Rhodium-Catalyzed, Three-Component Reaction of Diazo Compounds with Amines and Azodicarboxylates

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Received: October 6, 2004; Accepted: January 10, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A novel, three-component C–N bond forming reaction is described. Reaction of diazo compounds with both azodicarboxylates and arylamines in the presence of dirhodium acetate catalyst gives good yields of the corresponding aminal with high selectivity and, in most cases, N–H insertion side products were suppressed. This is the first example of a C–N bond formation from the addition of ammonium ylides to azodicarboxylates.

Keywords: ammonium ylides; C–N bond formation; diazo compounds; dirhodium acetate; multi-component reaction

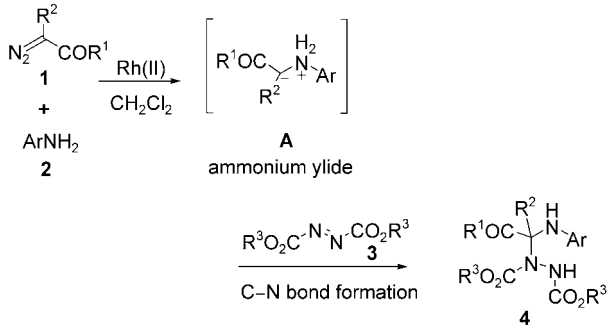
It is well known that metal-carbene complexes (or carbenoids) react with heteroatoms to form onium ylides. The chemisty of onium ylides is an area of continuing interest. For example, carbonyl, phosphorus, sulfur, oxonium and ammonium ylides, have been widely studied and utilized in organic synthesis.[1–4] In the study of ammonium ylides derived from metal carbenoids, [2,3]-sigmatropic[5] and [1,2]-Stevens[6] rearrangements have been shown to be powerful strategies for the synthesis of nitrogen heterocycles. In addition to rearrangement reactions, we have recently unveiled a novel C–C bond formation by nucleophilic addition of ammonium ylides to imines and arylaldehydes, whereby the ammonium ylides were *in situ* generated from phenyl diazoacetate and arylamines.[7]

Based on the mechanistic interpretation of the C–C bond formation, we anticipated that this novel strategy would be similarly applicable to other electrophiles and diazo compounds. Herein, we present the first example of a C–N bond formation reaction[8] of ammonium ylides with azodicarboxylates serving as electrophiles.

In addition to constructing complex chemical structures through selective multiple-bond formation[9] from a single synthetic step, the multi-component reaction also provides chances to explore new pathways. In this particular case, unsymmetrical aminals were formed by a novel three-component reaction comprising dirhodium acetate-catalyzed diazo decomposition of ethyl diazoacetate in the presence of an arylamine and an azodicarboxylate **3** (Scheme 1). We began exploration of the reaction by surveying the ability of different arylamines to react with ethyl diazoacetate and DEAD (diethyl azodicarboxylate). The three-components reaction proceeded smoothly to give aminal **4**. N–H insertion affording **5** was found to be a side reaction competing with the desired process. As shown in Table 1, the reaction gave almost entirely the C–N bond three-component products **4** in good isolated yields.

In general, the yield of **4** and the ratio of **4**/**5** were not affected by the substituent on the arylamines. In most cases (Table 1, entries a–d), good isolated yields of **4** were obtained, and N–H insertion [11] side products **5** were suppressed (**4**/**5** $>$ 99/1). But a significant amount of side product **5e** was formed when 2,4-dinitroaniline was used (Table 1, entry e). The structure of the C–N bond product **4b** was confirmed as an aminal by single crystal X-ray analysis[10] (Figure 1).

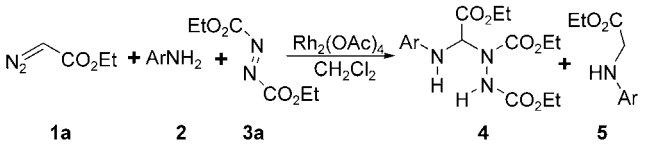
We further examined the scope of this process with different substitutions on the nitrogen atoms of azo compounds **3** (Table 2). EDA **1a** and aniline **2b** were em-



Scheme 1.

