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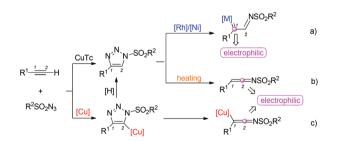
Base-induced synthesis of *N*-dialkylaminomethyl-2*H*-1,2,3-triazoles from *N*-sulfonyl-1,2,3-triazoles†

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A facile synthetic method to access *N*-dialkylaminomethyl-2*H*-1,2,3-triazoles has been developed *via* a novel reaction mode from *N*-sulfonyl-1,2,3-triazoles by a base induced reaction. Moreover, 4-phenyl-1*H*-1,2,3-triazoles can also give the same products even in the absence of a base at high temperature.

Introduction

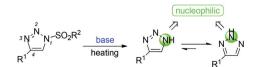
1,2,3-Triazoles are an important class of heterocycles in organic synthesis, medicinal chemistry and materials science. Among them, *N*-sulfonyl-1,2,3-triazoles, which can be easily prepared from copper(i)-catalyzed azide–alkyne cycloadditions, have attracted much attention of organic chemists because of their potential applications in accessing other heterocycles. Recently, investigation on the reaction types of these compounds has emerged at the forefront of current research. Several different reaction types have been found to date (Scheme 1).



Scheme 1 Formation of α -imino metal carbene and N-sulfonyl ketenimines.

In the presence of Rh/Ni catalysts, N-sulfonyl-1,2,3-triazoles will undergo a ring-opening process to afford α-imino metal carbenes.³⁻⁸ The C1 position with a strong electrophilic ability can be attacked by other nucleophiles. 4-6 Moreover, a nitrogen atom with an increased nucleophilic ability offers more synthetic flexibility. The α-imino metal carbenes can react with many other compounds to afford useful heterocycles (Scheme 1a). On the other hand, at high temperature, N-sulfonyl-1,2,3-triazoles can also undergo a ring-opening process to afford N-sulfonyl ketenimines, which can be attacked by nucleophiles at the C2 position or undergo pericyclic reactions (Scheme 1b). Indeed, in many reports, N-sulfonyl ketenimines were afforded by a one-pot strategy. 10-12 Cycloaddition between terminal alkynes and sulfonyl azides catalyzed by copper(1) afforded the N-sulfonyl triazolyl copper species, which can undergo a ring-opening rearrangement leading to the ketenimine intermediate upon the release of a dinitrogen molecule (Scheme 1c).

However, we recently also found that the sulfonyl group of *N*-sulfonyl-1,2,3-triazoles can undergo elimination to afford 4-phenyl-1*H*-1,2,3-triazoles as nucleophilic intermediates¹³ in the presence of a base at high temperature. Moreover, the intermediates could be converted into more stable 4-phenyl-2*H*-1,2,3-triazoles to trap other electrophiles in the N2-position (Scheme 2). Indeed, bis(dialkylamino)methane was chosen as a reaction partner, which could afford an electrophilic iminium ion. Herein, we would like to report these interesting new findings.



Scheme 2 Formation of 4-phenyl-2*H*-1,2,3-triazoles.

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Results and discussion

We initially utilized N-sulfonyl-1,2,3-triazole 1a (0.2 mmol) and tetrabenzylmethanediamine 2a (0.2 mmol) as substrates to examine the reaction outcomes. The results are shown in Table 1. To our delight, in the presence of 1.0 equiv. of K₂CO₃ as an additive, we found that 3aa was obtained in 39% yield determined by ¹H NMR spectroscopy along with the formation of HNBn2 (Table 1, entry 2). Subsequently, solvents were examined (Table 1, entries 3-8). The yield of 3aa had no obvious improvement when THF or toluene was used (Table 1, entries 3 and 4). While the use of high polar solvents such as DMF and DMSO afforded 3aa in higher yields (Table 1, entries 5 and 6). Then we turned our attention to identify the best base for this reaction. Both inorganic and organic bases were used in the reaction, and 1,4-diazabicyclo[2,2,2]octane (DABCO) was identified as the best base for the reaction, affording 3aa in 90% isolated yield. Meanwhile, the corresponding TsNBn2 was also obtained at the same time (Table 1, entry 14). The structure of 3aa has been unambiguously determined by the X-ray crystal structure of its analogue 3ha (Fig. 1).¹⁷

With the optimal conditions in hand, we next surveyed the substrate scope of this reaction and the results are shown in Table 2. At first, we synthesized a series of triazoles with different substituents on the aromatic ring and examined their reaction properties. As for substrates **2b-f**, with electron-donating groups on the aromatic ring, the desired products 3 were afforded in 67–72% yields. While for substrates **2g-l**, with electron-withdrawing groups, the corresponding products 3 were afforded in 67–81% yields. These results suggested that the substrates with electron-withdrawing groups on the aromatic

Table 1 Optimization of the reaction conditions

Entry	Additive	X	Solvent	T (°C)	Yield ^b (%)
1	_	_	DCE	100	25
2	K_2CO_3	1.0	DCE	100	39^c
3	K_2CO_3	1.0	THF	100	40
4	K_2CO_3	1.0	Toluene	100	51
5	K_2CO_3	1.0	DMF	100	70
6	K_2CO_3	1.0	DMSO	100	68
7	K_2CO_3	1.0	DMF	100	92
8	$NaHCO_3$	1.0	DMF	100	92
9	NaHCO ₃	1.0	DMF	100	86
10	NaOH	1.0	DMF	100	12
11	Et_3N	1.0	DMF	100	11
12	ⁱ Pr ₂ NH	1.0	DMF	100	11
13	DBU	1.0	DMF	100	58
14	DABCO	1.0	DMF	100	$96^d (90^e)$
15	DMAP	1.0	DMF	100	95

 a Unless otherwise specified, all reactions were performed with 1a (0.20 mmol), 2a (0.20 mmol) and additive (0.20 mmol). b Yields are determined by 1 H NMR using trimethoxybenzene as an internal standard. c HNBn $_2$ was obtained in 25% yield. d TsNBn $_2$ was obtained in 91% yield. e Isolated yield.

