Diazo Compounds

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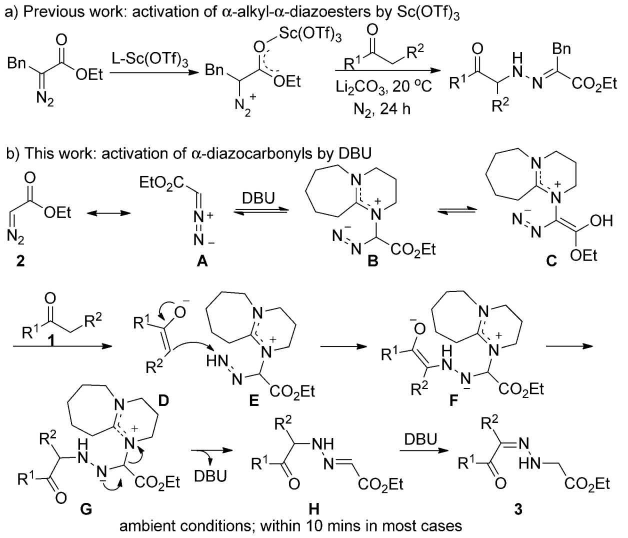
Activation of α-Diazocarbonyls by Organic Catalysts: Diazo Group Acting as a Strong N-Terminal Electrophile

Lei Li, Jia-Jia Chen, Yi-Jin Li, Xiu-Bin Bu, Qun Liu, and Yu-Long Zhao**

Abstract: *For the first time α-diazocarbonyls have been used as highly active N-terminal electrophiles in the presence of bicyclic amidine catalysts. The C–N bond-forming reactions of active methylene compounds as C nucleophiles with α-diazocarbonyls as N-terminal electrophiles proceed quickly under ambient conditions, in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), because of the formation of the reactive N-terminal electrophilic intermediates. DBU activates both the active methylene and α-diazocarbonyl. Importantly, this reaction is general for both active methylenes and α-diazocarbonyls, and the activation mode will lead to new synthetic applications of α-diazocarbonyls.*

α-Diazocarbonyls have been known since 1883 for the synthesis of ethyl diazoacetate (EDA), as reported by Curtius, and have attracted increasing interest because of their versatility.[1] These compounds have been extensively studied as metal carbene precursors,[2] 1,3-dipoles,[3] and C nucleophiles.[4] However, the utility of the electrophilic capability of their terminal nitrogen atom has rarely been studied, save for a few reports on the use of highly reactive organolithium, Grignard reagents, or acyl anion equivalents as C nucleophiles,[5] and NaH-mediated 1,3-aminoalkylation of α-amino-α-diazoesters to afford tetrasubstituted 1,2,3-triazolines, thus involving an intramolecular amination as the key step.[6]

In general, the terminal nitrogen atom of α-diazocarbonyls is much less electrophilic than the neighboring nitrogen atom.[4–7] Thus, the intermolecular nucleophilic attack on the terminal nitrogen atom of α-diazocarbonyls, by active methylenes such as C nucleophiles, is unfavored. Recently, Feng and co-workers developed an efficient C–N bond-forming reaction, namely, the α-functionalization of ketones, catalyzed by a *N,N′*-dioxide scandium complex, but the reaction is limited to α-alkyl-α-diazoesters.[7] Theoretical calculations at the B3LYP/6-31G* level of theory indicate that the carbonyl oxygen atom of ethyl α-alkyl-α-diazoester coordinates to the strong Lewis acid, $Sc(OTf)_3$, and enables the positive charge on the terminal nitrogen atom to increase greatly (Scheme 1a).[7] Herein, we report the first C–N bond-forming reaction of active methylenes, as the C nucleophiles, with various α-diazocarbonyls as N-terminal electrophiles by using DBU as a catalyst (Scheme 1b).[8,9] In the presence of either DBU or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), the terminal nitrogen atom of an α-diazocarbonyl turns out to be highly electrophilic, and the C–N bond-forming reactions can proceed quickly under ambient conditions.