 DOI: 10.1002/adsc.200404306

Table 1. Three-component reaction of EDA (**1a**) with arylamine (**2**) and DEAD (**3a**) catalyzed by dirhodium acetate.[a]

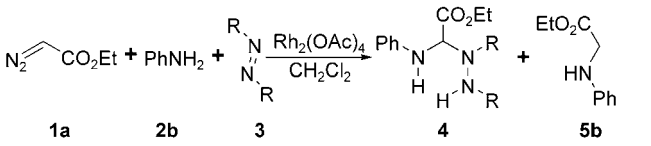


1a 2 3a 4 5

Entry	Ar	Yield [%][b] of Product **4a–e**	Ratio of **4**:**5**[c]
a	*p*-$OCH_3C_6H_4$ (**2a**)	61 (**4a**)	>99:1
b	C_6H_5 (**2b**)	75 (**4b**)	>99:1
c	*p*-ClC_6H_4 (**2c**)	72 (**4c**)	>99:1
d	*p*-$NO_2C_6H_4$ (**2d**)	68 (**4d**)	>99:1
e	2,4-$NO_2C_6H_4$ (**2e**)	60 (**4e**)	85:15

[a] Reaction conditions: to a refluxing CH_2Cl_2 mixture of arylamine (**2**, 1.1 equivs.), DEAD (**3a**, 1.1 equivs.) and $Rh_2(OAc)_4$ (0.01 equivs.) was added ethyl diazoacetate (**1a**, 1.0 equiv.) *via* a syringe pump over 1 h.
[b] Isolated yield of **4** after column chromatography purification.
[c] Determined by ^1H NMR of crude product.

Table 2. Effect of the nitrogen substitution of the electrophile on the three-component reaction.[a]



1a 2b 3 4 5b

Entry	R	Yield [%][b] of Product **4b**, **4f–g**	Ratio of **4**:**5b**[c]
a	CO_2Et (**3a**)	75 (**4b**)	>99:1
b	$CO_2CH(CH_3)_2$ (**3b**)	70 (**4f**)	>99:1
c	CO_2Bu-*t* (**3c**)	59 (**4g**)	>99:1
d	$C(CH_3)_2CN$ (**3d**)	–	0:100
e	Ph (**3e**)	–	0:100

[a] Reaction conditions: same as Table 1.
[b] Same as in Table 1.
[c] Same as in Table 1.

ployed to generate ammonium ylides, and 1 mol % $Rh_2(OAc)_4$ was used as the catalyst.

As shown in Table 2, the reaction proceeded well with azodicarboxylates (Table 2, entries a–c), but not with 2,2′-azobiisobutylnitrile (AIBN) (Table 2, entry d) and azobenzene (Table 2, entry e). The yields of C–N bond forming products gradually decreased when the more sterically hindered ester groups were attached to azodicarboxylates **3**, while still maintaining a high ratio of **4**/**5b** (Table 2, entries a–c). These results revealed that electron-withdrawing groups in **3** were critical for the success of the reaction. This is consistent with a proposed reaction pathway in which **4** is formed *via* a nucleophilic addition of the ammonium ylide to the azodicarboxylate, since a more electron-deficient azo compound **3** is a better electrophile.

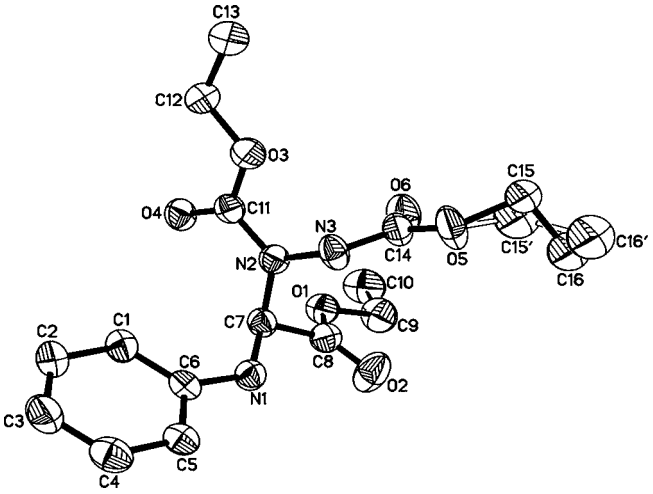
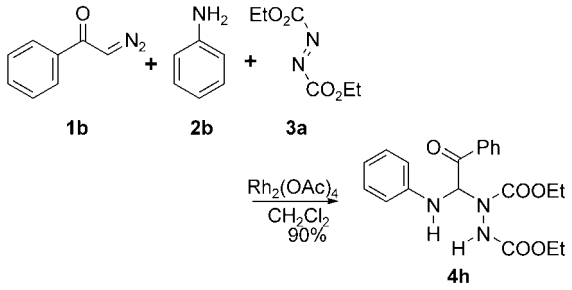
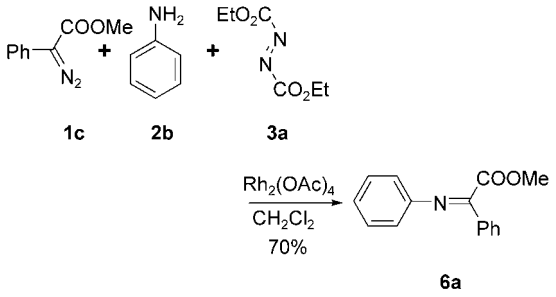


Figure 1. X-Ray structure of aminal **4b**.



