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Reductive Amination of Piperidines with Aldehydes Using Borane-Pyridine

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REDUCTIVE AMINATION OF PIPERIDINES WITH ALDEHYDES USING BORANE-PYRIDINE

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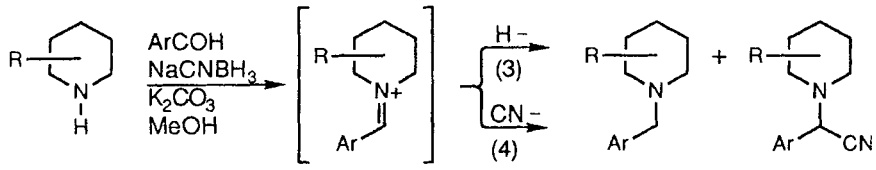
Abstract: Borane-pyridine complex (BAP) was found to be an excellent replacement for $NaCNBH_3$ in the Borch reduction. Assorted aromatic, heterocyclic and aliphatic aldehydes were reacted with various substituted piperidines using standardized conditions.

In the course of synthetic investigations, an efficient route to N-substituted piperidines was required. Initially the Borch procedure (aldehyde / $NaCNBH_3$) was used for the synthesis of a series of N-benzylpiperidines **3**[1] (Scheme 1). In several of the reactions an intractable impurity containing a nitrile **4** was produced, presumably by quenching of the iminium intermediate **2** with cyanide ion. The percent of this impurity decreased as the pH was elevated, but even under basic conditions ($MeOH/K_2CO_3$) enough of the impurity was present to render the product unusable. A search of the literature for a non-cyanide containing replacement for $NaCNBH_3$ led to the use of borane-pyridine complex (BAP).[2]

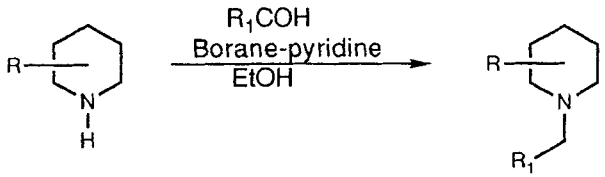
Scheme 1



1 2 3 4

BAP was found to be superior to $NaCNBH_3$ for this reductive amination. The nitrile impurity was eliminated, and reduction of the aldehyde was reduced or averted,[3] improving the yield and isolation of products (Scheme 2). The literature contains several examples of BAP reductive aminations,[4] but none involving a piperidine or a secondary amine.

Scheme 2



1 3

The scope of this reductive amination of piperidines with aldehydes was investigated. For the purpose of this study standardized conditions were used for all substrates: one equivalent of the aldehyde and piperidine were treated with one molar equivalent of BAP. The results are shown in Table 1.

The BAP did not reduce the olefinic bond in the substrates used: The double bond in the cinnamyl moiety (**A 3**), and 3,4-dehydropiperidine (Piperidine F) were not reduced. The ester was not

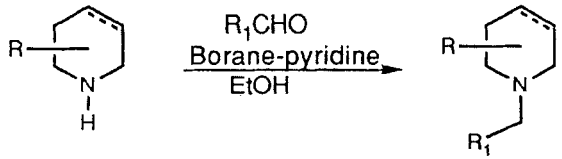
reduced by BAP and the alcohol did not need protection or interfere with the reductive amination. An attempt to use 3-piperidone or 4-piperidone resulted in products where the ketone was reduced.[5] Halogens [fluorine (**B 2, D 2 & E 3**), chlorine (**D 4**) and bromine (**A 2 & E 4**)] were unaffected by BAP. Potential complexing agents such as methoxy (**A, B, C, D & E 1**) and dimethylamino (**A 4, D 5 & E 5**) did not appear to affect the reactivity of BAP.

Furan (**A 9 & 10; B 8 & 9; C 5**) and thiophene (**A 11 &12**) achieved good conversions to products. Pyridine (**A 5, 6, 7 & 8; B 5, 6 & 7; C 2, 3 & 4; D 6**) in contrast did not achieve good conversions. The reaction was slow. Reduction of the aldehyde to the alcohol was the predominant product. The electron withdrawing effect of the pyridine ring inhibits formation of the iminium intermediate, which is also seen in the nitro substituted (**B 4 & D 3**) cases. An aliphatic aldehyde (**A 13**) also participated in this reductive amination, with concomitant reduction of the aliphatic aldehyde the only side reaction to occur.

BAP is compatible with both protic and aprotic solvents such as toluene or CH_2Cl_2[4]. These reactions can be performed in these aprotic solvents with results comparable to EtOH. In the above cases the alcohol was easily removed using chromatography. Excess aldehyde and controlled addition of BAP until the piperidine was consumed, achieved higher conversions to the desired product.

In summary, a convenient one-pot procedure has been developed to reductively aminate a secondary amine (piperidines) with aromatic, heteroaromatic and aliphatic aldehydes through a Borch type reduction, replacing $NaCNBH_3$ with the less expensive and less toxic borane-pyridine complex.