Scheme 1. Activation modes of α-diazocarbonyls as N-terminal electrophiles. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tf = trifluoromethanesulfonyl.

As part of our research on carbon–carbon and carbon–heteroatom bond-forming reactions,[9,10] we recently developed an efficient α-C–H functionalization reaction of α-amino carbonyls for C–C bond formation through a base-promoted intramolecular cross-dehydrogenative coupling (CDC).[11] These results and our interests in the synthetic applications of diazo compounds[12] prompted us to investigate the reactions of α-amino ketones with α-diazocarbonyls. Unexpectedly, the model reaction of the *N*-aryl α′-amino-α,β-unsaturated ketone **1a**[11] with EDA (**2a**), catalyzed by DBU (50 mol%), proceeded very rapidly at room temperature to give ethyl 2-{(*Z*)-2-[(*E*)-4-(4-chlorophenyl)-2-oxo-1-(*p*-tolylamino)but-3-en-1-ylidene]hydrazinyl}acetate (**3a**) in high yield, thus leaving the cinnamoyl moiety of **1a** intact (Table 1, entry 3).[13] Further increase in the amount of DBU did not improve the yield of **3a** (entries 4 and 5). 1,5-DBN was also an efficient catalyst, but afforded **3a** in a lower yield (entry 6), and other bases, such as 1,4-diazabicyclo-[2.2.2]octane (DABCO), triethylamine, NaOH, and Cs_2CO_3 were entirely ineffective (entries 7–10). Among the solvents tested, DMF seemed to be the best choice. A similar result was obtained using DMSO as the solvent (entry 11). Other

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[*] L. Li, J.-J. Chen, Y.-J. Li, X.-B. Bu, Q. Liu, Y.-L. Zhao
Department of Chemistry, Northeast Normal University
Changchun, 130024 (P.R. China)
E-mail: liuqun@nenu.edu.cn
zhaoyl351@nenu.edu.cn

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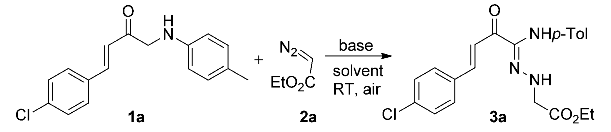
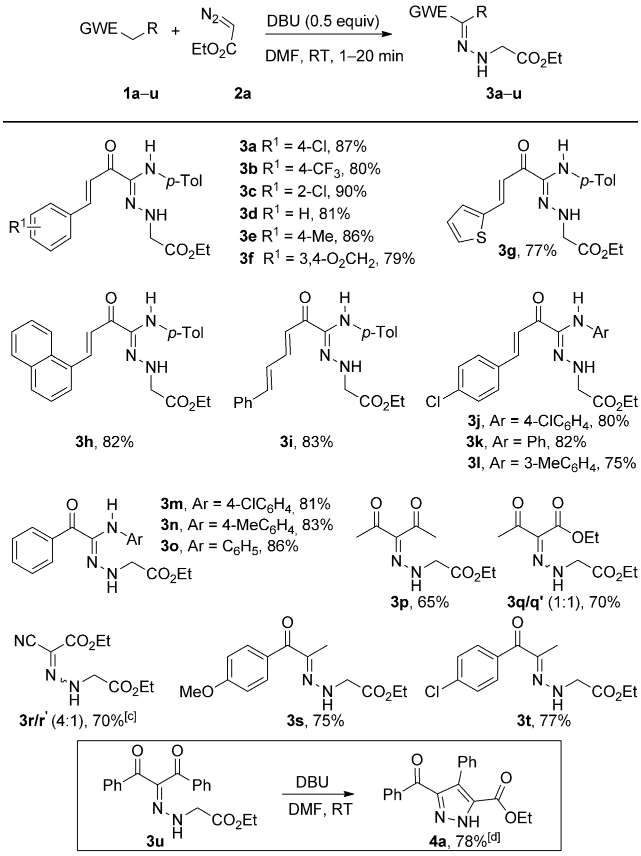
Table 1: Optimization of the reaction conditions.[a]