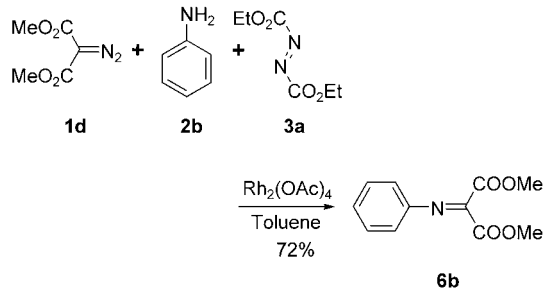
Scheme 2.



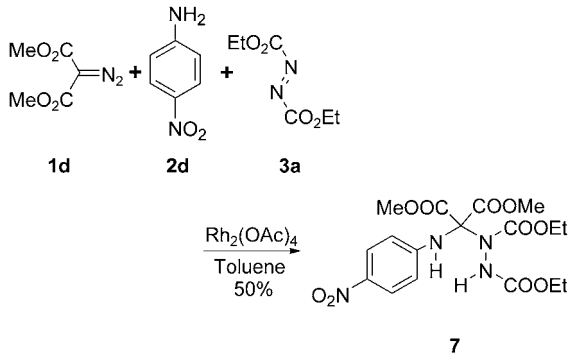
Scheme 3.

The reaction was further expanded to other α-diazo compounds. Reaction of 2-diazo-1-phenylethanone **1b**, aniline **2b** and DEAD **3a** in the presence of 1% $Rh_2(OAc)_4$ successfully afforded the desired C–N bond formation product **4h** in 90% yield after column chromatographic purification (Scheme 2).

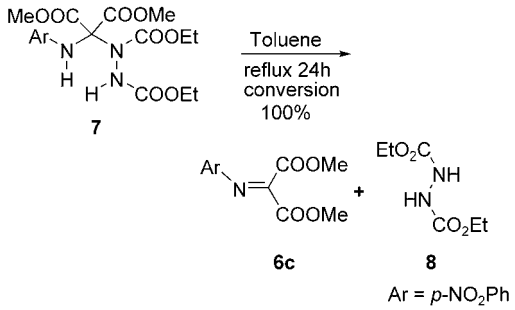
Interestingly, with methyl phenyldiazoacetate **1c**, a favorable diazo compound for the three-component C–C bond formation,[7] the reaction did not give the desired C–N bond product but the α-imino ester product **6a** instead (Scheme 3).



Scheme 4.



Scheme 5.



Scheme 6.

A similar reaction was observed with methyl diazomalonate. The reaction with aniline and DEAD generated the α-imino ester **6b** in 72% yield (Scheme 4).

However, the electronic features of the aniline **2** dramatically affected the reaction pathway. Treatment of diazomalonate **1d** and DEAD **3a** with more electronic deficient aniline, 4-nitroaniline **2d**, gave the desired C–N bond product **7** in 50% yield (Scheme 5).

Further investigations indicated that α-imino esters **6** were formed from a hydrazine elimination of the three-component products. Treatment of the three-component product **7** in refluxing toluene for 24 hours completely converted it to α-imino ester **6c** and hydrazine **8** (Scheme 6). This transformation was likely dependent on the stability of the aminal as well as the resulting imines. The stability was affected by the nature of diazo compounds as well as electronic features of the arylamines. Detailed investigations of this transformation will be reported in a separate publication.

In conclusion, we have unraveled a novel, three-component reaction for the preparation of aminals in good isolated yields whereby N–H insertion side products were suppressed. The aminal products may be used in the synthesis of densely functional α-hydrazino acid frameworks which represent an important class of compounds used for chemical modification of peptide backbones.[12]

Experimental Section

General Methods

Melting points are uncorrected. NMR spectra were recorded on a Bruker 300 MHz spectrometer. Mass spectra (EI) were recorded on a VG7070E spectrometer. Elemental analyses were performed on a Carlo Erba-1106 instrument. Dichloromethane was distilled over calcium hydride. Toluene was distilled over sodium benzophenone ketyl.