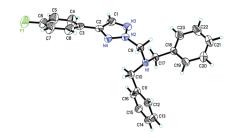
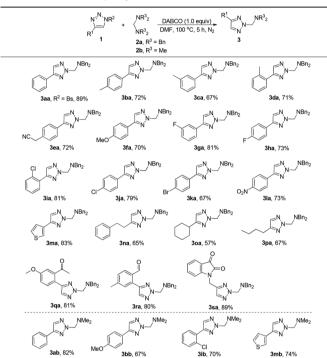


Fig. 1 The ORTEP drawing of 3ha.

Table 2 Reaction scope: synthesis of triazoles 3 from substrates 1^a



 a Conditions: 1 (0.20 mmol), 2 (0.20 mmol) and DABCO (0.20 mmol) were heated in DMF (2.0 ml) at 100 $^{\circ}{\rm C}$ for 5 h.

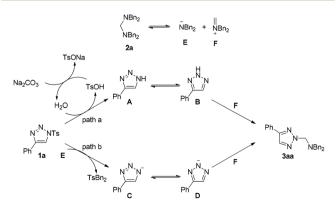
ring may be more conducive to the formation of 3 compared to those of electron-donating ones. When the benzene ring was replaced by the thiophene ring, product 3ma could also be afforded in good yield. The reaction could also tolerate various triazoles with aliphatic substituents, indicating a broad substrate scope, and giving the desired products 3na, 3oa and 3pa in moderate yields. Furthermore, the substrates bearing functional groups such as a carbonyl group could also afford the corresponding products 3qa, 3ra and 3sa in good yields. When the triazole was protected by the Bs group (4-bromophenylsulfonyl), the reaction also proceeded efficiently, giving the corresponding product 3aa in 89% yield. Finally, tetramethylmethanediamine 2b was also used in this reaction, affording the desired products 3ab, 3bb, 3ib and 3mb in 67–82% yields.

The next experiments mainly focused on the investigation of the mechanism of this reaction. The different by-products

Scheme 3 Control experiments.

of the reaction with different additives caught our attention (Table 1, entries 2 and 14). As shown in Scheme 3, several control experiments were performed. If DABCO was used as the additive, the corresponding TsNBn₂ was obtained in 91% yield along with the product 3aa in 90% yield (Scheme 3a). However, if Na₂CO₃ was used, HNBn₂ was obtained in 81% yield instead of TsNBn₂ (Scheme 3b). To eliminate the possibility that HNBn2 is derived from the decomposition of TsNBn2, another control experiment was also performed. 0.5 equiv. of TsNBn₂ was added to the Na₂CO₃-induced reaction, and it could be recovered in 94% yield after 5 h, suggesting that HNBn₂ is not derived from TsNBn₂ (Scheme 3c).

Based on the above results, two possible reaction pathways using substrates 1a and 2a as models are outlined in Scheme 4. As for substrate 2a, it will decompose to give intermediates E and F. When Na₂CO₃ is used as an additive, substrate 1a will decompose to form intermediate A in the presence of a trace amount of H2O in the solvent. TsOH is obtained at the same time, which can be neutralized by Na₂CO₃ to deliver H₂O again. Intermediate A can be converted into its resonance B, which can react with intermediate F to give the product 3aa (path a). If DABCO is used as an additive, substrate 1a reacts with E to give intermediate C and TsNBn₂. Intermediate D, derived from C, can also react with F to give the product 3aa (path b).



Scheme 4 Plausible reaction mechanisms.

Table 3 Reaction scope: synthesis of triazoles 3 from substrates 4^a

^a Conditions: 4 (0.20 mmol) and 2 (0.20 mmol) were heated in DMF (2.0 ml) at 100 °C for 5 h.

The investigations on the reaction mechanism suggested that the in situ generated 4-phenyl-1H-1,2,3-triazole could also react with 2a to give a similar product. As we expected, substrate 4a can react with 2a smoothly even in the absence of DABCO to give the product 3aa in 92% yield. This result also suggested that intermediate B is more stable than A. For substrates with electron-donating or -withdrawing groups on the aromatic ring, the reaction proceeded efficiently to give the desired products 3ba, 3ca and 3ga in 65%, 80% and 75% yields, respectively. Meanwhile, for the triazole with an aliphatic substituent, the corresponding product 3na was formed in 65% yield. In addition, in the case of thiophene-tethered triazole 4m, the reaction also proceeded smoothly to afford the desired product 3ma in 75% yield (Table 3).

In summary, a new base-induced reaction mode of N-sulfonyl-1,2,3-triazoles has been established, thereby providing a simple procedure for preparation of triazoles bearing dialkylaminomethyl groups. In this reaction, a wide range of substrates can tolerate this reaction. Moreover, 4-phenyl-1H-1,2,3triazoles can also give the same product even in the absence of a base. The potential applications and extension of the substrate scope of this novel synthetic methodology are currently underway in our laboratory.

Acknowledgements

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