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Oxaziridine-Mediated Amination of Primary Amines: Scope and Application to a One-Pot Pyrazole Synthesis

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ABSTRACT

Electrophilic amination of primary aliphatic and aromatic amines is reported using a diethylketomalonate-derived oxaziridine to afford the corresponding *N*-Boc hydrazines in good to excellent yields. The method allows a one-pot synthesis of pyrazoles from primary amines.

Electrophilic amination provides a conceptually powerful means for the incorporation of nitrogen into molecular frameworks.[1] Pioneering work by Collet and co-workers has established that aldehyde-derived *N*-Boc-oxaziridines such as **1** and **2** can effect electrophilic amination of various nucleophiles.[2] However, oxidation often competes with amination in their reaction with heteroatom nucleophiles. They cleanly convert secondary amines to the corresponding protected hydrazines,[3] but low yields are observed with primary amines since these undergo competitive imine formation with the aldehyde released when the oxaziridines effect amination.[2] Recently we have reported the novel *N*-Boc-oxaziridine **3** as an extremely effective nitrogen transfer reagent for the electrophilic amination of a range of allylic and propargylic sulfides which subsequently underwent [2,3]-sigmatropic rearrangement.[4] We reasoned that **3** may effect efficient amination of primary amines since the byproduct of amination is a ketone, diethyl ketomalonate. The product N-protected alkyl hydrazines are potentially highly useful for the construction of a large range of valuable heterocycles,[5] but very few are commercially available, providing a strong stimulus for the investigation of this chemistry.[6] Here we report our successful studies in this area, and the development of a one-pot synthesis of pyrazoles from primary amines.

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(1) Reviews: (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947−1980. (b) Greck, C.; Genet, J. P. *Synlett* **1997**, 741−748. (c) Mulzer, J.; Altenbach, H. -J. *Organic Synthesis Highlights*; VCH: Weinheim, Germany, 1991; p 45−53. (d) Dembach, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281−1286. (e) Genet, J. P.; Greck, C.; Lavergne, D. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinham, Germany, 2000; pp 65−102.

(2) (a) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691−1709.(b) Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845−8848.

(3) (a) Vidal, J.; Drouin, J.; Collet, A. *J. Chem. Soc. Chem. Commun.* **1991**, 435−437. (b) Vidal, J.; Guy, L.; Stérin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791−4793. (c) Vidal, J.; Damestoy, S.; Collet, A. *Tetrahedron Lett.* **1995**, *36*, 1439−1442. (d) Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. *J. Org. Chem.* **2004**, *69*, 2367−2373.

(4) (a) Armstrong, A.; Cooke, R. S. *Chem. Commun.* **2002**, 904−905. (b) Armstrong, A.; Cooke, R. S.; Shanahan, S. E. *Org. Biomol. Chem.* **2003**, *1*, 3142−3143.

(5) Monosubstituted hydrazines are important intermediates en route to the synthesis of, for example, pyrazoles: (a) Stauffer, S. R.; Huang, Y. R.; Aron, Z. D.; Coletta, C. J.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2001**, *9*, 151−161. Indazoles (b) Boudreault, N.; Leblanc, Y. *Org. Synth.* **1996**, *74*, 241−247. Imidazolinones (c) Bozzini, S.; Nitti, P.; Pitacco, G.; Pizzioli, A.; Russo, C. *J. Heterocycl. Chem.* **1996**, *33*, 1217−1221. Cinnolines (d) Wunsch, B.; Nerdinger, S.; Hofner, G. *Liebigs Ann.* **1995**, 1303−1312.

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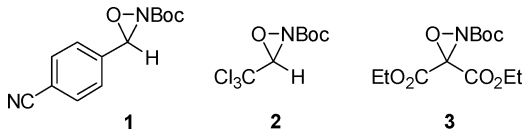
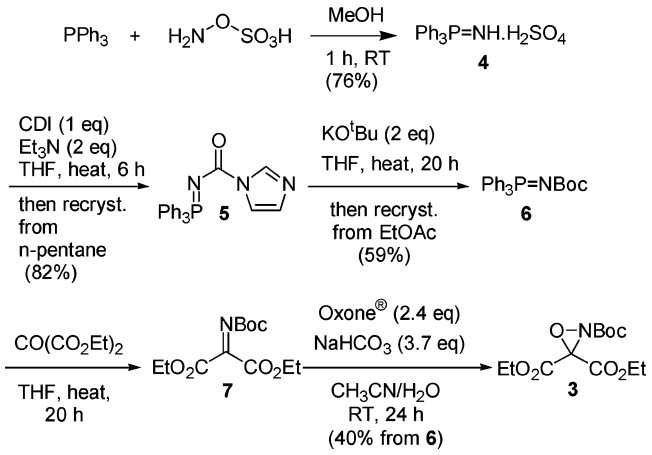


