazoles.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of 1,5-Disubstituted 1,2,3-Triazoles. Enaminone **1** (0.2 mmol), amine **2** (0.2 mmol), tosylhydrazine **3** (0.3 mmol), I_2 (0.1 mmol) were charged in a 25 mL round-bottom flask equipped with a stirring bar. DMSO (2 mL) was added, and the mixture was stirred at110 °C for 12 h (TLC) at open air atmosphere. Upon completion, the vessel was allowed to cool down to room temperature, and 5 mL water was added. The resulting mixture was extracted with ethyl acetate (3 × 8 mL), the organic layers were combined and dried overnight with anhydrous $MgSO_4$. After filtration, the solvent was removed from the solution under reduced pressure. The residue was then subjected to flash silica gel column chromatography to provide pure products by using mixed ethyl acetate (EA) and petroleum ether (PE) as eluent (V_{PE}/V_{EA} = 5:1).

*(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (**4a**).* Yield: 40 mg; 71%. Brown solid; mp 65−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.91 (d, J = 7.6 Hz, 2 H), 7.67 (t, J = 7.2 Hz, 1 H), 7.53 (t, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H), 6.98 (dd, J = 7.8 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 160.5, 137.9, 136.8, 134.3, 134.2, 129.6, 129.5 0.128.9, 126.4, 114.4, 55.6; ESI-HRMS Calcd for $C_{16}H_{14}N_3O_2[M + H]^+$ 280.1081, found 280.1087.

*(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)(p-tolyl)methanone (**4b**).* Yield: 39 mg; 67%. Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 7.82 (d, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 160.5, 145.6, 137.6, 134.3, 134.2, 129.8, 129.7, 129.5, 126.4, 114.3, 55.6, 21.8; ESI-HRMS Calcd for $C_{17}H_{16}N_3O_2[M + H]^+$ 294.1237, found 294.1243.

*(4-Methoxyphenyl)(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)-methanone (**4c**).* Yield: 36 mg; 58%. White solid; mp 147−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.91 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H), 6.99−6.95 (m, 4 H), 3.90 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 164.7, 160.4, 137.1, 134.4, 132.2, 129.5, 126.2, 114.3, 114.2, 55.7, 55.6; ESI-HRMS Calcd for $C_{17}H_{16}N_3O_3[M + H]^+$ 310.1186, found 310.1190.

*(4-Fluorophenyl)(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)-methanone (**4d**).* Yield: 34 mg; 57%. White solid; mp 96−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.96 (t, J = 6.0 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.20 (t, J = 7.6 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 2 H), 3.86 (s, 3 H); ^{13}C NMR (100 MHz, CDCl3) δ 182.2, 166.4 (d, J = 256.1 Hz), 160.6, 137.7, 134.0, 133.1, 132.3 (d, J = 9.0 Hz), 129.4, 126.4, 116.3 (d, J = 21.8 Hz), 114.4, 55.6; ESI-HRMS Calcd for $C_{16}H_{13}FN_3O_2[M + H]^+$ 298.0986, found 298.0998.

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*(4-Chlorophenyl)(3-(4-methoxyphenyl)-3H-1,2,3-triazol-4-yl)-methanone (**4e**)*. Yield: 38 mg; 60%. White solid; mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.86 (d, J = 8.0 Hz, 2 H), 7.51 (d, J = 8.4 Hz, 2 H), 7.40 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 3.86 (s, 3 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 160.6, 141.0, 137.9, 135.0, 133.9, 130.9, 129.4, 129.3, 126.4, 114.4, 55.6; ESI-HRMS Calcd for $C_{16}H_{13}ClN_3O_2[M + H]^+$ 314.0691, found 314.0701.

*(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)(4-(trifluoromethyl)-phenyl)methanone (**4f**)*. Yield: 38 mg; 55%. Brown solid; mp 81−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 8.00 (d, J = 8.4 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2 H), 3.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 160.7, 139.6, 138.4, 135.5, 135.2, 133.7, 129.8, 129.3, 126.5, 126.0 (q, J = 3.3 Hz), 114.4, 55.6; ESI-HRMS Calcd for $C_{17}H_{13}F_3N_3O_2[M + H]^+$ 348.0954, found 348.0963.