Ethyl [*N,N'*-Bis(ethoxycarbonyl)hydrazino]-phenylaminoacetate (4b)

To 10 mL of a CH_2Cl_2 solution of $Rh_2(OAc)_4$ (3.6 mg, 0.0081 mmol), aniline **2b** (82.8 mg, 0.89 mmol) and DEAD **3a** (154.8 mg, 0.89 mmol) was added ethyl diazoacetate **1a** (92.2 mg, 0.81 mmol) in 5 mL of CH_2Cl_2 under an argon atmosphere *via* a syringe pump over 1 h under reflux. After completion of the addition, the reaction mixture was cooled to room temperature. The solvent was removed and a portion of the crude mixture was subjected to ^{1}H NMR analysis for determination of the product ratio. The crude product was purified by flash chromatography on silica gel by using 10% EtOAc-light petroleum ether as eluent to give **4b** as a solid, yield: 75%. R_f = 0.35 (30% EtOAc/light petroleum); mp 97.8–98.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (m, 2H), 6.81 (m, 1H), 6.74 (m, 2H), 6.21 (br, 2H), 5.03 (s, 1H), 4.33 (m, 4H), 4.14 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 155.7 (two C=O carbons), 143.7, 129.6, 119.5, 113.9, 67.1, 63.2, 62.7, 62.4, 14.6, 14.4, 14.2; EI-MS (70 eV): *m/z* (rel. intensity) = 353 [M^+, 4], 280 [(M – COOEt)$^+$, 7], 178 [$C_{10}H_{12}NO_2^+$, 84], 104 [$C_7H_6N^+$, 100], 77 [$C_6H_5^+$, 89]; anal. calcd. for $C_{16}H_{23}N_3O_6$: C 54.38, H 6.56, N 11.89; found: C 54.34, H 6.57, N 11.88.

A single crystal **4b** was grown in hexane and ethyl acetate solution. Products **4a**–**4h**, **6a**, **6b** and **7** were obtained by the same procedure.

Dimethyl 2-(4-Nitrophenylimino)-malonate (6c)

A toluene solution (8.0 mL) of **7** (40 mg. 0.09 mmol) was refluxed for 24 h. The reaction mixture was cooled to room temperature. The solvent was removed, and a portion of the crude mixture was subjected to ^{1}H NMR analysis for determination of the conversion. The crude product was purified by flash

chromatography on silica gel by using 15% EtOAc-light petroleum ether as eluent to give **6c**; yield: 23.4 mg (0.088 mmol, 98%). $R_f = 0.53$ (30% EtOAc/light petroleum); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.24$ (m, 2H), 7.04 (m, 2H), 4.01 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.3$, 160.8, 153.4, 152.9, 146.1, 125.0, 119.5, 54.1, 53.2; EI-MS (70 eV): *m/z* (rel. intensity) = 266 [$(M+1)^+$, 267]; anal. calcd. for $C_{11}H_{10}N_2O_6$: C 49.63, H 3.79, N 10.52; found: C 50.01, H 3.95, N 10.40.

Acknowledgements

We are grateful for financial support from the Chinese Academy of Sciences and National Science Foundation of China (Grant No. 20202011). We thank Prof. Kaibei Yu of Chengdu Institute of Organic Chemistry for the X-ray measurements.

References and Notes

[1] For carbonyl ylides, see: a) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; b) M. P. Doyle, M. A. Mckervey,; T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley and Sons, New York, **1998**; c) C. D, Lu, Z. Y. Chen, H. Liu, W. H. Hu, A. Q. Mi, M, P. Doyle, *J. Org. Chem.* **2004**, *69*, 4856.

[2] For phosphonium ylides, see: a) B. E. Maryanoff, A. B. Retiz, *Chem. Rev.* **1989**, *89*, 863; b) V. K. Aggarwal, J. R. Fulton, C. G. Sheldon, J. D. Vicente, *J. Am. Chem. Soc*, **2003**, *125*, 6034.

[3] For sulfonium ylides, see: a) L. R. Reddy, H. J. Gais, C. W. Woo, G. Raabe, *J. Am. Chem. Soc*, **2002**, *124*, 10427; b) T. Mori, Y. Sawada, A. Oku, *J. Org. Chem*. **2000**, *65*, 3620; c) V. K. Aggarwal, J. Richardson, *Chem. Commun*. **2003**, 2644; d) V. K. Aggarwal, J. L. Vasse, *Org. Lett*. **2003**, *5*, 3987.

