DABCO-Mediated aza-Michael addition of 4-aryl-1,2,3-triazoles to cycloalkenones. Regioselective synthesis of disubstituted 1*H*-1,2,3-triazoles

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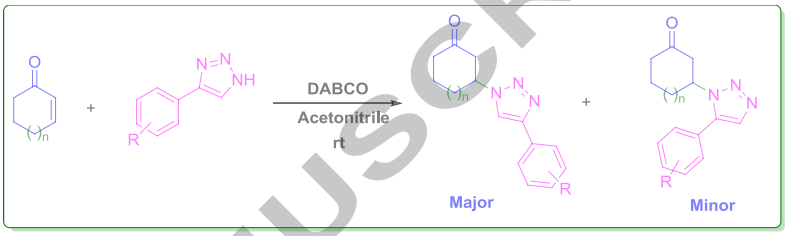

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ABSTRACT

Aza-Michael addition of 4-aryl-1*H*-1,2,3-triazoles to 2-cycloalken-1-ones has been studied in the presence of DABCO as organic base. The reactions were carried out in acetonitrile at room temperature to provide 1,4-disubstituted 1*H*-1,2,3-triazoles as major adducts and 1,5-disubstituted 1*H*-1,2,3-triazoles as minor adducts. Though the reaction times are longer (4–8 days), the two regioisomers were separated by using column chromatography and the adducts were obtained in very good to excellent combined chemical yields. The electron-rich and electron-poor substituents on aryl moiety of 4-aryl-triazoles could tolerate the reaction conditions to afford the title adducts.

The C–N bond formation between nitrogen-containing heterocycles and carbon electrophiles has long been a mainstay in organic synthesis due to the ubiquitous nature of aza-heterocycles in pharmaceuticals as well as in materials sciences.[1] The synthesis of triazoles has always been of great interest.[2] This is due in part to the fact that triazoles are key structural motifs in products with a variety of biological properties including analgesic, antiviral, anti-inflammatory, antimicrobial, antiproliferative anticonvulsant, and anticancer effects.[3] Relevant pharmaceuticals based on the triazole core include, for example, the broad-spectrum cephalosporin antibiotic cefatrizine, the antifungal fluconazole, the penicillin-derived antibiotic tazobactam and the anti-epileptic rufinamide.[4] The latter one is among the best-selling five-membered heterocyclic medicaments in recent years. Further, triazole skeleton is a constituent of many modified nucleosides, nucleotides and oligonucleotides which display various biological effects.[5]

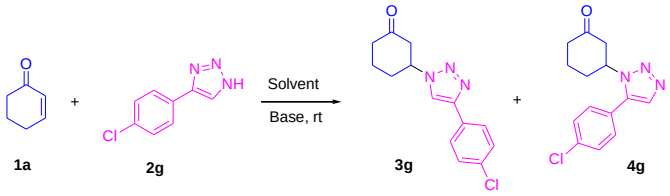
The dipolar [3+2] cycloaddition of azides and alkynes is the most efficient method for the synthesis of 1,2,3-triazoles.[6,7] The reaction was comprehensively studied by Huisgen[6]. Later, Sharpless[7a-c] and Meldal[7d,e] developed copper-catalysed azides-alkynes cycloaddition (CuAAC) through "click chemistry" concept. Since the triazoles are stable entities, they are chemically less reactive. The 1,4-conjugate addition of these triazoles to α,β-unsaturated carbonyls represents a powerful synthetic approach to functionalize triazoles. Given the importance of triazole scaffolds, we sought to synthesize disubstituted triazoles *via* conjugate addition to α,β-unsaturated cycloalkenones by using organic base. There are few reports on the conjugate addition of triazoles and cycloalkenones by "click-chemistry" in the presence of metal salts.[8] Herein we report our preliminary results on DABCO-mediated aza-Michael addition of 4-aryl-1,2,3-triazoles[9] to cycloalkenones under metal-free conditions.