*(3,4-Dichlorophenyl)(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)-methanone (**4g**)*. Yield: 40 mg; 58%. White solid; mp 164−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.99 (s, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 7.61 (d, J = 8.4 Hz, 1 H), 7.39 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 3.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 160.7, 139.1, 138.0, 136.2, 133.8, 133.5, 131.3, 131.1, 129.2, 128.4, 126.5, 114.4, 55.6; ESI-HRMS Calcd for $C_{16}H_{12}Cl_2N_3O_2[M + H]^+$ 348.0301, found 348.0313.

*(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)(o-tolyl)methanone (**4h**)*. Yield: 38 mg; 65%. Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.48−7.41 (m, 3 H), 7.30 (d, J = 8.6 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 3.86 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 160.5, 139.0, 138.9, 136.6, 135.4, 132.5, 132.0, 130.0, 129.6, 126.5, 125.6, 114.3, 55.6, 20.5; ESI-HRMS Calcd for $C_{17}H_{16}N_3O_2[M + H]^+$ 294.1237, found 294.1252.

*(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)(3-nitrophenyl)-methanone (**4i**)*. Yield: 34 mg; 53%. Brown solid; mp 136−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s 1 H), 8.51 (d, J = 8.0 Hz, 1 H), 8.23 (d, J = 6.8 Hz, 1 H), 8.15 (s, 1 H), 7.76 (t, J = 8.0 Hz, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 3.86 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 160.7, 148.4, 138.3, 137.9, 134.8, 133.4, 130.4, 129.1, 128.3, 126.6, 124.3, 114.4, 55.6; ESI-HRMS Calcd for $C_{16}H_{13}N_4O_4[M + H]^+$ 325.0931, found 325.0936.

*Benzo[d][1,3]dioxol-5-yl(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methanone (**4j**)*. Yield: 46 mg; 71%. Brown solid; mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.40 (3 H, overlapped signal), 6.98 (d, J = 8.0 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 1 H), 6.10 (s, 2 H), 3.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 160.4, 153.2, 148.7, 137.1, 134.3, 131.4, 129.5, 127.1, 126.2, 114.4, 108.8, 108.2, 102.3, 55.6; ESI-HRMS Calcd for $C_{17}H_{14}N_3O_4[M + H]^+$ 324.0979, found 324.0979.

*(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-1-yl)-methanone (**4k**)*. Yield: 44 mg; 66%. Brown solid; mp 92−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (t, J = 4.4 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 7.96−7.86 (m, 3 H), 7.58−7.50 (m, 3 H), 7.45 (d, J = 8.8 Hz, 2 H), 6.96 (d, J = 9.2 Hz, 2 H), 3.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 160.5, 139.1, 135.9, 134.2, 133.9, 130.5, 130.4, 129.6, 128.6, 128.5, 127.1, 126.4, 125.2, 124.2, 114.3, 55.6; ESI-HRMS Calcd for $C_{20}H_{16}N_3O_2[M + H]^+$ 330.1237, found 330.1239.

*(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)(naphthalen-2-yl)-methanone (**4l**)*. Yield: 45 mg; 68%. White solid; mp 142−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 8.15 (s, 1 H), 7.98−7.91 (m, 4 H), 7.68−7.61 (m, 2 H), 7.45 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.4 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 160.5, 137.9, 136.1, 134.4, 134.1, 132.3, 132.2, 129.8, 129.5, 129.4, 129.1, 128.0, 127.4, 126.4, 124.3, 114.4, 55.6. ESI-HRMS Calcd for $C_{20}H_{16}N_3O_2[M + H]^+$ 330.1237, found 330.1238.