Our original reported synthesis of oxaziridine **3**[4a] involved aza-Wittig reaction of diethyl ketomalonate with an iminophosphorane derived from (potentially hazardous) N−Boc-azide, followed by oxidation of the resulting imine with mCPBA/BuLi. An early aim was to develop an improved synthesis. We developed a novel route to **3** that is amenable to large-scale synthesis (Scheme 1).

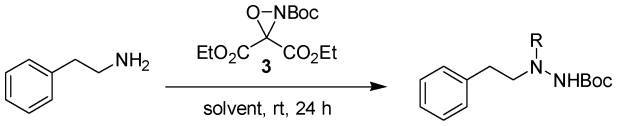
Scheme 1. Novel Route to Oxaziridine **3**[a]



Thus, amination of triphenylphosphine with hydroxylamine-*O*-sulfonic acid and subsequent N-protection via the acyl imidazolide **5** afforded iminophosphorane **6**.[7] Following aza-Wittig reaction with diethyl ketomalonate, we were able to effect oxidation of imine **7** with aqueous Oxone in CH_3CN/H_2O.[8]

With quantities of **3** in hand, we tested its reaction with a sample primary amine, 2-phenylethylamine **8a**, in a range of solvents (Table 1). Initial reaction in CH_2Cl_2 afforded a moderate yield of desired product **9a**, with unreacted oxaziridine **3** also recovered (entry 1). Interestingly, the novel diaminated product **10a** was also isolated, and this was a significant side product in several other solvents (entries 2−5). Highest yield was obtained using toluene as solvent (entry 6). Overall yields based on aminating agent were good, indicating that **3** is an efficient nitrogen transfer reagent. Imine byproducts were not detected. To minimize the amount of diamination product **10a**, we repeated the reaction in CH_2Cl_2 using 2.0 equiv of amine relative to oxaziridine (entry 9). This resulted in an improved yield of 75% **9a** (based on oxaziridine) and may offer a useful strategy when relatively cheap amines are used as substrates.

Table 1. Amination of 2-Phenylethylamine **8a** Using Oxaziridine **3**[a]



entry	solvent	**9a** (%)	**10a** (%)	**3** (%)
1	CH_2Cl_2	41	8	25
2	Et_2O	45	15	10
3	THF	48	19	10
4	Acetone	52	18	7
5	Petrol	54	22	<5
6	$PhCH_3$	62	<5	20
7	CH_3CN	37	<5	40
8	EtOH	50	<5	30
9[b]	CH_2Cl_2	75	8	-

[a] Oxaziridine (0.7 equiv), amine (1.0 equiv), solvent (0.12 M in amine), rt under nitrogen, 24 h. The yields quoted are isolated yields based on oxaziridine **3**. [b] Amine/oxaziridine ratio 2:1, 24 h.

While the above study suggested toluene to be the optimum solvent, we considered that use of CH_2Cl_2 would have practical advantages, particularly if the method was to be applied to parallel synthesis. We therefore investigated a wider range of substrates using both solvents and a 1:1 ratio of amine/oxaziridine (Table 2).[9] In some cases, small amounts of imine byproduct **11** were observed. Table 2 reveals excellent amination for a range of unbranched and branched aliphatic amines (entries 1−4), with use of toluene as solvent offering superior yields. For aromatic amines (entries 5−7), higher yields of **9** were obtained in CH_2Cl_2. A higher proportion of diamination product **10** was obtained with the electron rich substrate **8f** (compare entries 6 to 5, 7). The use of nonaromatic aliphatic amines, cyclopropylamine, cyclohexylamine and heptylamine afforded poor to modest yields of the corresponding hydrazine products in both solvent systems (entries 8−10). However, gratifyingly the methodology tolerates the use of amino acid derivatives and heteroaromatics to afford promising quantities of the monoaminated products (entries 11−13).

