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Synthesis of Carbamates from Diethoxycarbonyl Hydrazine Derivatives by E1cB Eliminative Cleavage of the *N*−*N*′-Bond Rather than Reduction

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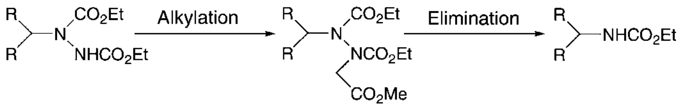
ABSTRACT

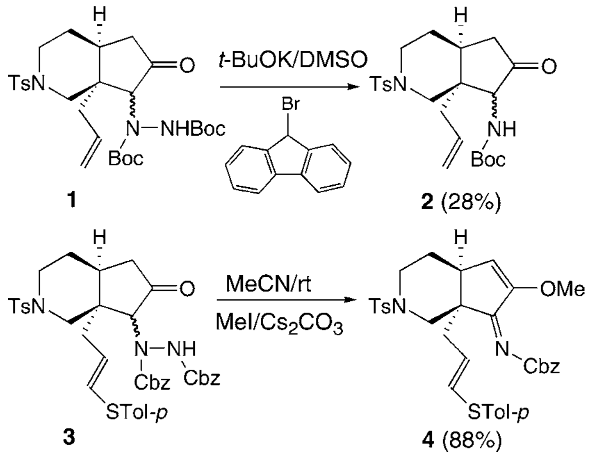


Treatment of diethoxycarbonyl hydrazine derivatives with methyl bromoacetate/Cs_2CO_3/MeCN at 50 °C followed by heating to 80 °C resulted in N−N′ bond cleavage to the corresponding carbamates.

Traditional methods that are used to cleave the *N*−*N*′ bond in *N*,*N*′-alkyl(aryl), *N*,*N*′-monoacyl, diacyl, and triacyl derivatives involve exposure of these compounds to classical reduction conditions such as Raney nickel,[1] Na/NH_3,[2] Li/NH_3,[3] SmI_2,[4] B_2H_6,[5] $NiCl_2{\cdot}2H_2O$−LiDTBB (cat.),[6] and R_3Si−H.[7] Oxidative cleavage of the *N*−*N*′ bond has also been reported,[8] and there are also sporadic reports of eliminative methods to rupture *N*−*N*′ bonds.[9]

During research directed toward the synthesis of some marine alkaloids, we discovered two complementary methods to cleave the *N*−*N*′ bond in hydrazine derivatives. Treatment of **1** with *t*-BuOK/DMSO in the presence of fluorenyl bromide[9] resulted in **2**, albeit in less than practical yields,

Scheme 1



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(1) Raney nickel: Hinman, R. L. *J. Org. Chem.* **1957**, *22*, 148–150. Sinha, P.; Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 3841–3744.

(2) Na/NH_3, Zn/AcOH, Al amalgam: Mellor, J. M.; Smith, N. N. *J. Chem. Soc.*, *Perkin Trans. 1* **1984**, *292*, 7–2931. Na/NH_3: Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, *21*, 3493–3496. Wasserman, H. H.; Matsuyama, H. *J. Am. Chem, Soc.* **1981**, *103*, 461–462. Wendler, N.; Kuo, C. H. *Tetrahedron Lett.* **1984**, *25*, 2291–2294. Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594–5598.

(3) Li/NH_3: Brimble, M. A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5261–5263. Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219–6223. Vedejs, E.; Meier, G. P. *Tetrahedron Lett.* **1979**, *20*, 4185–4188.

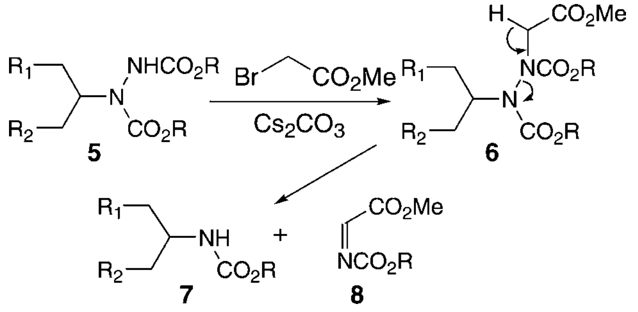
(4) SmI_2/THF: Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575–1577, and references thereinSmI_2/HMPA: Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491–4493. SmI_2/THF: Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637–640. Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329–8330.