[4] For oxonium ylides, see: a) M. P. Pirrung, J. A. Werner, *J. Am. Chem. Soc.* **1986**, *108*, 6060; b) A. Padwa, S. F. Hornbuckle, G. E. Fryxell, P. D. Stull, *J. Org. Chem*. **1989**, *54*, 817; c) F. G. West, T. H. Eberlein, R. W. Tester, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2857; d) R. W. Tester, F. G. West, *Tetrahedron Lett.* **1998**, *39*, 4631.

[5] For [2,3]-shifts of ammonium ylides, see: a) M. P. Doyle, W. H. Tamblyn, V. Bagheri, *J. Org. Chem*. **1981**, *46*, 5094; b) M. P. Doyle, V. Bagheri, E. E. Claxton, *J. Chem. Soc. Chem. Commun*. **1990**, 46; c) J. S. Clark, P. B. Hodgson, *J. Chem. Soc. Chem. Commun*. **1994**, 2701; d) D. L. Wright, R. M. Weekly, R. Graff, M. C. McMills, *Tetrahedron Lett.* **1996**, *37*, 2165.

[6] For [1,2]-shifts of ammonium ylides, see: a) W. D. Ollis, M. Rey, I. O. Sutherland, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1009; b) F. G. West, B. N. Naidu, *J. Am. Chem. Soc.* **1993**, *115*, 1177; c) K. W. Glaeske, A. M. Arif, F. G. West, *Org. Lett*. **1999**, *1*, 31; d) J. A. Vanecko, F. G. West, *Org. Lett.* **2002**, *4*, 2813.

[7] Y. H. Wang, Y. X. Zhu, Z. Y. Chen, A. Mi, W. H. Hu, M. P. Doyle, *Org. Lett.* **2003**, *5*, 3923.

[8] For C–N bond formation, see: a) T. D. Quach, R. A. Batey, *Org. Lett*. **2003**, *5*, 4397; b) F. Y. Kwong, S. L. Buchwald, *Org. Lett*. **2003**, *5*, 793; c) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. Buchwald, *J. Am. Chem. Soc*. **2003**, *125*, 6653; d) I. V. Vrcek, V. Pilepic, S. Ursic, *Tetrahedron. Lett.* **2004**, *45*, 699.

[9] For multiple-bond formation, see: a) P. Wipf, C. R. J. Stephenson, K. Okumura, *J. Am. Chem. Soc.* **2003**, *125*, 14694; b) I. Ugi, *Pure Appl. Chem.* **2001**, *73*, 187; c) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; d) H. Bienayme, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321; e) L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366.

[10] a) Crystal data for **4b**: $C_{16}H_{23}N_3O_6$, MW = 353.37, Monoclinic, space group Cc, $a = 9.514(1)$ Å, $b = 21.178(3)$ Å, $c = 9.742(1)$ Å, $\beta = 109.441°$, $V = 1851.1(4)$ Å^3, $Z = 4$, $\rho_{calcd.} = 1.268$ Mg/m^3, $F(000) = 752$, $\lambda = 0.71073$ Å, $T = 292(2)$ K, μ (Mo-Kα) = 0.098 mm^{-1}. Data for the structure were collected on a Siemens P-4X four-circle diffractometer. Intensity measurements were performed on a crystal (dimensions $0.56 \times 0.28 \times 0.28$ mm) in the range $3.84 < 2\theta < 55.98°$. Of the 2548 measured reflections, 2379 were independent ($R_{int} = 0.0088$). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least squares on F^2. The final refinements converged at $R_1 = 0.0407$ for $I > 2\sigma(I)$, $wR_2 = 0.0874$ for all data. The final difference Fourier synthesis gave a min/max residual electron density of –0.253/+ 0.203 e Å^{-3}; b) CCDC-238733 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; or deposit@ ccdc.cam.ac.uk].

[11] For reviews of this area, see: a) G. Maas, *Top. Curr. Chem.* **1987**, *137*, 75; b) H. M. L. Davies, in: *Comprehensive Organic Synthesis*, (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, Vol. 4, Chapter 4.8; c) A. Padwa, K. E. Krumpe, *Tetrahedron* **1992**, *48*, 5385; d) F. A. Bouffard, *J. Am. Chem. Soc*. **1980**, *102*, 6161.

[12] a) J. C.; Hannach, J. Vidal, J. C. Mulatier, A. Collet, *J. Org. Chem*. **2004**, *69*, 2367; b) U. Oguz, G. G. Guilbeau, M. L. Mclaughlin, *Tetrahedron Lett.* **2002**, *43*, 2873.

