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Communications

Synthesis of Amines by the Intermolecular Schmidt Reaction of Aliphatic Azides with Carbocations

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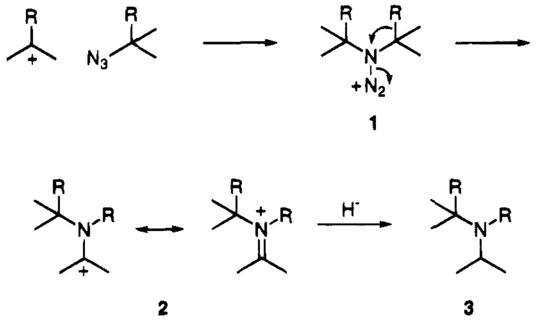
We wish to describe the intermolecular Schmidt reaction of aliphatic azides with carbocations (Scheme 1). Rearrangement of the intermediate aminodiazonium ion **1** produces the iminium ion **2** which may be reduced to an amine upon treatment with sodium borohydride.

The reaction of hydrazoic acid (HN_3) with carbon electrophiles (e.g., carbocations, protonated ketones, acylium ions) produces aminodiazonium ion intermediates which undergo 1,2-rearrangement with the loss of dinitrogen in a fashion similar to that shown in Scheme 1. These processes are known as Schmidt reactions.[1-8] Until the recent independent reports by Aubé *et al.* and ourselves, Schmidt reactions were thought to be limited to the use of hydrazoic acid. Aubé reported the intramolecular Schmidt reaction of aliphatic azides with ketones to produce fused-bicyclic lactams.[9-11] We reported the intramolecular Schmidt reaction of aliphatic azides with carbocations, a process that affords bridged or fused 1-azabicyclic compounds.[12-14] While the success of these reactions over earlier work might at first be attributed to their intramolecular nature, Aubé later reported *inter*molecular Schmidt reactions of azides with ketones promoted by Lewis acids.[15] We now report that aliphatic azides undergo intermolecular Schmidt reactions with certain carbocations to produce iminium ions and thus amines.

Scheme 1. Intermolecular Schmidt Reaction of Azides with Carbocations



As is often the case with 1,2-rearrangements to electron-deficient centers, the regioselectivity of the migration is difficult to predict because there are at least three factors which must be considered: (1) The inherent migratory aptitude of the migrating group, (2) the stability of the newly developing positive charge at the migration origin, and (3) stereoelectronic factors (i.e., the migrating group and the leaving group prefer an antiperiplanar geometry). A good discussion of these factors in a related 1,2-migration, namely the Stieglitz-type rearrangement of *N*-(arenesulfonoxy)amines, may be found in the work of Hoffman.[16] Comparison of our regioselectivities to Hoffman's will be made where appropriate. A more detailed discussion may be found in the supporting information.

Table 1 lists the reactions of *n*-butyl azide with benzylic alcohols in the presence of either tin tetrachloride or triflic acid. Aminodiazonium ions **1** derived from the primary benzylic alcohols **4a-e** rearrange primarily by hydrogen migration to produce **6a-e** (after hydride reduction of the intermediate iminium ion), although a considerable amounts of aryl migration is evident leading to anilines **5a-e**. These results are comparable to the Stieglitz-type 1,2-rearrangement of *N*-(arenesulfonoxy)benzylamine, where hydrogen migrates to nitrogen faster than phenyl.[16] When the benzylic alcohol is secondary (**4f-h**), migration of aryl, hydrogen, and alkyl in the intermediate aminodiazonium ion is observed, with aryl migration predominating, producing **5f-h**, **6f,g**, and **7f-h**. This is the "normal" trend in related 1,2-migrations to nitrogen, although the significant amount of alkyl migration versus hydrogen migration is unusual.[16] Schmidt reactions of the cyclic benzylic alcohols **4i-k** with *n*-butyl azide show a smooth dependence of the aryl:alkyl migration ratio on ring size. Migration of the ring methylene group is preferred over phenyl migration for the cyclobutanol **4i**, producing the ring expansion product **7i** as the major product. Nonregioselective migration is observed when the cyclopentanol **4j** is used, and selective phenyl migration over ring expansion is observed for the cyclohexanol **4k**. The latter migratory preference is similar to that observed in the Stieglitz-type rearrangement of 1-(*N*-(arenesulfonoxy)amino)-1-phenylcyclohexane, where phenyl migration is observed to the exclusion of aryl migration.[16] The cyclobutanol **4l** leads exclusively to the ring expansion products **7l** and **7l′** in excellent yield. Schmidt reaction of the cyclic secondary benzylic alcohol **4m** with *n*-butyl azide illustrates the regioselectivity of a cyclopentanol where the arene is fused to the ring rather than appended to it. In contrast to the cyclic benzylic alcohols **4i-l**, hydrogen rather than aryl

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[7] Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368.

[8] For leading references on the reaction of aliphatic azides with non-carbon electrophiles such as boranes and carbenes, see ref 13.

[9] Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966.

[10] Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141−1147.

[11] For an application of Aubé's intramolecular Schmidt reaction, see: Le Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933−2935.

[12] Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291−5294.

[13] Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183−10194.

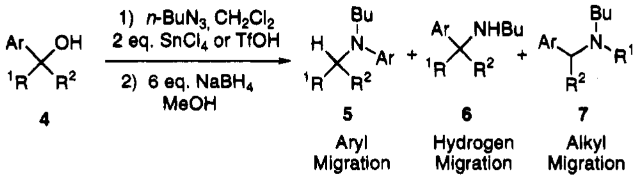
[14] Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682−2684.