Initially the reaction between 2-cyclohexen-1-one (**1a)** and 4-chlorophenyl triazole **2g** in acetonitrile at room temperature in the presence of triethylamine (20 mol%) afforded two regioisomers in low yield after three days. The major adduct **3g** and the minor adduct **4g** were isolated in 23 and 5% yield, respectively (Table 1, entry 1). Encouraged by this early result, we explored numerous reaction parameters such as base, solvent and temperature to improve the selectivity and yield of the addition products. The Michael addition of **2g** with **1a** was performed by using DABCO as base in 20–80 mol% in acetonitrile at ambient temperature (entries 2–5). The yields of the products were gradually increased, and with 80 mol% of DABCO, the adducts **3g** and **4g** were isolated in 74% and 22% yield, respectively, after 4 days (entry 5). Other bases such as DBU and DIPEA provided the addition products **3g** and **4g** in moderate yield (entries 6 and 7). The reactions were then tested in various solvents such as dichloromethane, 1,4-dioxane, 1,2-dichloroethane, chloroform and methanol; however, varying amounts of regioisomers were isolated (entries 8–12). DABCO-mediated reaction of **1a** with **2g** in acetonitrile at elevated temperature furnished two adducts in excellent combined yield albeit with diminished regioselectivity (entries 13 and 14). While the reaction of **1a** and **2g** under reflux condition in 2.5 d provided the products **3g** in 58% and **4g** in 40% isolated yield (entry 15), and that with DABCO (100 mol%) at room temperature in 3.5 d afforded the products **3g** in 65% and **4g** in 32% isolated yield (entry 16). The formation of disubstituted triazoles in varying amounts appears to be result of steric factor, where the major 1,4-disubstituted triazole experiences less steric hindrance during the reaction.

Aiming to expand the synthetic potential of this transformation, the reaction of cyclohexenone **1a** was studied with variously substituted 4-aryl-1,2,3-triazoles **2** (Table 2). To our delight, enone **1a** could smoothly undergo Michael addition with triazoles

Table 1

Conjugate addition of 4-(4-chlorophenyl)-1*H*-1,2,3-triazole to 2-cyclohexen-1-one[a].



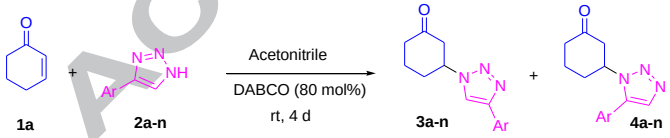
Entry	Base (mol%)	Solvent	Time (d)	Yield[b] (%)	
				3g	**4g**
1	TEA (20)	ACN	3	23	5
2	DABCO (20)	ACN	3	45	10
3	DABCO (40)	ACN	3	52	13
4	DABCO (60)	ACN	4	63	15
5	**DABCO (80)**	**ACN**	**4**	**74**	**22**
6	DBU (80)	ACN	4	65	9
7	DIPEA (80)	ACN	4	63	13
8	DABCO (80)	DCM	4	66	20
9	DABCO (80)	1,4-Dioxane	4	58	19
10	DABCO (80)	DCE	4	63	15
11	DABCO (80)	$CHCl_3$	4	59	13
12	DABCO (80)	CH_3OH	4	36	7
13[c]	DABCO (80)	ACN	3	54	38
14[d]	DABCO (80)	ACN	3	55	35
15[e]	DABCO (80)	ACN	2.5	58	40
16	DABCO (100)	ACN	3.5	65	32

[a] All the reactions were carried out in solvent (1 mL) using 2-cyclohexen-1-one (**1a**, 6 eqiv) and 4-(4-chlorophenyl)-1*H*-1,2,3-triazole (**2g**, 0.2 mmol, 1 equiv) in the presence of base at room temperature unless otherwise mentioned. [b] Isolated yield. [c] Carried out at 50 °C. [d] Carried out at 70 °C. [e] Carried out at reflux temperature.

2b-e bearing differently substituted phenyl groups to afford **3a-n** as major adducts along with **4a-n** as minor adducts in good to excellent combined yields (entries 2–5). The aryl triazoles **2g,i,k** with substituents in position 3 or 4 provided the adducts in better chemical yield in comparison to their isomers **2f,h,j** with substituents at position 2 which may be due to the steric factor (entries 6 and 7; 8 and 9; 10 and 11). Similar trend has been observed in the reactions of substrates **2g,h,j,l** having dimethoxy (entries 10 and 11) and dichloro (entries 7 and 12) groups. The trimethoxy derivative **2m** and naphthalene derivative **2n** also afforded the products **3m**/**4m** and **3n**/**4n** in very good yield under similar conditions.

