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A NEW SYNTHESIS OF SECONDARY ALLYLIC ALIPHATIC AND AROMATIC AMINES.

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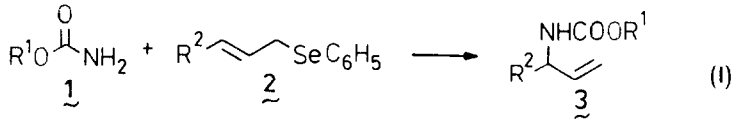
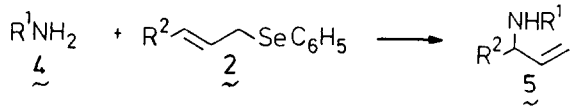
Summary: Treatment of a variety of aliphatic or aromatic primary amines with an N-chlorosuccinimide-activated allylic selenide affords in modest to good yield the corresponding allylically rearranged secondary amines. Examples are reported which define the scope and limitations of this process.

Recent reports from these laboratories have defined preparatively useful conditions under which a carbamate (**1**) or amide and an allylic selenide (**2**) may be oxidatively coupled with N-chlorosuccinimide (NCS) to afford, in synthetically useful yield, an allylically rearranged protected primary amine (**3**) (equation I).[2] The utility of this reaction in synthesis would be greatly enhanced if primary amines (**4**) (rather than carbamates and amides) could serve as the source of nucleophilic nitrogen (equation II), thus providing a direct synthesis of secondary amines (**5**). This Letter describes a modification of the selenide to amine rearrangement protocol which was necessary in order to achieve the coupling of primary aliphatic and aromatic amines to allylic selenides. Using this technology, a variety of secondary amines have been synthesized and some distinct limitations of the reaction have been uncovered.



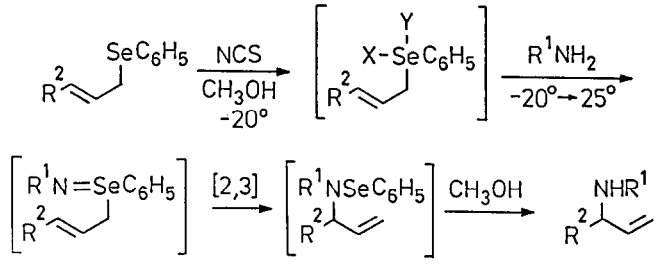
1 **2** **3** (I)



4 **2** **5** (II)

Attempts to achieve the process depicted by equation II using our published protocol[2a] (treatment of a methanolic solution of the selenide, primary amine, and triethylamine at 0° with NCS) afforded only a low yield of the corresponding rearranged secondary amine. We reasoned that this failure reflected in some way the propensity of the primary amine **4** and product **5** to undergo undesired oxidative side reactions, and that these might be supressed by a modification in which the allylic selenide was oxidatively activated with one equivalent of NCS prior to the addition of the primary amine **4**. The success of such an approach is intimately tied to the stability of the selenium (IV) intermediate, which must survive long enough to be trapped by the subsequently added primary amine. Literature precedent exists for the generation of selenium (IV) intermediates in this manner[3], but precedent also exists for several pathways for the decomposition of this intermediate which are in this context unproductive.[4]

Treatment of a cold (-20°) methanolic solution of an allylic selenide (1.25 equiv) and triethylamine (5.0 equiv) with N-chlorosuccinimide (NCS, 1.25 equiv) for 5 minutes afforded a colorless, clear solution. TLC analysis (silica gel) of the solution could be used to demonstrate the consumption of the allylic selenide. Interestingly, the TLC signature of the putative selenium (IV) intermediate, whose structure we have not investigated, is the corresponding allylically rearranged alcohol which presumably results from hydrolysis of the intermediate on silica gel to the allylic selenoxide, which then yields the allylic alcohol by well established processes[6]. Addition of a primary aliphatic or aromatic amine (1.0 equiv), followed by warming of the mixture to 25° over 0.5 h, and standard workup, including column chromatography on silica gel, provided the secondary amines[7] illustrated in entries 1-13 of the Table. Also of practical importance are several other experimental observations. One attempt to generate the selenium (IV) intermediate with NCS at -20°, warm to 25° for 0.5 h, and finally cool to -20° and trap with a primary amine met with failure. We believe this reflects the thermal lability of the intermediate.[4] Reactions conducted in tetrahydrofuran or methylene chloride were unsuccessful. Finally, in some cases, the use of excess NCS in the activation step severely depressed the final yield of rearranged amine.