Entry	Base [equiv]	Solvent	*t* [min]	Yield [%][b]
1	DBU (0.2)	DMF	3	38
2	DBU (0.4)	DMF	1	70
3	DBU (0.5)	DMF	1	86
4	DBU (0.6)	DMF	1	85
5	DBU (1.0)	DMF	1	85
6	DBN (0.5)	DMF	1	65
7	DABCO (0.5)	DMF	30	–
8	Et_3N (0.5)	DMF	30	–
9	NaOH (0.5)	DMF	20	–
10	Cs_2CO_3 (0.5)	DMF	10	–
11	DBU (0.5)	DMSO	1	80
12	DBU (0.5)	MeCN	20	67
13	DBU (0.5)	THF	6	32
14	DBU (0.5)	DCE	4	37
15	DBU (0.5)	EtOH	30	–

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), and solvent (2.0 mL) at RT and open air. [b] Yield of isolated product. DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

Table 2: DBU-catalyzed nucleophilic addition of active methylenes to EDA.[a,b]



3a R^1 = 4-Cl, 87%
3b R^1 = 4-CF_3, 80%
3c R^1 = 2-Cl, 90%
3d R^1 = H, 81%
3e R^1 = 4-Me, 86%
3f R^1 = 3,4-O_2CH_2, 79%
3g, 77%
3h, 82%
3i, 83%
3j, Ar = 4-ClC_6H_4, 80%
3k, Ar = Ph, 82%
3l, Ar = 3-MeC_6H_4, 75%
3m, Ar = 4-ClC_6H_4, 81%
3n, Ar = 4-MeC_6H_4, 83%
3o, Ar = C_6H_5, 86%
3p, 65%
3q/q' (1:1), 70%
3r/r' (4:1), 70%[c]
3s, 75%
3t, 77%
3u
4a, 78%[d]

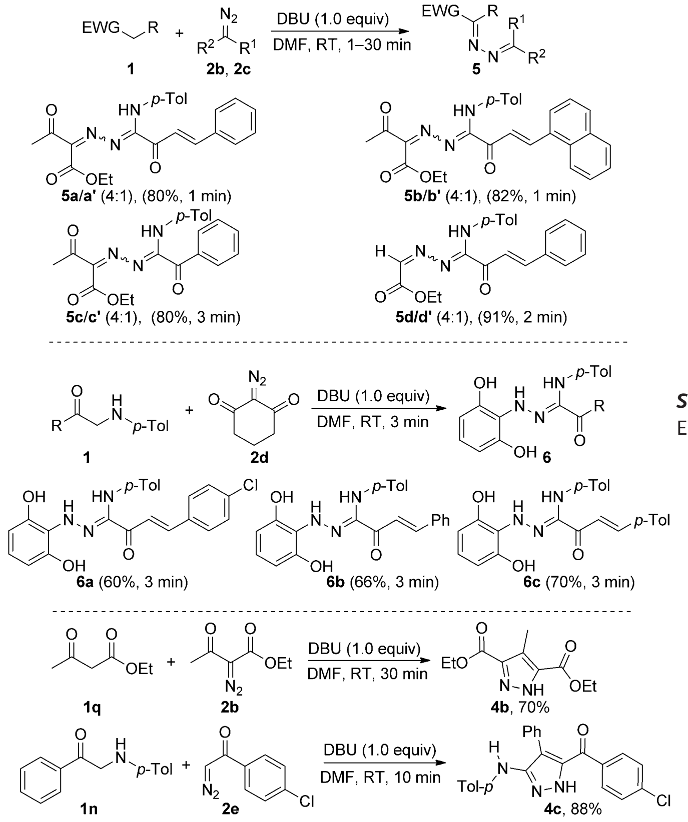
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), DBU (0.1 mmol), and DMF (2.0 mL) at RT for 1–20 min. [b] Yield of isolated product. [c] The reaction was performed at RT for 2 h. [d] The reaction was performed at RT for 5 h.

