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# $SmI_2$-PROMOTED KETYL RADICAL ADDITION TO O-BENZYL FORMALDOXIME. A NEW AMINOMETHYLATION

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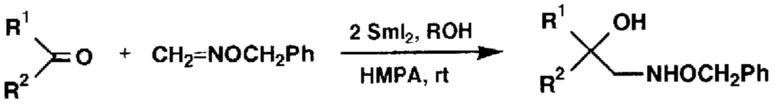
*Summary: Reductive coupling of carbonyl compounds with O-benzyl formaldoxime was promoted by $SmI_2$ affording the corresponding aminomethyl alcohols under mild conditions.*

Aminomethylation is an important reaction in organic synthesis and both *electrophilic* and *nucleophilic* reactions have so far been developed for the aminomethylation of active methylene compounds (Mannich reaction) and for the preparation of 2-amino alcohols,[1,2] respectively We report here a new aminomethylation of carbonyl compounds via *radical process*, in which $SmI_2$-promoted ketyl radical formation followed by its addition to *O*-benzyl formaldoxime proceeds rapidly under mild conditions (eq 1) [3,4,5]



(1)

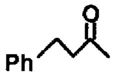
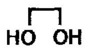
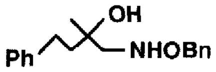
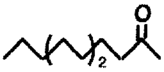
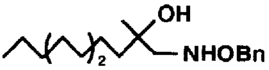
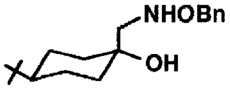
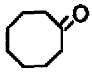
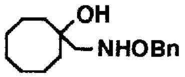
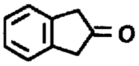
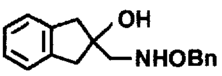
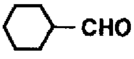
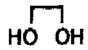
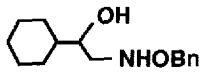
A solution of $SmI_2$ in THF (0.1 mol $dm^{-3}$, 3 ml) was added to a mixture of carbonyl compounds (0.13 mmol), *O*-benzyl formaldoxime (34 1 mg, 0.25 mmol), alcohols (0.5 mmol), and HMPA (0.5 ml) and the mixture was stirred at room temperature for 5 min, at which time purple color faded and white precipitate was produced. Usual workup followed by chromatographic purification gave the corresponding aminomethyl alcohols in moderate to good yields as shown in the table.

The addition of HMPA is indispensable[6] in the present reaction as it has been recognized in other electron transfer reactions promoted by $SmI_2$.[7] The choice of proton source is also important to get good results. Although both aldehydes and ketones could be used as substrates, the present approach is restiricted only to aminomethylation; the reaction of 4-phenyl-2-butanone with other *O*-benzyl oximes prepared from benzaldehyde, crotonaldehyde, 2-phenylpropionaldehyde, and 4-*tert*-butylcyclohexanone did not give the coupling products.

It is interesting from the mechanistic point of view that the reaction of 4-tert-butylcyclohexanone afforded a mixture of diastereomers with high axial-attack stereoselection (run 3),[8,9] which may be interpreted in terms of the preferred configuration of the ketyl intermediate with orbital extention of the radical lobe in the axial direction [10] Similar radical process has been proposed for the electroreductive aminoalkylation[4] while the sense of stereoselection was opposite.[11]

The N-benzyloxy group of the coupling products could be easily eliminated to form the corresponding free aminomethyl alcohols by $PtO_2$-catalyzed hydrogenolysis.

Table. $SmI_2$-promoted aminomethylation of carbonyl compounds

| Entry | Substrate | ROH | Product | %Yield (ratio) |
|---|---|---|---|---|
| 1 |  |  |  | 83 |
| 2 | 〃 | none | 〃 | 42 |
| 3 |  | s-BuOH |  | 59 |
| 4 |  | t-BuOH |  | 57 (94:6) |
| 5 |  | t-BuOH |  | 45 |
| 6 |  |  |  | 50 |
| 7 |  |  |  | 59 |

## References and Notes

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2. Nucleophilic aminoalkylation other than aminomethylation. a) Roskamp, E J.; Pedersen, S. F *J. Am. Chem Soc.*, **1987**, 109, 6551; b) Imamoto, T ; Nishimura, S *Chem Lett.*, **1990**, 1141.

3. Presented at the 60th Meeting of the Chemical Society of Japan, Hiroshima, October (1990).

4. During the course of the preparation of this manuscript, very useful aminoalkylation (but no example of aminomethylation) via electroreductive coupling of ketones with *O*-methyl oximes has been reported: Shono T., Kise, N., Fujimoto, T. *Tetrahedron Lett.*, **1991**, *32*, 525

5. Oxime ethers have been known as good acceptors for ketyl radicals as well as alkyl radicals: a) Corey, E. J., Pyne, S. G *Tetrahedron Lett.*, **1983**, *24*, 2821; b) Hart, D. J., Seely, F. L *J. Am. Chem. Soc.*, **1988**, *110*, 1631; c) Bartlett, P A ; McLaren, K. L.; Ting, P. C. *ibid.*, **1988**, *110*, 1633; d) Enholm, E. J.; Burroff, J. A ; Jaramillo, L M. *Tetraheron Lett.*, **1990**, *31*, 3727.

6. In the absence of HMPA decomposition of the oxime ether and simple reduction of the carbonyl compounds took place slowly and no coupling products were obtained.

7. For previous works utilizing the $SmI_2$-THF-HMPA system, see Ujikawa, O ; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett* , **1989**, *30*, 2837, Kusuda, K.; Inanaga, J.; Yamaguchi, M *ibid.*, **1989**, *30*, 2945 and references cited therein.

8. The stereoconfiguration was determined by converting the mixture to the corresponding aminomethyl alcohols ($H_2/PtO_2$), which were compared with the authentic ones prepared from a diastereomeric mixture of 4-*tert*-butyl-1-iodomethylcyclohexanol (ax-OH/eq-OH=14/1)[12] by successive treatment with potassium phthalimide and hydrazine.

9. Carbon-carbon bond formation at axial site was highly favored also on the reaction with styrene (ax-OH/eq-OH=2/98). Ujikawa, O.; Inanaga, J., Yamaguchi, M., unpublished result.

10. Lloyd, R V.; Causey, J. G. *J Chem. Soc., Perkin II*, **1981**, 1143.

11 It has been pointed out that the degree of pyramidalization of ketyls (anion radicals) depends upon their counter cations Pradhan, S. K. *Tetrahedron*, **1986**, *42*, 6351.

12 Tabuchi, T ; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett* , **1986**, *27*, 3891.

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