(5) Diborane. Feuer, H.; Brown, F. *J. Org. Chem.* **1970**, *35*, 1468–1471.

(6) $NiCl_2{\cdot}2H_2O$−Li−DTBB(cat.): Alonso, F.; Radivoy, G.; Yus, M. *Tetrahedron* **2000**, *56*, 8673–8678.

10.1021/ol902313v

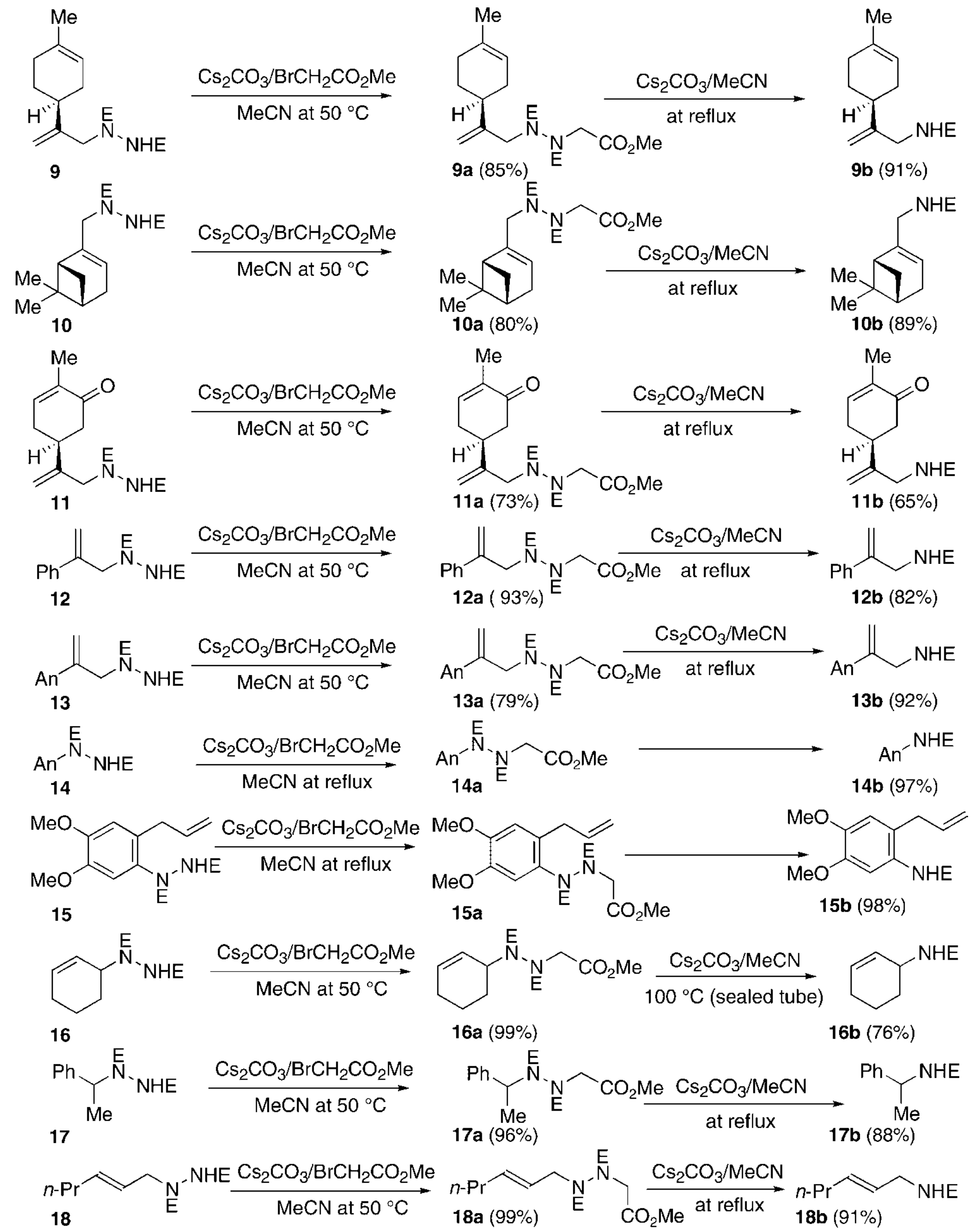
Scheme 2. Eliminative Pathway



Scheme 1.[10] Presumably, this reaction proceeds by *N*-alkylation followed by fluorenyl anion formation and elimination of *N*-Boc-fluorenylimine resulting in **2**. We also observed that treatment of **3** with MeI/Cs_2CO_3/MeCN or allyl bromide/Cs_2CO_3/MeCN gave **4** in good yield. While the latter reaction (**3** → **4**) is clearly much more efficient, the former transformation (**1** → **2**) directly converts a dialkoxycarbonyl hydrazine derivative into a α-carbamoyl ketone, which in general, would be more useful.