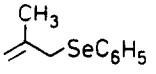
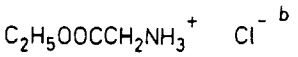
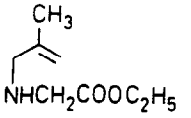
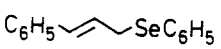
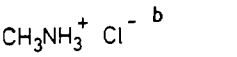
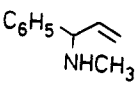
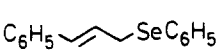
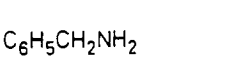
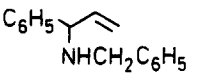
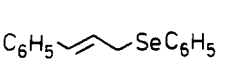
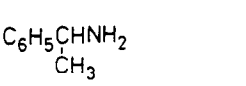
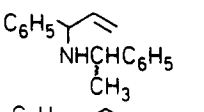
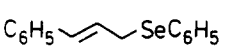
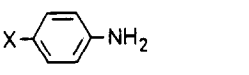
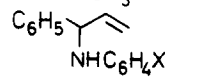
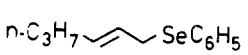
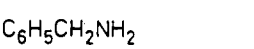
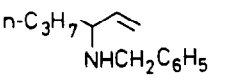
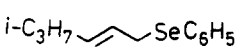
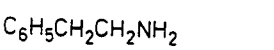
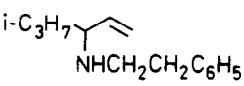
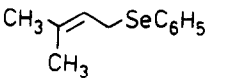
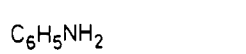
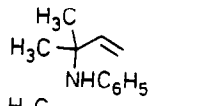
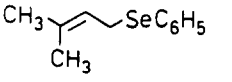
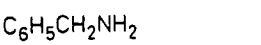
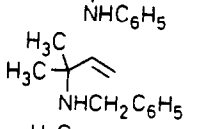
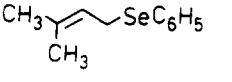
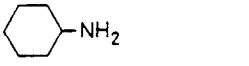
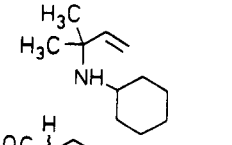
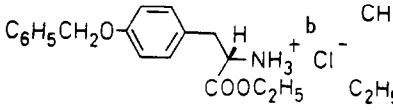
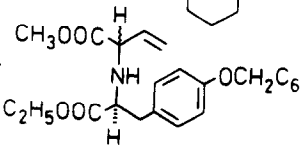


Inspection of the Table reveals several synthetically important points. The primary amine component of the reaction may enter equally well as the free base or as as a salt (entries 1,2,14). The yields of rearranged secondary amines are good in those cases where relatively uncrowded components are joined (entries 1,2,3,5,6), but drop considerably when highly substituted groups are brought together (entries 12,13). An attempt to produce a secondary amine in which both alpha carbon atoms were fully substituted was unsuccessful (data not shown). Allylation of aniline derivatives was most successful for electron deficient anilines (entries 5,6).[8]

Despite the successes recorded herein, some care must be exercised in the application of this process. Structural and functional variation in either the selenide or primary amine may require modification of the standard procedure. For example, early attempts to use the standard procedure to prepare the unusual iminodiacid derivative indicated in entry 14, failed completely. Subsequent experimentation revealed that in this case, the selenium (IV) intermediate was insufficiently stable at -20°. Coupling was achieved by brief treatment of the selenide with one equivalent of NCS at -78°, followed by warming to -60°, addition of O-benzyl tyrosine ethyl ester hydrochloride, and finally prolonged stirring at -40°.

Procedures now exist for incorporating as a starting component in the selenide to amine allylic rearrangement what are probably the four most common forms of a primary amine: Aliphatic, aromatic, amide, and carbamate.[2] From a synthetic perspective, two aspects of this reaction are noteworthy. This rearrangement permits the covalent joining of two organic fragments (the selenide and primary amine) under mild conditions, with neither component in large excess. This might prove important in applications which involve starting materials of limited availability. Secondly, the reaction permits the coupling of the

TABLE

Entry	Selenide	Amine	Product	Yield[a]
1		 [b]		67
2		 [b]		83
3				74(66[c])
4				60[d]
				
5		X = NO_2		95
6		Br		87
7		H		60
8		OCH_3		48
9				60
10				54
11				72
12				42
13				19
14				61[d,e]

a. See endnote 7. b. An additional equivalent of triethylamine was used in this reaction. c. 15 mmol scale. d. Product is a *ca.* 1:1 mixture of diastereoisomers. e. Diastereomeric products could be separated by chromatography on silica gel.

two organic fragments in a regiocontrolled (and potentially stereocontrolled[2b]) manner with formation of a primary, secondary, or tertiary carbon to nitrogen bond. For these reasons, we believe that this reaction will find general application in organic synthesis.