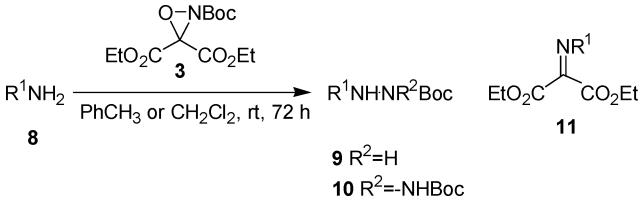
(6) An alternative synthetic approach involves reductive amination of aldehydes with hydrazates. Recent examples in the literature include, for example: (a) Weber, D.; Berger, C.; Eickelmann, P.; Antel, J.; Kessler, H. *J. Med. Chem.* **2003**, *46*, 1918−1930. (b) Xu, Z.; Singh, J.; Swinden, M. D.; Zheng, B.; Kissick, T. P.; Patel, B.; Humora, M. J., Quiroz, F.; Dong, L.; Hsieh, D. -M.; Heikes, J. E.; Pudipeddi, M.; Lindrud, M. D.; Srivastava, S. K.; Kronenthal, D. R.; Mueller, R. H. *Org. Process Res. Dev.* **2002**, *6*, 323−328. (c) Kruse, L. I.; Kaiser, C.; DeWolf, W. E.; Finkelstein, J. A.; Frazee, J. S.; Hilbert, E. L.; Ross, S. T.; Flaim, K. E.; Sawyer, J. L. *J. Med. Chem.* **1990**, *33*, 781−789. However, this approach has not been used to prepare hydrazines with a stereocenter α-to nitrogen. A more recent approach which does provide hydrazines with a stereocenter α-to nitrogen involves the hydrohydrazination reaction of olefins with azodicarboxylates see Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676−5677. However, the products were all prepared as their racemates.

(7) Tomcufcik, A. S.; Emma, J. E.; Eudy, N. H.; Marsico, J. W.; Newman, H. US Patent No. 4767749, 1988; *Chem. Abstr.* **1988**, *109*, 231197.

(8) Armstrong, A.; Draffan, A. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2861−2873.

(9) DSC testing on oxaziridine **3** showed a broad exotherm at 100 °C. We therefore recommend that this reagent is not heated above room temperature and that it is kept in the freezer when not in use. TSU testing on benzylamine **8b** as substrate with oxaziridine **3** in CH_2Cl_2 showed no exotherm or pressure buildup; therefore no thermal hazards are expected from the normal reaction at room temperature.

Table 2. Conversion of Primary Amines **8** to *N*-Boc Hydrazines **9**[a]

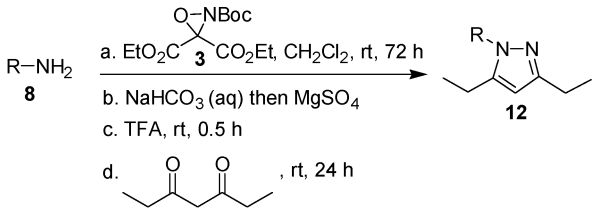


			(i) $PhCH_3$			(ii) CH_2Cl_2		
entry	amine **8**	R^1	**9** (%)	**10** (%)	**3** (%)	**9** (%)	**10** (%)	**3** (%)
1	**a**	$PhCH_2CH_2$	67	13	4	45	5	30
2	**b**	$PhCH_2$	75	<2	2	52[b]	10	5
3	**c**	PhCH(Me)	75			32		
4[c]	**d**	PhCH(Ph)	80			54		
5	**e**	Ph	55	10[d]	5	71	5[d]	5
6[c]	**f**	4-OMe-C_6H_4	45	19		51	10	
7	**g**	4-CN−C_6H_4	60	8		70	6	
8	**h**	cyclopropyl	34[e]		28	29[e]		25
9	**i**	cyclohexyl	45	5[d]	20	43	6[d]	23
10	**j**	*n*-heptyl	11	35	<5	<5	41	<5
11	**k**	$PhCH_2CH(CO_2Et)$	65		16	53		20
12	**l**	$(CH_3)_2CHCH(CO_2Et)$	50	15	8	44	15	9
13	**m**	3-$NH_2CH_2C_5H_5N$	35[f]	15	20	42[f]	12	20

[a] Oxaziridine (1.0 equiv), amine (1.0 equiv), solvent (0.17 M in amine), rt under nitrogen, 72 h. The yields quoted are isolated yields. [b] Reaction worked up after 25.5 h. [c] For entry 4: (i) <5% **11**, (ii) 23% **11**. For entry 6: (i) 13% **11**, (ii) 10% **11**. [d] Inseparable mixture of bisaminated material and oxaziridine **3**. [e] Reactions worked up after 48 h. [f] Amination occurs on the benzylic primary amine of 3-(aminomethyl)pyridine. This was confirmed by a downfield shift of the signals in the corresponding ^1H and ^{13}C spectra at positions 2 and 6 of the pyridine ring for the bisaminated product **10**.

