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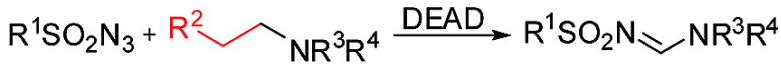

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An Unexpected Diethyl Azodicarboxylate-Promoted Dehydrogenation of Tertiaryamine and Tandem Reaction with Sulfonyl Azide

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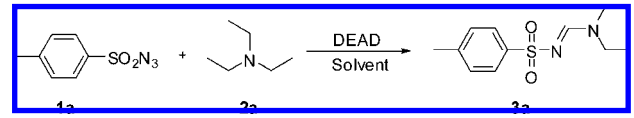
Construction of complex molecules via convenient methods is highly required due to modern environmental concerns. The methodology of cross dehydrogenative coupling could be well-fitted for this criterion.[1,2] Thereinto, activation of the hydrogen located at the α-position of the nitrogen atom represents an efficient method.[2] This may be due to the nitrogen atom not only activating the adjacent sp^3 C−H bond but also stabilizing the in situ formed intermediates. However, simultaneous activation or elimination of both the α and *β* hydrogens of a nitrogen atom remains a challenge.[3]

Amidine derivatives are structurally unique and possess a variety of interesting chemical properties. Accordingly, they have been widely used in medicinal and synthetic chemistry.[4] Also, substituted amidines are useful intermediates for the synthesis of a variety of heterocyclic compounds and metal complexes.[5] Traditional syntheses of amidines rely basically on the functional group transformation from such precursors as thioamides, isonitriles, and aldoximes.[6] With the requirement of more efficient synthesis of sulfonyl amidine derivatives, Chang recently reported tandem reactions of sulfonyl azides, alkynes, and secondary amines either intermolecularly or intramolecularly.[7] Herein we wish to report a very simple and efficient synthesis of sulfonyl amidines via a novel reaction, where diethyl azodicarboxylate[8] (DEAD)-activated elimination of both the α- and *β*-hydrogens of tertiary amine afforded enamine, followed by a tandem 1,3-dipolar addition reaction with sulfonyl azide (*Caution: Azides and diazoalkanes may be hazardous and/or explosive*).

With the interest of synthesizing potentially bioactive nitrogen-containing compounds,[9] we have focused on the application of sulfonyl azides. Recently, we reported the MCRs of sulfonyl azides, terminal alkynes, and carbodiimides catalyzed by copper.[9a] As a extension, a three-component reaction of *p*-toluenesulfonyl azide, phenylacetylene, and DEAD catalyzed by CuI in the presence of triethylamine was further conducted. However, sulfonyl amidine **3a** as a major product was unexpectedly isolated in 15% yield. This prompted us to undertake further investigation so as to elucidate the source for the formation of **3a**, and it was finally found that the reaction of *p*-toluenesulfonyl azide, triethylamine, and DEAD in CH_3CN could afford **3a** in 32% yield (Table 1, entry 1), indicating that CuI and phenylacetylene did not participate in the reaction. A literature survey found that DEAD could form a 1:1 adduct with *N*,*N*-dimethyl aniline, which involved reaction of the α-hydrogen adjacent to the nitrogen atom of *N*,*N*-dimethyl aniline.[10] Huisgen later proposed an alternative mechanism where the key step was a zwitterionic intermediate.[11] Combined with the literature findings[12] and aforementioned experimental results, we envisioned it is probable that enamine may be formed in this system. Correspondingly, a tentative mechanism was proposed in Scheme 1. First, triethylamine underwent nucleophilic addition to DEAD and forms a