Table 2

Conjugate addition of 4-aryl 1*H*-1,2,3-triazoles **2** to 2-cyclohexen-1-one (**1a**).[a]



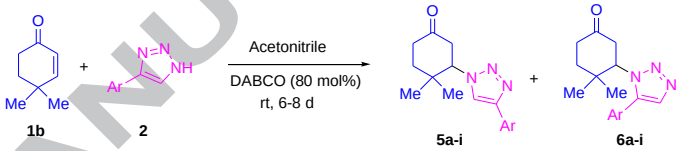
Entry	Aryl group in **2/3/4**	Yield[b] (%)		
		3	**4**	**3+4**
1	Phenyl	**3a** (62)	**4a** (17)	79
2	3-Methoxyphenyl	**3b** (71)	**4a** (18)	89
3	4-Methoxyphenyl	**3c** (66)	**4c** (28)	94
4	4-Methylphenyl	**3d** (63)	**4d** (19)	82
5	4-Isopropylphenyl	**3e** (71)	**4e** (22)	93
6	2-Chlorophenyl	**3f** (68)	**4f** (21)	89
7	4-Chlorophenyl	**3g** (74)	**4g** (22)	96
8	2-Nitrophenyl	**3h** (60)	**4h** (15)	75
9	3-Nitrophenyl	**3i** (60)	**4i** (22)	82
10	2,5-Dimethoxyphenyl	**3j** (61)	**4j** (28)	89
11	3,4-Dimethoxyphenyl	**3k** (71)	**4k** (28)	99
12	2,3-Dichlorophenyl	**3l** (56)	**4l** (30)	86
13	2,4,5-Trimethoxyphenyl	**3m** (67)	**4m** (21)	88
14	2-Methoxynaphthalen-1-yl	**3n** (66)	**4n** (14)	80

[a] All the reactions were carried out in acetonitrile (1 mL) using 2-cyclohexen-1-one (**1a**, 6 equiv) and a 4-aryl 1,2,3-triazole (**2**, 0.2 mmol, 1 equiv) in the presence of DABCO (80 mol%) for 4 days at room temperature. [b] Isolated yield.

To further illustrate the scope of this protocol, the reactions of 4,4-dimethyl-2-cyclohexen-1-one (**1b**) have been studied with 4-aryl triazoles under DABCO mediated conjugate addition (Table 3). The reactions proceeded slowly due to the steric congestion on the sp^3 carbon neighbouring to the electrophilic centre where the nucleophilic attack is taking place. However, the adducts were isolated in good to high combined chemical yields with diminished regioselectivity. The reactivity pattern observed in cyclohexenone **1a** was also reflected in the reactions of **1b** (Table 3). The chlorophenyl, nitrophenyl and dimethoxyphenyl triazoles with substitutions in position 3 or 4 provided the corresponding adducts in higher chemical yield in comparison to their isomers with substituents at position 2. This may be attributed to the steric hindrance around aromatic system in addition to that present on the neighbouring carbon adjacent to electrophilic centre (Table 3, entries 3 and 4; 6 and 7; 8 and 9).

Table 3

Conjugate addition of 4-aryl 1*H*-1,2,3-triazoles **2** to 4,4-dimethyl-2-cyclohexen-1-one (**1b**) [a]



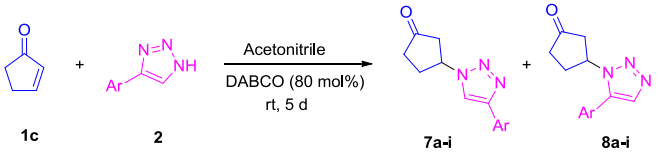
Entry	Aryl group in **5/6**	Time (d)	Yield[b] (%)		
			5	**6**	**5+6**
1	4-Methoxyphenyl	7	**5a** (47)	**6a** (21)	68
2	4-Isopropylphenyl	7	**5b** (51)	**6b** (19)	70
3	2-Chlorophenyl	7	**5c** (53)	**6c** (21)	74
4	4-Chlorophenyl	7	**5d** (58)	**6d** (30)	88
5	2-Bromophenyl	7	**5e** (48)	**6e** (14)	62
6	2-Nitrophenyl	8	**5f** (46)	**6f** (24)	70
7	3-Nitrophenyl	6	**5g** (64)	**6g** (19)	83
8	2,5-Dimethoxyphenyl	7	**5h** (42)	**6h** (28)	70
9	3,4-Dimethoxyphenyl	7	**5i** (51)	**6i** (27)	78

[a] All the reactions were carried out in acetonitrile (1 mL) using 4,4-dimethyl-2-cyclohexen-1-one (**1b**, 6 equiv) and 4-aryl 1,2,3-triazole (**2**, 0.2 mmol, 1 equiv) in the presence of DABCO (80 mol%) at room temperature. [b] Isolated yield.