We next turned our attention to the application of our amination methodology to heterocyclic synthesis. Since unprotected alkyl hydrazines can be unstable,[10] their in situ generation and reaction with electrophiles offered an attractive possibility for investigation. We elected to study the synthesis of 1,3,5-trisubstituted pyrazoles since these are key components of a number of important biological compounds that have attracted considerable industrial attention.[11] Initially we took the hydrazine products **9a**,**b** and **9e** as representative examples for screening with a symmetrical 1,3-diketone, hepta-3,5-dione, to avoid issues of regioisomerism in the final pyrazole products. The respective hydrazines were dissolved in dichloromethane and treated with TFA for 0.5 h, followed by the addition of hepta-3,5-dione (1.0 equiv). The reactions were left to stir for 24 h and monitored by TLC. Removal of the solvent in vacuo and purification by flash column chromatography gratifyingly afforded the desired pyrazole products in quantitative yields. With a view to developing this chemistry into a one-pot pyrazole synthesis, we felt that it would be advantageous to be able to remove the diethyl ketomalonate side product from the initial electrophilic amination by aqueous extraction. This should facilitate a cleaner, more efficient synthesis of the desired pyrazole products and make the final chromatographic purification a simple filtration. Pleasingly, it was discovered that washing with saturated aqueous sodium hydrogencarbonate resulted

Scheme 2. One-Pot Synthesis of 1,3,5-Trisubstituted Pyrazoles[a]



entry	amine	R	pyrazole **12** Yield (%)
1	**8a**	$PhCH_2CH_2$	36
2	**8b**	$PhCH_2$	59
3	**8c**	Ph(CH)Me	43
4	**8e**	Ph	51
5	**8g**	4-CN-Ph	42

[a] The yields quoted are isolated yields.

(10) Krivis, A. F.; Supp, G. R. *Prepr. Papers, Am. Chem. Soc., Div. Fuel Chem.* **1967**, *11*, 137−141.

(11) For example, Celecoxib: Schnitzer, T. J.; Kong, S. X.; Mitchell, J. M.; Mavros, P.; Watson, D. J.; Pellissier, J. M.; Straus, W. L. *Clin. Ther.* **2003**, *25*, 3162−3172. Tartrazine: Shah, K. M. *Handbook of Synthetic Dyes and Pigments*; Multi-tech Publishing Co.: India, 1998. Sildenafil (Viagra): Moreland, R. B.; Goldstein, I; Kim, N. N.; Traish, A. *Trends Endocrinol. Metab.* **1999**, *10*, 97−104. Martell, A. M.; Graul, A.; Rabasseda, X.; Castaner, R. *Drugs Fut.* **1997**, *22*, 138−143. Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Biorg. Med. Chem. Lett.* **1996**, *6*, 1819−1824. Boolell, M.; Allen, M. J.; Ballard, S. A.; Gepi-Attee, S.; Muirhead, G. J.; Naylor, A. M.; Osterloh, I. H.; Gingell, C. *Int. J. Urol. Res.* **1996**, *8*, 47−52.

in almost complete removal of diethyl ketomalonate from a CH_2Cl_2 solution. Armed with this knowledge we therefore screened a selection of amines **8** in a novel one-pot approach as outlined in Scheme 2. Thus, the amination reaction mixture was washed with saturated aqueous $NaHCO_3$ and the aqueous layer removed by pipet before sequential addition of solid $MgSO_4$, TFA and the 1,3-diketone. Evaporation of the reaction mixture and filtration on silica then afforded the pyrazole in acceptable overall yield.

In summary, we have reported a simple and efficient procedure for the electrophilic amination of primary amines under metal free conditions, affording synthetically versatile, mono-Boc-protected hydrazines. Additionally, easy removal of the byproduct in the amination step has allowed us to develop a one-pot synthesis of functionalized pyrazoles from primary amines which has potential for application to library synthesis. Further development of the amination technology and extension of the approach to a wider range of valuable nitrogen heterocycles is underway.

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Supporting Information Available: Experimental procedures and spectroscopic characterization information for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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