*(3-(4-Methoxyphenyl)-3H-1,2,3-triazol-4-yl)(thiophen-2-yl)-methanone (**4m**)*. Yield: 28 mg; 50%. White solid; mp 128−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.68 (d, J = 2.8 Hz, 2 H), 7.28 (d, J = 7.6 Hz, 2 H), 7.08 (t, J = 4.4 Hz, 1 H), 6.85 (d, J = 7.6 Hz, 2 H), 3.71 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 160.0, 142.7, 136.4, 136.0, 134.6, 133.6, 128.8, 128.3, 126.0, 113.8, 55.1; ESI-HRMS Calcd for $C_{14}H_{12}N_3O_2S[M + H]^+$ 286.0645, found 286.0644.

*(3-Phenyl-3H-1,2,3-triazol-4-yl)(p-tolyl)methanone (**4ba**)*. Yield: 28 mg; 54%. White solid; mp 120−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.83 (d, J = 8.4 Hz, 2 H), 7.49 (s, 5 H), 7.33 (d, J = 7.6 Hz, 2 H), 2.46 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 145.2, 137.3, 136.0, 134.0, 133.6, 129.33, 129.27, 129.21, 128.8, 124.5, 21.4; ESI-HRMS Calcd for $C_{16}H_{14}N_3O[M + H]^+$ 264.1131, found 264.1137.

*p-Tolyl(1-p-tolyl-1H-1,2,3-triazol-4-yl)methanone (**4bb**)*. Yield: 39 mg; 71%. Orange solid; mp 74−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.82 (d, J = 8.4 Hz, 2 H), 7.37−7.26 (m, 6 H), 2.45 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 145.7, 140.0, 137.6, 134.3, 134.1, 129.8, 129.7, 127.3, 124.7, 122.2, 21.8, 21.3; ESI-HRMS Calcd for $C_{17}H_{16}N_3O[M + H]^+$ 278.1288, found 278.1289.

*(1-(4-Chlorophenyl)-1H-1,2,3-triazol-5-yl)(p-tolyl)methanone (**4bc**)*. Yield: 35 mg; 59%. Pale yellow solid; mp 91−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.83 (d, J = 6.8 Hz, 2 H), 7.44 (s, 4 H), 7.33 (d, J = 6.8 Hz, 2 H), 2.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 145.9, 137.9, 135.8, 135.0, 134.4, 134.0, 129.8, 129.7, 129.5, 126.3, 21.9; ESI-HRMS Calcd for $C_{16}H_{13}ClN_3O[M + H]^+$ 298.0742, found 298.0743.

*(3-(4-Bromophenyl)-3H-1,2,3-triazol-4-yl)(p-tolyl)methanone (**4bd**)*. Yield: 42 mg; 61%. White solid; mp 113−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.83 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 8.8 Hz, 2 H), 7.39−7.33 (m, 4 H), 2.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 146.0, 138.0, 135.5, 134.3, 134.0, 132.5, 129.8, 129.7, 126.5, 123.9, 21.9; ESI-HRMS Calcd for $C_{16}H_{12}BrN_3ONa[M + Na]^+$ 364.0056, found 364.0066.

*p-Tolyl(1-o-tolyl-1H-1,2,3-triazol-4-yl)methanone (**4be**)*. Yield: 36 mg; 65%. Yellow solid mp 90−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.42 (t, J = 7.2 Hz, 1 H), 7.36−7.28 (m, 5 H), 2.45 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 145.5, 137.1, 136.1, 135.2, 134.8, 134.1, 131.0, 130.3, 129.7, 129.6, 126.9, 126.6, 21.8, 17.5; ESI-HRMS Calcd for $C_{17}H_{16}N_3O[M + H]^+$ 278.1288, found 278.1289.

*(3-(2-Chlorophenyl)-3H-1,2,3-triazol-4-yl)(p-tolyl)methanone (**4bf**)*. Yield: 36 mg; 61%. White solid; mp 122−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.63−7.60 (m, 1 H), 7.51−7.48 (m, 3 H), 7.33 (d, J = 7.6 Hz, 2 H), 2.46 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 145.5, 137.0, 135.6, 134.8, 133.7, 131.3, 130.2, 129.7, 129.6, 128.6, 127.8, 21.8; ESI-HRMS Calcd for $C_{16}H_{13}ClN_3O[M + H]^+$ 298.0742, found 298.0755.