A representative experimental procedure follows:

N-(p-Bromophenyl)-1-phenyl-2-propenyl amine. A solution of 250 mg (0.915 mmol) of cinnamyl phenyl selenide and 463 mg (4.58 mmol) of triethylamine in 4.6 ml of dry methanol was cooled to -25°. N-Chlorosuccinimide (122 mg, 0.915 mmol) was added and the cold mixture was stirred for 5 min at -20°. *The colorless solution was treated with 126 mg (0.732 mmol) of p-bromoaniline and allowed to warm to* 25° over *ca.* 0.5 h. The volatiles were removed *in vacuo* and the residue was chromatographed on silica gel (5% ethyl acetate/hexanes) to provide 183 mg (87%) of N-(p-bromophenyl)-1-phenyl-2-propenyl amine as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.5 (1H, br, NH); 4.88 (1H, d, J=6 Hz, C<u>H</u>NH); 5.23 (1H, d, J=9 Hz, -CH=C<u>H</u>H); 5.25 (1H, d, J=17 Hz, -CH=CH<u>H</u>); 6.02 (1H, ddd, J=17, 9, and 6Hz, C<u>H</u>=CH_2); 6.47 (2H, d, J=9 Hz, -C_6H_4-); 7.20 (2H, d, J=9 Hz, -C_6H_4-), 7.2-7.4 (5H, m, -C_6H_5); IR (neat, NaCl) 3420 (NH); 3080; 3060; 3030; 1595; 1495 cm^{-1}; MS (ei) m/e. 289, 287 (M^+, 8); 157, 155 (C_6H_4Br, 4); 130 (6); 117 ($C_6H_5CHCH{=}CH_2$, 100); 115 (37); 104, 103, 102, 91, 90, 89, 78, 77, 76, 75.[9]

References and Endnotes

1. a) Undergraduate Research Associate; b) Searle Scholar, 1984-1987.

2. a) Shea, R.G.; Fitzner, J.N.; Fankhauser, J.E.; Hopkins, P.B. J. Org. Chem. 1984, 49, 3647; b) Fitzner, J.N.; Shea, R.G.; Fankhauser, J.E.; Hopkins, P.B. J. Org. Chem. 1985, 50, 419; c) Fitzner, J.N.; Pratt, D.V.; Hopkins, P.B. Tetrahedron Lett. 1985, 26, 1959.

3. Detty, M.R. J. Org. Chem. 2980, 45, 274.

4. a) Hori, T.; Sharpless, K.B. J. Org. Chem. 1979, 44, 4208; b) Marino, J.P.; Larsen, R.D. J. Am. Chem. Soc. 1981, 103, 4642; c) Takeki, K.; Yasumura, M.; Negoro, K. J. Org. Chem. 1983,48, 54.

5. All of the allylic selenides utilized herein were prepared by the displacement of allylic mesylates or halides with sodium phenyl selenide. See Clive, D.J. Tetrahedron 1978, 34, 1049.

6. Sharpless, K.B.; Lauer, R.F. J. Am. Chem. Soc. 1972, 94, 7154.

7. The reported yields represent chromatographically homogeneous substances of greater than 95% purity. All products were characterized by ^{1}H NMR (500 or 80 MHz), IR, and low resolution MS. Selected compounds were analyzed by high resolution MS or C, H, N combustion analysis. ^{1}H NMR data (500 MHz, $CDCl_3$) for selected secondary amine products follows [entry: chemical shift (δ), integral (H's), multiplicity (s,d,t,q,m), J(Hz)]: **1**: 1.28, 3, t; 1.77, 3, s; 2.10, 1, bs; 3.22, 2, s; 3.40, 2 , s; 4.19, 2, q; 4.87, 2, s; **3**: 1.8, 1, bs; 3.74, 1, s; 3.75, 1, s; 4.23, 1, d, 7; 5.12, 1, d, 10; 5.21, 1, d, 18; 5.97, 1, ddd, 7, 10, 18; 7.2-7.4, 10, m; **5**: 4.8, 1, bs; 5.05, 1, d, 7; 5.28, 1, d, 19; 5.32, 1, d, 10; 6.05, 1, ddd, 7, 10, 19; 6.55, 2, d, 9; 7.35, 5, m; 8.07, 2, d, 9; **14a**: 1.18, 3, t; 2.97, 2, m; 3.49, 1, t; 3.72, 3, s; 3.83, 1, d, 7; 4.12, 2, dq; 5.04, 2, s; 5.24, 1, d, 8; 5.28, 1, d, 12; 5.77, 1, ddd, 7, 8, 12; 6.89, 2, d, 9; 7.12, 2, d, 9; 7.2-7.5, 5, m; **14b**: 1.16, 3, t; 2.92, 2, m; 3.50, 1, t; 3.68, 3, s; 3.86, 1, d, 7; 4.10, 2, dq; 5.04, 2, s; 5.22, 1, d, 7; 5.26, 1, d, 11; 5.77, 1, ddd, 7,7,11; 6.89, 2, d, 8; 7.11, 2, d, 8; 7.2-7.5, 5, m.

8. A major by-product in the case of aniline (entry 7) appears (500 MHz ^{1}H NMR, MS evidence) to bear X=phenylseleno in the secondary amine product, presumably resulting from electrophic aromatic substitution on the aniline ring.

9. We thank the Dreyfus Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, Research Corporation, and Scripps Immunology Clinic for financial support.

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