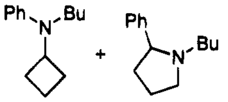
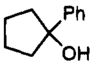
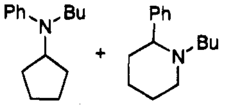
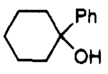
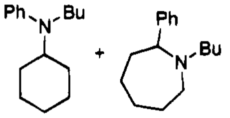
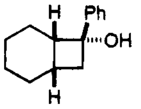
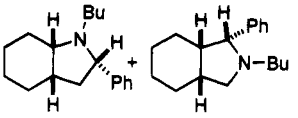
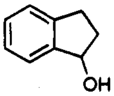
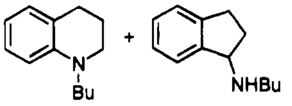
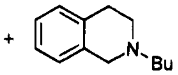
[15] Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637.

[16] Hoffman, R. V.; Kumar, A. *J. Org. Chem.* **1985**, *50*, 1859−1863.

0022-3263/95/1960-4960$09.00/0

Table 1. Intermolecular Schmidt Reactions of n-BuN$_3$ with Benzylic alcohols

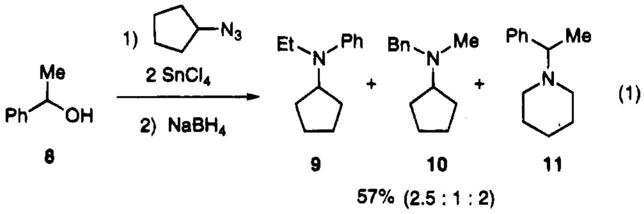


Benzylic Alcohol[a]	Ar	R^1	R^2	Yield (%)[b]	Products (Ratio)[c]
4a	4-Ph-Ph	H	H	77	**5a**, **6a** (1 : 2.85)
4b	4-Me-Ph	H	H	61	**5b**, **6b** (1 : 5.8)
4c	4-MeO-Ph	H	H	97	**5c**, **6c** (1 : 1.94)
4d	3,4-(MeO)$_2$-Ph	H	H	98	**5d**, **6d** (1 : 1.33)
4e	3,4-(OCH$_2$O)-Ph	H	H	100	**5e**, **6e** (1 : 2)
4f	Ph	Me	H	81	**5f**, **6f**, **7f** (4.3 : 1 : 1.2)
4g	4-MeO-Ph	Me	H	97	**5g**, **6g**, **7g** (12.3 : 2.5 : 1)
4h	4-MeO-Ph	n-Pr	H	91	**5h**, **7h** (3.6 : 1)
4i[d]				97	 **5i** **7i** (1 : 5.1)
4j[d]				66	 **5j** **7j** (1.1 : 1)
4k[d]				82	 **5k** **7k** (2.4 : 1)
4l				91	 **7l** **7l'** (1 : 1)[e]
4m[d]				73	 **5m** **6m**  **7m** (8 : 28 : 1)

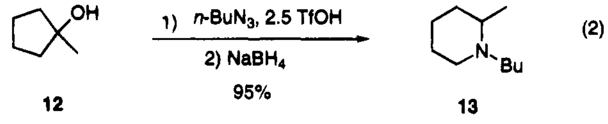
[a] All reactions carried out with SnCl$_4$ unless otherside noted. [b] Yields of isolated, purified products. [c] Ratio based on separated products. [d] Triflic acid (TfOH). [e] Ratio based on integration of purified mixture.

migration is now observed as the major process, producing **6m** as the major product. It is also useful to contrast this result with that from the acyclic secondary benzylic alcohols **4f-h**, where aryl migration was predominant.

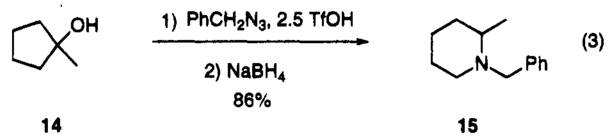
The scope of the intermolecular Schmidt reaction of carbocations with aliphatic azides extends beyond n-butyl azide and benzylic cations, as illustrated by eqs 1–4.



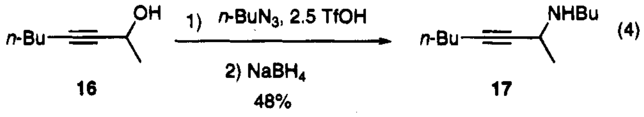
8 **9** **10** **11**



12 **13**



14 **15**



16 **17**

In summary, the scope of the intermolecular Schmidt reaction of carbocations with azides has now been extended to include aliphatic azides. A variety of amines, both acyclic and cyclic, can be prepared by a simple protocol. The regioselectivity of the rearrangement is quite variable, but some trends have been identified. In cases where mixtures of regioisomers are observed, it is generally easy to separate the products by silica gel chromatography, since the anilines are much less polar than the aliphatic amines. Benzylic, tertiary aliphatic, and propargylic carbocations have been found to be useful reaction partners. Further exploration of the scope and regioselectivity of this process is underway. In particular, the further development of a useful rationale for the regioselectivity of 1,2-rearrangements in N,N-disubstituted aminodiazonium ions is being carried out and will be reported in a full account of this work. The supporting information should be consulted for a brief overview of the regioselectivity issue. Finally, a comparison of this process with the previously known Stieglitz-type rearrangements of amines bearing a good leaving group on nitrogen [e.g., N-chloro- and N-(arenesulfonoxy)amines] is in order. While the regioselectivities are similar, the Schmidt route has the advantage of convergency, with two new C–N bonds being formed in one operation.

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Supporting Information Available: Experimental procedures for the preparation of all new compounds and discussion of the regioselectivity of the intermolecular Schmidt rearrangement (27 pages).

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