To expand the scope of the reaction, the optimized procedure was also extended to the addition of aryl triazole to 2-cyclopenten-1-one (**1c**). These reactions proceeded with acceptable selectivity to afford adducts **7** and **8** in good to excellent yields (Table 4). Interestingly, the substitution pattern of substituents on the phenyl moiety did not show any effect on the combined yields of the Michael adducts. These reactions proceeded with acceptable selectivity to afford adducts **7** and **8** in good to excellent yields (Table 4).

Table 4

Michael addition of 4-aryl 1*H*-1,2,3-triazoles **2** to 2-cyclopenten-1-one (**1c**).[a]



Entry	Aryl group in **7/8**	Yield[b] (%)		
		7	**8**	**7+8**
1	Phenyl	**7a** (71)	**8a** (25)	96
2	3-Methoxyphenyl	**7b** (61)	**8b** (16)	77
3	4-Methoxyphenyl	**7c** (78)	**8c** (14)	92
4	4-Isopropylphenyl	**7d** (72)	**8d** (19)	91
5	2-Chlorophenyl	**7e** (66)	**8e** (22)	88

6	4-Chlorophenyl	**7f** (68)	**8f** (19)	87
7	3-Nitrophenyl	**7g** (51)	**8g** (14)	65
8	2,5-Dimethoxyphenyl	**7h** (72)	**8h** (21)	93
9	3,4-Dimethoxyphenyl	**7i** (67)	**8i** (20)	87

[a] All the reactions were carried out in acetonitrile (1 mL) using 2-cyclopenten-1-one (**1c**, 6 equiv) and 4-aryl 1,2,3-triazole (2, 0.2 mmol, 1 equiv) in the presence of DABCO (80 mol%) at room temperature. [b] Isolated yield.

The melting points of 1,4-disubstituted analogues are in general lower than those of 1,5-disubstituted analogues and the former isomers are less polar than the latter as indicated by TLC analysis. The structures of all the aza-Michael adducts were based on the ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR, spectral analyses. The C-3 of cycloalkanone moiety of major adducts **3**, **5** and **7** resonates at downfield, whereas that of minor adducts **4**, **6** and **8** resonates at upfield in ^{13}C NMR. For example, C-3 of cyclohexanone moiety of **3g** resonates at 62.7 ppm and that of **4g** appears at 59.0 ppm upfield. The regiochemistry of the adduct **5i** was further confirmed by its single crystal X-ray structure[10] (Fig. 1) and that of the other adducts **3-8** is derived by comparing the chemical shifts of their NMR spectra with that of **5i**.