*(3-(3-Chlorophenyl)-3H-1,2,3-triazol-4-yl)(p-tolyl)methanone (**4bg**)*. Yield: 37 mg; 63%. White solid; mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.83 (d, J = 7.6 Hz, 2 H), 7.55 (s, 1 H), 7.48 (d, J = 6.8 Hz, 1 H), 7.42 (t, J = 7.6 Hz, 1 H), 7.38−7.33 (m, 3 H), 2.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 145.9, 137.9, 137.4, 134.9, 134.4, 134.0, 130.2, 130.0, 129.8, 129.7, 125.4, 123.3, 21.9; ESI-HRMS Calcd for $C_{16}H_{12}ClN_3ONa[M + Na]^+$ 320.0561, found 320.0565.

*(3-(3-Nitrophenyl)-3H-1,2,3-triazol-4-yl)(p-tolyl)methanone (**4bh**)*. Yield: 33 mg; 53%. Pale yellow solid; mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 8.40 (d, J = 8.0 Hz, 1 H), 8.14 (s, 1 H), 7.89−7.84 (m, 3 H), 7.73 (t, J = 8.8 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 2 H), 2.48 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 148.4, 146.2, 138.4, 137.5, 134.5, 133.8, 131.1, 130.2, 129.9, 129.8, 124.5, 120.6, 21.9; ESI-HRMS Calcd for $C_{16}H_{13}N_4O_3[M + H]^+$ 309.0982, found 309.0991.

*(3-(2,4-Dimethylphenyl)-3H-1,2,3-triazol-4-yl)(p-tolyl)methanone (**4bi**)*. Yield: 37 mg; 64%. Pale yellow solid; mp 90−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 7.82 (d, J = 7.6 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.18−7.11 (m, 3 H), 2.46 (s, 3 H), 2.40 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 145.5, 140.4 137.1, 135.1, 134.4, 134.1, 133.5, 131.7, 129.7, 127.3, 126.6, 21.8, 21.3, 17.4; ESI-HRMS Calcd for $C_{18}H_{18}N_3O[M + H]^+$ 292.1444, found 292.1453.

*(1-(Quinolin-8-yl)-1H-1,2,3-triazol-5-yl)(p-tolyl)methanone (**4bj**)*. Yield: 38 mg; 60%. White solid; mp 206−209 °C; ^{1}H NMR (400 MHz,

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J. Org. Chem. 2015, 80, 9028−9033

$CDCl_3$) δ 8.44 (s, 1 H), 8.19 (d, J = 4.4 Hz, 2 H), 8.08 (s, 1 H), 7.98 (d, J = 7.6 Hz, 1 H), 7.92 (d, J = 7.2 Hz, 2 H), 7.75 (t, J = 7.2 Hz, 1 H), 7.33 (d, J = 6.0 Hz, 3 H), 2.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 150.4, 144.8, 140.5, 137.7, 136.2, 135.9, 134.1, 133.9, 130.0, 129.7, 129.4, 128.6, 126.4, 126.3, 122.0, 21.8; ESI-HRMS Calcd for $C_{19}H_{15}N_4O[M + H]^+$ 315.1240, found 315.1240.

*Phenyl(1-(p-tolyl)-1H-1,2,3-triazol-5-yl)methanone (**4aa**).* Yield: 35 mg; 66%. Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.91 (d, J = 7.6 Hz, 2 H), 7.65 (t, J = 7.2 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 140.0, 138.0, 136.7, 134.3, 134.2, 134.1, 129.8, 129.6, 129.0, 124.8, 21.2; ESI-HRMS Calcd for $C_{16}H_{14}N_3O[M + H]^+$ 264.1131, found 264.1131.

*(1-(4-Bromophenyl)-1H-1,2,3-triazol-5-yl)(4-methoxyphenyl)-methanone (**4ca**).* Yield: 43 mg; 60%. White solid; mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 7.92 (d, J = 8.8 Hz, 2 H), 7.60 (d, J = 8.8 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H), 7.00 (d, J = 8.8 Hz, 2 H), 3.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.0, 164.8, 137.5, 135.5, 134.4, 132.4, 132.2, 129.2, 126.4, 123.8, 114.4, 55.8; ESI-HRMS Calcd for $C_{16}H_{13}BrN_3O_2[M + H]^+$ 358.0186, found 358.0193.