solvents, such as acetonitrile, THF, and 1,2-dichloroethane (DCE) gave lower yields (entries 12–14), and **3a** was not observed (TLC analysis) when using ethanol as the solvent (entry 15). This above C–N bond-forming reaction is highly chemoselective and catalyst dependent (Table 1). To our knowledge, the reaction of **1a** with **2a** to form **3a** represents the first intermolecular nucleophilic addition with α-diazocarbonyls as N-terminal electrophiles catalyzed by bicyclic amidines.[1–8]

Under the optimal reaction conditions (Table 1, entry 3), the scope and generality of the reactions for active methylenes were examined and the results are summarized in Table 2. The reaction showed broad tolerance for various substituents (**1a–u**). All of selected *N*-aryl α′-amino-α,β-unsaturated ketones (**1a–l**) bearing phenyl, electron-deficient and electron-rich aryl, heteroaryl, 1-naphthyl, and (*E*)-phenylvinyl groups at the β-position of the enone moiety reacted smoothly with **2a** to give the desired (1*Z*,3*E*)-2-oxo-*N*,4-diarylbut-3-enehydrazonamides **3a–l** in high to excellent yields within 1–2 minutes. In contrast, the N-aryl groups of **1a–l** can be either electron-deficient or electron-rich. Similarly, the (*Z*)-2-oxo-*N*,2-diarylacetohydrazonamides **3m–o** were prepared in high yields under identical reaction conditions (7–8 min) for the reactions of **2a** with the α-amino ketones **1m–o** bearing various N-aryl groups.

In addition, it was proved that the desired products, ethyl 2-[2-(2,4-dioxopentan-3-ylidene)hydrazinyl]acetate (**3p**), (*E*)- and (*Z*)-ethyl 2-[2-(2-ethoxy-2-oxoethyl)hydrazono]-3-oxobutanoates (**3q/q′**), (*Z*)- and (*E*)-ethyl 2-cyano-2-[2-(2-ethoxy-2-oxoethyl)hydrazono]acetates (**3r′/r**), (*E*)-ethyl 2-{2-[1-(4-methoxyphenyl)-1-oxopropan-2-ylidene]hydrazinyl}acetate (**3s**), and (*E*)-ethyl 2-{2-[1-(4-chlorophenyl)-1-oxopropan-2-ylidene]hydrazinyl}acetate (**3t**) can also be obtained in high yields, from reactions of **2a** with selected active methylenes (Table 2). For the reaction of ethyl 2-cyanoacetate (**1r**) with **2a** to give **3r′/r**, a longer reaction time was required. Under identical reaction conditions, the reaction of **2a** with 1,3-diphenylpropane-1,3-dione (**1u**) gives ethyl 3-benzoyl-4-phenyl-1*H*-pyrazole-5-carboxylate (**4a**) in 78% yield by intramolecular condensation of **3u** after a prolonged reaction time. Clearly, the formation of **4a** provides a new and efficient approach to functionalized 1*H*-pyrazole derivatives by using **2a** as a 1,3-N,C dipole.

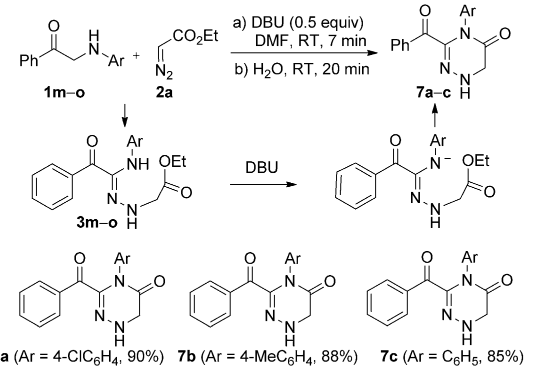
Besides the results demonstrating the generality of the active methylenes in their reactions with **2a** as the N-terminal electrophile, a series of α-diazocarbonyls were examined (Scheme 2). Catalyzed by DBU, the reaction of the active methylene compound **1d** with ethyl 2-diazo-3-oxobutanoate (**2b**) proceeded rapidly under ambient conditions within 1 minute to afford the corresponding addition-aerobic oxidation products (with molecular oxygen as the oxidant) **5a/a′** in 50% yield.[12] When 1.0 equivalent of DBU was used, **5a/a′** were obtained in 80% yield with (*Z*)-ethyl 2-{(*Z*)-[(*E*)-4-(4-chlorophenyl)-2-oxo-1-(*p*-tolylamino)but-3-en-1-ylidene]-hydrazono}-3-oxobutanoate (**5a**) as the major isomer. Under the optimized reaction conditions, **5b/b′** and **5c/c′** were prepared in high yields from the reaction of **2b** with the