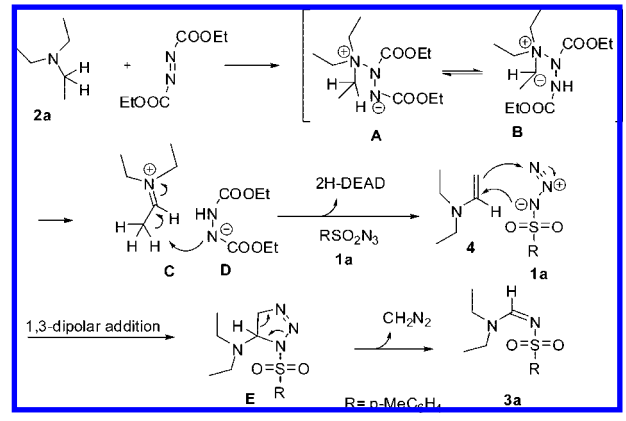
Table 1. DEAD Promoted Synthesis of **3a**[a]



entry	solvent	time (h)	yield (%)[b]
1	CH_3CN	6	32[c]
2	DMSO	2	11
3	DMF	4	25
4	hexane	6	29
5	CH_3NO_2	4	21
6	CH_2Cl_2	4	47
7	$ClCH_2CH_2Cl$	4	49
8	toluene	4	56
9	THF	4	62
10	1,4-dioxane	4	68
11[d]	1,4-dioxane	5	76

[a] *p*-Toluenesulfonyl azide (1 mmol), triethylamine (1 mmol), DEAD (1 mmol) in solvent (3 mL) under ambient temperature unless otherwise specified. [b] Isolated yields. [c] 2H-DEAD was isolated in 87% yield. [d] Reaction temperature: 10−15 °C for 1 h, then ambient temperature for 4 h.

Scheme 1. Proposed Mechanism



1:1 adduct **A**, which can be in equilibrium with **B** by undergoing an intramolecular hydrogen transfer. The adduct finally cleaves to form an ion pair consisting of imine cation **C** and 1H-DEAD **D**. The nitrogen anion of **D** further abstracts the *β*-hydrogen of the nitrogen atom of triethylamine to generate enamine **4** with itself being transformed into 2H-DEAD. Enamine **4** reacts with **1a** through 1,3-dipolar addition and produces triazoline **E**, which is unstable and releases one molecule of CH_2N_2 to afford product **3a**. The mechanism was subsequently supported by successful capture of enamine **4** and CH_2N_2 using chalcone and benzoic acid as the respective capturing reagent (see Supporting Information (SI)).

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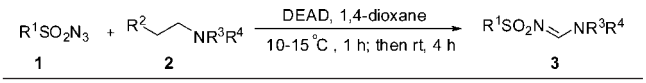
Table 2. DEAD Promoted Synthesis of Sulfonyl Amidines[a]



1 2 3

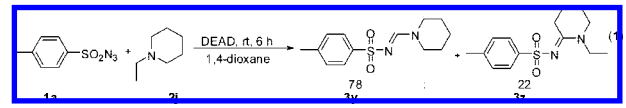
entry	R^1	R^2; R^3; R^4	yield (%)[b]
1	4-$CH_3C_6H_4$ (**1a**)	H; Et; Et (**2a**)	**3a**; 76
2	2,4,6-$(CH_3)_3C_6H_2$ (**1b**)	H; Et; Et (**2a**)	**3b**; 71
3	Ph (**1c**)	H; Et; Et (**2a**)	**3c**; 64
4	2-phthanyl (**1d**)	H; Et; Et (**2a**)	**3d**; 73
5	2-$MeOOCC_6H_4$ (**1e**)	H; Et; Et (**2a**)	**3e**; 72
6	4-$Pr^iC_6H_4$ (**1f**)	H; Et; Et (**2a**)	**3f**; 73
7	4-ClC_6H_4 (**1g**)	H; Et; Et (**2a**)	**3g**; 71
8	4-$CH_3OC_6H_4$ (**1h**)	H; Et; Et (**2a**)	**3h**; 66
9	3-$NO_2C_6H_4$ (**1i**)	H; Et; Et (**2a**)	**3i**; 65
10	2-thienyl (**1j**)	H; Et; Et (**2a**)	**3j**; 62
11	4-$CH_3C_6H_4CH_2$ (**1k**)	H; Et; Et (**2a**)	**3k**; 78
12	$CH_3(CH_2)_3$ (**1l**)	H; Et; Et (**2a**)	**3l**; 91
13[c]	**1a**	H; Me; Me (**2b**)	**3m**;46
14	**1a**	Et; Bu; Bu (**2c**)	**3n**; 74
15	**1a**	Bu; Hexyl; Hexyl (**2d**)	**3o**; 63
16	**1a**	H; Et; *c*-Hexyl (**2e**)	**3p**; 57
17[d]	**1a**	H; Et; Ph (**2f**)	**3q**; 51
18[d]	**1a**	H; Et; 3-MeC_6H_4 (**2g**)	**3r**; 21
19[d]	**1a**	H; Ph; Bn (**2h**)	**3s**; 34
20[e]	**1a**	H; morpholine (**2i**)	**3t**; 82
21[e]	**1d**	H; morpholine (**2i**)	**3u**; 79
22[e]	**1i**	H; morpholine (**2i**)	**3v**; 75
23[f]	$(PhO)_2PON_3$	H; Et; Et (**2a**)	**3w**;42
24[f]	$PhCH_2OCON_3$	H; Et; Et (**2a**)	**3x**; 15