*(4-Chlorophenyl)(1-(4-chlorophenyl)-1H-1,2,3-triazol-5-yl)-methanone (**4da**).* Yield: 36 mg; 57%. White solid; mp 127−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 7.87 (d, 2 H, J = 8.0 Hz), 7.54−7.43 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 141.3, 138.2, 136.0, 134.9, 134.8, 133.8, 130.9, 130.0, 129.5, 126.4;33; ESI-HRMS Calcd for $C_{15}H_{10}Cl_2N_3O[M + H]^+$ 318.0195, found 318.0215.

*(3-(4-Bromophenyl)-3H-1,2,3-triazol-4-yl)(4-chlorophenyl)-methanone (**4db**).* Yield: 42 mg; 58%. Pale yellow solid; mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.87 (d, J = 8.4 Hz, 2 H), 7.64 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 8.8 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 141.3, 138.2, 135.4, 134.8, 133.8, 132.5, 130.9, 129.5, 126.6, 124.1; ESI-HRMS Calcd for $C_{15}H_9BrClN_3ONa[M + Na]^+$ 383.9510, found 383.9524.

*(3-(4-Bromophenyl)-3H-1,2,3-triazol-4-yl)(4-(trifluoromethyl)-phenyl)methanone (**4ea**).* Yield: 44 mg; 56%. White solid; mp 126−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11(s, 1 H), 8.04 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 139.3, 138.7, 135.8, 135.4, 135.3, 133.6, 132.5, 129.8, 126.7, 126.1(q, J = 3.0 Hz), 124.3; ESI-HRMS Calcd for $C_{16}H_{10}BrF_3N_3O[M + H]^+$ 395.9954, found 395.9966.

*(1-(4-Chlorophenyl)-1H-1,2,3-triazol-5-yl)(3,4-dimethoxyphenyl)-methanone (**4fa**).* Yield: 42 mg; 61%. White solid; mp 162−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.57 (d, J = 9.6 Hz, 1 H), 7.50−7.43 (m, 5 H), 6.96 (d, J = 8.4 Hz, 1 H), 4.00 (s, 3 H), 3.94 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 154.8, 149.6, 137.4, 135.8, 135.0, 134.4, 129.5, 129.4, 126.1, 125.5, 110.8, 110.2, 56.3, 56.1; ESI-HRMS Calcd for $C_{17}H_{15}ClN_3O_3[M + H]^+$ 344.0796, found 344.0784.

*(1-(4-Chlorophenyl)-1H-1,2,3-triazol-5-yl)(naphthalen-2-yl)-methanone (**4ga**).* Yield: 41 mg; 62%. White solid; mp 159−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 8.14 (s, 1 H), 7.95−7.89 (m, 4 H), 7.66 (t, J = 7.2 Hz, 1 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.48−7.42 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 138.1, 136.1, 135.8, 135.1, 134.4, 134.0, 132.4, 132.3, 129.8, 129.6, 129.5, 129.2, 128.0, 127.5, 126.3, 124.2; ESI-HRMS Calcd for $C_{19}H_{13}ClN_3O[M + H]^+$ 334.0742, found 334.0743.

*Benzo[d][1,3]dioxol-5-yl(1-(4-bromophenyl)-1H-1,2,3-triazol-5-yl)methanone (**4ha**).* Yield: 44 mg; 59%. White solid; mp 194−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.40−7.36 (m, 3 H), 6.91 (d, J = 8.0 Hz, 1 H), 6.12 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 153.4, 148.9, 137.4, 135.5, 134.3, 132.5, 131.2, 127.1, 126.4, 108.8, 108.3, 102.4; ESI-HRMS Calcd for $C_{16}H_{11}BrN_3O_3[M + H]^+$ 371.9978, found 371.9999.