Scheme 2. DBU-catalyzed reactions of the α-diazocarbonyls **2b-e**.[a,b] [a] Reaction conditions: **1** (0.2 mmol), α-diazocarbonyls **2b-e** (0.24 mmol), DBU (0.2 mmol), and DMF (2.0 mL) at RT and open to air for 1–30 min. [b] Yield of the isolated products.

corresponding active methylenes.[14] When ethyl 2-diazo-2-(phenylsulfonyl)acetate (**2c**) was used as the N-terminal electrophile, (*E*)- and (*Z*)-ethyl 2-{(*E*)-[(*E*)-4-(4-chlorophenyl)-2-oxo-1-(*p*-tolylamino)but-3-en-1-ylidene)]hydrazono} acetates (**5d/d′**) were produced in excellent overall yield by an addition/aerobic oxidation/dephenylsulfonylation sequence. In addition, in the case of 2-diazocyclohexane-1,3-dione (**2d**) as the N-terminal electrophile, the addition/oxidation/aromatization products **6a–c** were obtained in high yields. In the case of the reaction of **1q** with **2b**, the addition/deacetylation/intramolecular condensation product **4b** was produced in 70% yield (also see the synthesis of **4a** in Table 2). Similarly, when 1-(4-chlorophenyl)-2-diazoethanone (**2e**) was used as the N-terminal electrophile, the addition-cyclization reaction also proceeded well to give (4-chlorophenyl)[4-phenyl-3-(*p*-tolylamino)-1*H*-pyrazol-5-yl]methanone (**4c**) in 88% yield.

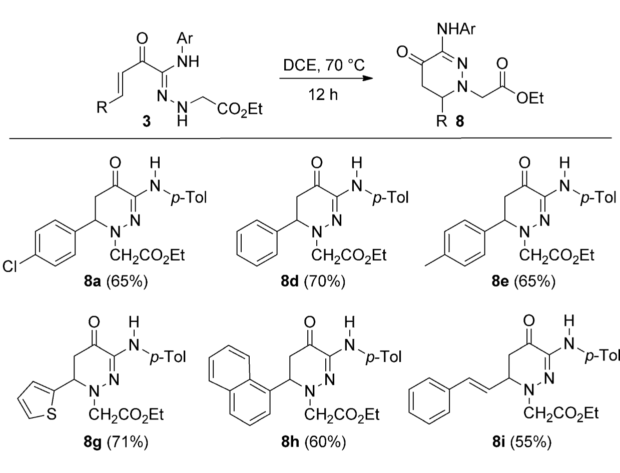
Interestingly, when the reactions of the α-amino carbonyls **1m–o** with **2a** were performed under identical reaction conditions, and the reaction mixture quenched with water, the 1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **7a–c** were obtained in high yields (Scheme 3). The formation of **7a–c** may proceed via **3m–o** followed by intramolecular amidation. This [4+2] annulation reaction with diazoacetates as 1,4-N,C dielectrophiles provides a new reactivity mode for α-diazoestes and a concise access to 1,2,4-triazinones in a single operation under mild reaction conditions.[15]



Scheme 3. Synthesis of 1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (**7**). EWG = electron-withdrawing group.