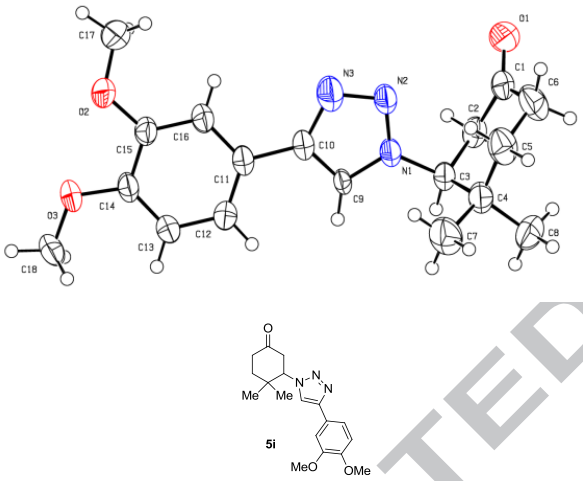
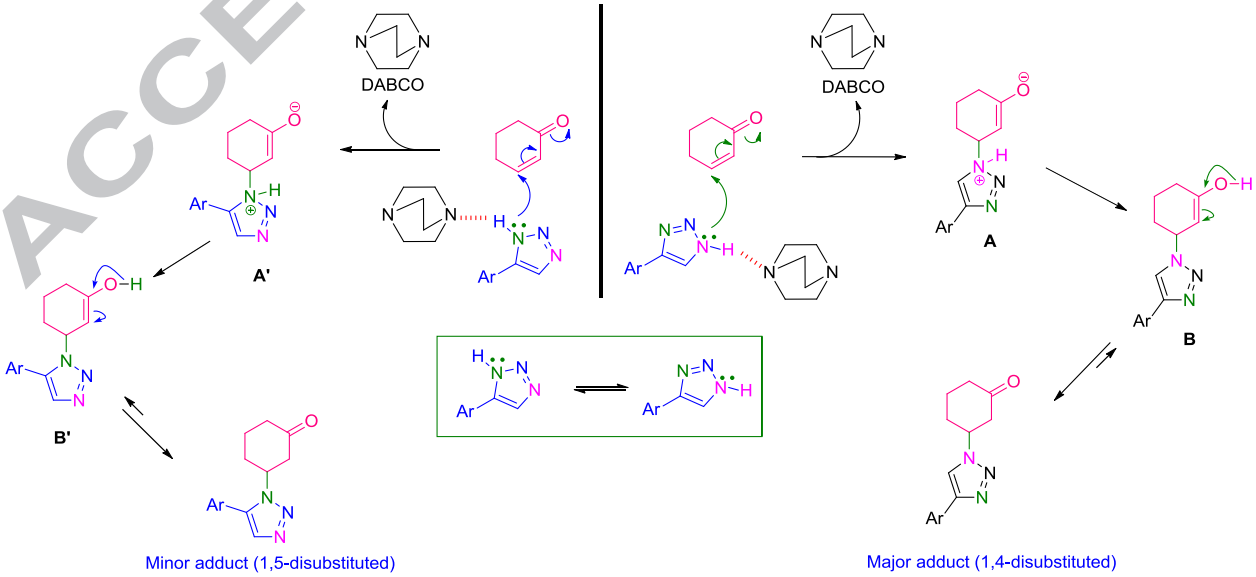


Figure 1 ORTEP plot of the crystal structure of Michael adduct **5i** (numbering is arbitrary).

A plausible mechanism for the conjugate addition of 4-aryl 1*H*-1,2,3-triazoles to 2-cyclohexen-1-one **1a** is depicted in Scheme 1. The organic base, DABCO activates the Michael donor, 4-aryl-1*H*-1,2,3-triazole through H-bond formation with N-H of triazole. Thus the activated triazole gets enhanced nucleophilicity and attacks the β-carbon of 2-cyclohexen-1-one leading to the formation of enol derivative **B** (**B′**) *via* "Zwitter ion" **A** (**A′**). The less stable enol **B** (**B′**) tautomerises to the target disubstituted triazole as Michael adduct.

Conclusion

In conclusion, we have illustrated the DABCO-mediated synthesis of disubstituted 1,2,3-triazoles by aza-Michael reaction of 4-aryl-1,2,3-triazoles with 2-cycloalken-1-ones. The stability of the 1,2,3-triazoles clearly reflected in the slow reactions of Michael addition. However, this protocol provided the disubstituted adducts in good combined yields.



Scheme 1 Plausible reaction mechanism for the formation of disubstituted triazoles.

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Supplementary Material

Electronic Supplementary Information (ESI) available: [Experimental procedures, spectroscopic data, copies of ^{1}H NMR, ^{13}C NMR]. See DOI: 10.1039/x0xx00000x.

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10 CCDC 1494708 contains the supplementary crystallographic data for compound **5i**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/ retrieving.html (or from deposit@ccdc.cam.ac.uk).

Highlights

Ms. Title: *DABCO-Mediated aza-Michael addition of 4-aryl-1,2,3-triazoles to cycloalkenones. Regioselective synthesis of disubstituted 1H-1,2,3-triazoles amines*

- Metal-free synthesis of disubstituted triazoles through aza-Michael reaction.
- A novel DABCO-promoted synthesis of disubstituted 1*H*-1,2,3-triazoles is unraveled.
- Disubstituted 1*H*-1,2,3-triazoles were obtained in excellent combined yields.
- The EWGs and ERGs on aryl moiety of Michael donor could tolerate the reaction.