It was envisioned that alkylation of **5** with methyl bromoacetate would give **6**, which can undergo elimination to give **7** and the known dehydroglycine derivative **8**, Scheme 2.[11] We anticipated that the very electrophilic imine **8** would

Scheme 3. Conversion of *N*,*N'*-Diethoxycarbonyl Hydrazines into Carbamates



E = CO_2Et, An = C_6H_4OMe-4

react with the carbonate anion to give a water-soluble adduct and be washed out in an aqueous workup.

The *N*,*N'*-diethoxycarbonyl hydrazines **9**−**18** (see the Supporting Information for their synthesis and references) were *N*-alkylated using methyl bromoacetate[12] in dry MeCN and Cs_2CO_3 at 50 °C to give **9a**−**13a** and **16a**−**18a**, respectively, in the indicated yields, Scheme 3. In general, it proved beneficial to isolate and purify these compounds prior to the elimination step. In the case of compounds **14** and **15**, the same alkylation was carried out at reflux (ca. 82 °C) and led directly to the elimination products **14b** (97%) and **15b** (98%), respectively.

The adduct **9a** and Cs_2CO_3 in dry MeCN was heated at reflux for 18 h to give the carbamate **9b** (91%). If water is present in the reaction the elimination is very slow (ca. 15% conversion in 72 h), and using either K_2CO_3 or Li_2CO_3 as the base gave no reaction. When **9a** was treated with Cs_2CO_3 in MeCN/D_2O and heated at reflux for 18 h the recovered starting material had the $-NCH_2CO_2Me$ portion converted into $-NCD_2CO_2Me$, thus providing evidence for a E1cB mechanism for the reaction, the slow step being the breaking of the *N*−*N* bond.[13]

In all of the reactions to form the carbamates we have not detected the imine **8** or its hydrate.

The conversions of **11a** → **11b**, **12a** → **12b**, **13a** → **13b**, and **17a** → **17b** are noteworthy since the use of reductive reaction conditions to cleave the *N*−*N* bond would be expected to result in competitive reduction of the enone, styrene, and benzylic amine, respectively.

This method of cleaving the *N*−*N'*-bond has the potential to find wide use in the conversion of hydrazines (and derivatives) into amines (and derivatives) under mild non-reducing reaction conditions.

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Supporting Information Available: Complete experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Polymethylhydrosiloxane, Pd−C, $(Boc)_2O$: Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Synlett* **2001**, *156*, 1–1562.

(8) For an oxidative method of cleaving the N−N bond, see: Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem., Int. Ed* **2000**, *39*, 2893–2897. Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 831–833. (b) Fernández, R.; Ferrete, A.; Llera, J. M.; Magriz, A.; Martín-Zamora, E.; Díaz, E.; Lassaletta, J. M. *Chem.*−*Eur. J.* **2004**, *10*, 737–745.

(9) References to eliminative cleavage of N−N bonds in acyclic systems : Adam, W.; Pastor, A.; Wirth, T. *Org. Lett.* **2000**, *2*, 1295–1297. Gong, Y.; Bausch, M. J.; Wang, L. *Tetrahedron Lett.* **2001**, *42*, 1–4. Touré, B. B.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 8429–8436. References to eliminative cleavage of N−N bonds in cyclic systems: Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1986**, *51*, 1537–1540. Forrest, A. K.; Schmidt, R. R. *Tetrahedron Lett.* **1984**, *25*, 1769–1772.

(10) Unpublished results.

(11) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, *22*, 4607–4610. Abood, N. A.; Nosal, R. *Tetrahedron Lett.* **1994**, *35*, 3669–3672.

(12) The use of other alkylating agents such as phenacyl bromide gave complex mixtures.

(13) Kice, J. L; Kupczyk-Subotkowska, L. *J. Org. Chem.* **1990**, *55*, 1523–1527.