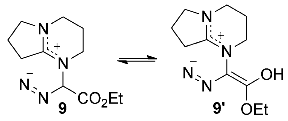
To explore the synthetic potential of the products **3**, the cyclizations of **3a**, **3d**, **3e**, and **3g–i** were examined (Scheme 4). As a result, the cyclization of **3a** proceeded smoothly, in DCE at 70°C, by an isomerization/intramolecular aza-Michael sequence to give 3-(*p*-tolyamino)-5,6-dihydropyridazin-4(1*H*)-one (**8a**) in 65% yield after 12 hours. Similarly, the *N*-aryl 3-amino-5,6-dihydropyridazinone derivatives **8d**, **8e**, and **8g–i** were also obtained in good to high yields.[16]

To understand the mechanisms for the formation of **3**, control experiments were carried out. The product **3n** was produced in 80% yield when the reaction of **1n** with **2a** was carried out under a nitrogen atmosphere. In comparison, no reaction was observed by treating (*E*)-1-phenyl-2-(*p*-tolylimino)ethanone with **2a** under identical reaction conditions. These results indicate that (*E*)-1-phenyl-2-(*p*-tolylimino)ethanone, which could be formed by aerobic oxidation of **1n** in the presence of a base, is not involved for the formation of **3n**. Furthermore, the ^{1}H NMR studies of the reaction of α-diazocarbonyls with a series of bases were conducted to gain information for the formation of **3**. Testing the mixture of **2a** with either DBU, DBN, DABCO, or triethylamine (TEA) at room temperature showed that: 1) the mixture of **2a** with TEA or DABCO gave nothing



Scheme 4. Synthesis of N-aryl 3-amino-5,6-dihydropyridazinones (**8**).

but their separate signals on the spectrum (see the Supporting Information), 2) the mixture of **2a** with DBU led to a quick reaction (within 1 min) to afford two new species, and 3) similar result was observed from a mixture of **2a** with DBN (see Figure S1).[17] Based on the above experimental results (Table 2) and related reports,[5–7] a possible mechanism for the formation of **3** is proposed (Scheme 1b). At first, as the crucial step, the key intermediates **B** and **C**, which are in equilibrium, may be formed through a nucleophilic attack of DBU (or DBN, see Scheme 5) as the nucleophile[8] at the α-carbon atom of **2a** which is activated by an amidine.



Scheme 5. Activated intermediates **9**/**9′**.

In the ^{1}H NMR spectrum of the intermediates (Scheme 1), all signals for the intermediates **9**/**9′** shifted to lower field compared to those of either **2a** or DBN (Scheme 5), thus suggesting that both the **2a** and DBN units become more electron-poor than the isolated molecules. Because the tethered quaternary ammonium unit is a strong electron-withdrawing group, the terminal nitrogen atom of **9**/**9′** should be highly electrophilic and thus initiate the C–N bond-formation reaction in a highly chemoselective manner, even under very mild reaction conditions. In comparison, although DABCO is more nucleophilic than the bicyclic amidines DBU and DBN,[8,18] DABCO is ineffective because of its larger steric hindrance, which may inhibit the formation of intermediates like **9**/**9′**.

In conclusion, an efficient C–N bond-forming reaction between active methylene compounds as C nucleophiles and α-diazocarbonyls as N-terminal electrophiles has been developed. This reaction is highly chemoselective and can proceed under mild ambient conditions. This C–N bond-forming reaction is general for both active methylenes and α-diazocarbonyls. Importantly, this research provides a new model for the activation of various α-diazocarbonyls, which makes the terminal nitrogen atom very reactive towards electrophiles. Further work will be focused on the synthetic applications arising from this new activation model.

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[13] CCDC 1060447 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[17] The observation of three groups of signals for **9**/**9′** at $\delta = 1.25$ (t, $J = 7.2$ Hz, 1.5 H) and $\delta = 1.29$ (t, $J = 7.2$ Hz, 1.5 H), $\delta = 4.17$ (q, $J = 7.2$ Hz, 1 H) and $\delta = 4.28$ (q, $J = 7.2$ Hz, 1 H), and $\delta = 5.06$ (t, broad, 1 H), can be assigned to the absorptions of the ethoxy and the acidic hydrogen atoms of the intermediates **9**/**9′**, respectively, and they result from the electron-withdrawing ammonium unit tethered to **2a**. One of the two species was observed by testing the mixture of **2a** and DBU without stirring (see the Supporting Information).

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