[a] Standard conditions: sulfonyl azide (1 mmol), amine (1 mmol), DEAD (1 mmol), 1,4-dioxane (3 mL), 10−15 °C for 1 h, then room temperature for 4 h unless otherwise noted. [b] Isolated yields. [c] DEAD (1.5 mmol), **2b** (2.2 mmol). [d] Neat, DEAD (3 mmol), 75 °C, 6 h. [e] DEAD (2 mmol), **2e** (2 mmol), 75 °C, 2 h. [f] DEAD (3 mmol), 2**a** (3 mmol).

In light of the conciseness of the reaction to produce sulfonyl amidine, the conditions were then optimized to make the reaction synthetically valuable. Several solvents were screened besides CH_3CN (Table 1). As could be summarized, the use of DMSO, DMF, hexane, and CH_3NO_2 did not produce any improvement (Table 1, entries 2−5), and only a slight increase in yields was observed when the reaction was carried out in CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, or THF (Table 1, entries 6−9). Finally, it was found that a higher yield (76%) could result from lowering the reaction temperature (Table 1, entry 11).

Under the optimized conditions, a wide range of tertiary amines and sulfonyl azides were successfully coupled and the corresponding *N*-sulfonylamidines were obtained in good to excellent yields (Table 2). In the cases where the tertiary amines **2a, 2b**, and **2e**−**2i** were used, only one kind of enamine could be formed respectively from the elimination of two hydrogen atoms, which coupled with sulfonyl azide each to give a sole kind of *N*-sulfonylamidine with release of diazomethane.[12] The morpholine ring remained unaffected in this system (Table 2, entries 20−22). In the case of tri-*n*-butylamine and tri-*n*-hexylamine, there should be one molecule of diazopropane or diazopentane (see SI) being released (Table 2, entries 14−15).[13] As far as the sulfonyl azides were concerned, a number of structural varieties of sulfonyl azides were successfully used in this coupling reaction. From the results, electronic effects and the positions of substitutents did not appear to exert much appreciable influence on the efficiency. 2-Thienylsulfonyl azide also served as a good partner (Table 2, entry 10). It should be noted that several functional groups such as methoxycarbonyl, methoxy, halo, and nitro could be well tolerated (Table 2, entries 5, 7−9). Moreover, the *p*-methylbenzylsulfonyl and alkyl substituted sulfonyl azide also participated in this reaction readily, and the desired products were obtained smoothly (Table 2, entries 11−12). It is worth mentioning that diphenylphosphoryl azide and benzyloxycarbonyl azide could be successfully used in this reaction system (Table 2, entries 23−24). Unfortunately, use of benzoyl azide as the substrate failed.

In the case of *N*-ethylpiperidine, it was found that the major product was **3y**, which indicated that it was more difficult for the cyclic hydrogens to be eliminated and the steric effect may account for the observation (eq 1). The ratio **3y/3z** is ∼78:22 in 65% overall yield. Product **3z** may be formed by hydrogen migration accompanied by one molecule of nitrogen being released after the 1,3-dipolar addition.



In conclusion, an efficient DEAD-promoted dehydrogenation of tertiary amine to afford enamine and subsequent tandem reaction with sulfonyl azide are successfully established, notably without the assistance of metal. The reaction described here is mild, general, and efficient, thus providing an extremely preferable method for synthesis of a variety of *N*-sulfonyl amidine derivatives.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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