*Ethyl 4-(5-(4-methylbenzoyl)-1H-1,2,3-triazol-1-yl)benzoate (**4bk**).* Yield: 38 mg; 57%. Pale yellow solid; mp 119−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 2 H), 8.07 (s, 1 H), 7.82 (d, J = 7.6 Hz, 2 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 7.6 Hz, 2 H), 4.40 (q, J = 7.2 Hz, 2 H), 2.46 (s, 3 H), 1.40 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 165.3, 145.9, 139.9, 137.8, 134.5, 134.0, 131.7, 130.6, 129.8, 129.7, 124.7, 61.4, 21.8, 14.3; ESI-HRMS Calcd for $C_{19}H_{18}N_3O_3[M + H]^+$ 336.1343, found 336.1337.

*3-(4-Methoxyphenyl)-3H-1,2,3-triazole-4-carbonitrile (**7**).* Yield: 16 mg; 40%. White solid; mp 139−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1 H), 7.65 (d, J = 9.2 Hz, 2 H), 7.09 (d, J = 9.2 Hz, 2 H), 3.91 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 139.7, 127.5, 124.2, 117.7, 114.6, 108.3, 55.3; ESI-HRMS Calcd for $C_{10}H_9N_4O[M + H]^+$ 201.0771, found 201.0771.

Typical Procedure for the Stepwise Synthesis 4a Using Intermediate 10. The synthesis of **10** was peformed using **1a** and **2a** following the standard procedure in the synthesis of 1,2,3-triazole **4**, but the eluent consists of V_{PE}/V_{EA} = 5:1 mixture was employed for the silica gel column chromatographic purification. Repeated reaction was performed to accumulate enough sample for subsequent experiment. The synthesis of **4a** using **10** was conducted via identical operation in the three-component synthesis of 1,2,3-triazoles **4**.

*(Z)-3-((4-Methoxyphenyl)amino)-1-phenylprop-2-en-1-one (**10**).*[20] Yield: 53 mg; 52% (0.4 mmol scale). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.19 (d, 1 H, J = 11.8 Hz), 7.93 (d, 2 H, J = 8.0 Hz), 7.45 (d, 4 H, J = 8.0 Hz), 7.06 (d, 2 H, J = 8.0 Hz), 6.89 (d, 2 H, J = 8.0 Hz), 5.98 (d, 1 H, J = 8.0 Hz), 3.80 (s, 3 H).

Procedure for the Wittig Elaboration in the Synthesis of 5-Vinyl 1,2,3-triazole. Triazole **4a** (0.5 mmol) and Witting reagent **8** (1.5 mmol) were charged in a 25 mL round-bottom flask equipped with a stirring bar. DMSO (2 mL) were added and the mixture was stirred at110 °C for 12 h (TLC). After cooling down to room temperature, 5 mL water was added, and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The organic layers were combined and dried overnight with anhydrous $MgSO_4$. The solid was filtered away and the solvent was removed from the solution under reduced pressure. The acquired residue was subjected to flash silicon column chromatography to provide pure product **9** by using mixed ethyl acetate (EA) and petroleum ether (PE) as eluent (V_{PE}/V_{EA} = 4:1).

*Methyl-3-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-5-yl)-3-phenyl acrylate (**9**).* Yield: 52 mg; 78%. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 7.28−7.21 (m, 3 H), 7.16 (d, J = 8.8 Hz, 2 H), 7.03 (d, J = 7.2 Hz, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 6.12 (s, 1 H), 3.80 (s, 3 H), 3.58 (s, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 160.2, 141.6, 138.1, 135.6, 135.4, 129.1, 128.7, 127.9, 126.6, 121.6, 114.4, 55.6, 51.6; ESI-HRMS Calcd for $C_{19}H_{18}N_3O_3[M + H]^+$ 336.1343, found 336.1333.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01121.

Experimental procedure, characterization data as well as ^{1}H/^{13}C NMR spectra of all products. (PDF)

Crystallographic data of **4l**. (CIF)

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Notes

The authors declare no competing financial interest.

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