Table 1[a]



1 3

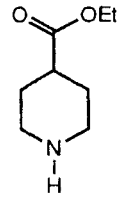
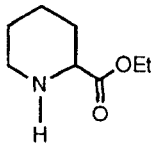
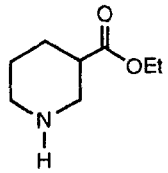
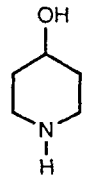
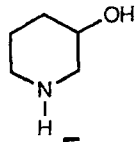
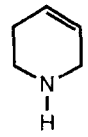
Piperidine 1	Entry	R_1 in 3	%Yield
 A	1	4-Methoxyphenyl	81
	2	4-Bromophenyl	74
	3	Cinnamyl	45
	4	4-Dimethylaminophenyl	60
	5	2-Pyridyl	26
	6	6-Methyl-2-pyridyl	30
	7	3-Pyridyl	28
	8	4-Pyridyl	27
	9	2-Furanyl	71
	10	3-Furanyl	79
	11	2-Thiophenyl	80
	12	3-Thiophenyl	88
	13	Hexyl	51
 B	1	4-Methoxyphenyl	52
	2	2-Fluorophenyl	62
	3	3,4-Dimethoxyphenyl	25
	4	3-Nitrophenyl	13
	5	2-Pyridyl	25
	6	3-Pyridyl	21
	7	4-Pyridyl	12
	8	2-Furanyl	75
	9	3-Furanyl	80

Table 1 continued [a]

Piperidine **1**	Entry	R_1 in **3**	%Yield
 **C**	1	4-Methoxyphenyl	58
	2	2-Pyridyl	22
	3	3-Pyridyl	43
	4	4-Pyridyl	35
	5	3-Furanyl	89
 **D**	1	4-Methoxyphenyl	55
	2	2-Fluorophenyl	44
	3	3-Nitrophenyl	28
	4	4-Chlorophenyl	70
	5	4-Dimethylaminophenyl	84
	6	4-Pyridyl	36
 **E**	1	4-Methoxyphenyl	63
	2	2-Methylphenyl	56
	3	3-Trifluoromethylphenyl	51
	4	4-Bromophenyl	60
	5	4-Dimethylaminophenyl	59
 **F**	1	Phenyl	51

a. One equivalent of the piperidine and aldehyde were combined in ethanol and one molar equivalent of BAP was added. The reaction was followed by tlc. When one of the components was consumed the reaction was worked up.

Experimental Procedure

All starting materials were commercially available and were used without further purification. The products were chromatographed on Silica-gel 60 (Merck), eluting with either a EtOAc/toluene or a $EtOH/CH_2Cl_2$ system. Spectra (NMR and IR) were consistent for the reported products. Elemental analyses were within ±0.40% of the theoretical values.

General Procedure

Ethyl 1-(4-Methoxybenzyl)-4-piperidinecarboxylate (Piperidine A, Entry 1) Ethyl 4-piperidinecarboxylate (12.5 g; 0.08 moles) and 4-methoxybenzaldehyde (11.4 g; 0.081 mole) were dissolved in ethanol (150 ml). Borane-pyridine complex (8.0 ml; 0.08 moles) was added and the reaction mixture was stirred for 4 hr. Tlc (EtOAc/toluene) indicated that the aldehyde was consumed and tlc 5%$EtOH/CH_2Cl_2$/0.25%NH_4OH indicated that the piperidine was still present. Additional aldehyde and later BAP was added until the piperidine was consumed. The reaction mixture was concentrated, and partitioned between H_2O and CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$ and concentrated to an oil which was chromatographed on silica, eluting with $EtOH/CH_2Cl_2$. Unreacted aldehyde was the first component to elute followed by the alcohol then the desired amine isolated in 89% yield as an oil. ^1H NMR ($CDCl_3$) δ: 1.25 (t, 3H, J=5Hz), 1.68-1.90 (m, 4H), 2.0 (t of d, 2H, J=8Hz & J=3Hz), 2.20-2.31 (m, 1H), 2.85 (d of t, 2H, J=8Hz & J=3Hz), 3.42 (s, 2H), 3.80 (s, 3H), 4.12 (q, 2H, J=5Hz), 6.85 (d, 2H, J=6), 7.21 (d, 2H, J=6); IR ($CHCl_3$): C=O 1724 cm^{-1}; Elemental Analysis: $C_{16}H_{23}NO_3$, M.W. 277.36 Calculated: C, 69.29%; H, 8.36%; N, 5.05%. Found: C, 69.37%; H, 8.45%; N, 4.77%.

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1. a) Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, 93, 2897-2904. b) Borch, R.F.; Hassid, A.I. *J. Org. Chem.* **1972**, 37, 1673-1674. c) Lane,C.F. *Synthesis*, **1975**, 135-146.

2. a) Peiter, A.; Rosser, R.M.; Mills, S. *J. Chem. Soc. Perkin Trans. I* **1984**, 717-720. b) Kikugawa, Y; Ogawa, Y. *Chem. Pharm. Bull.* **1979**, 27, 2405-2410. c) Kabalka, G. W. *J. Organomet. Chem.*, **1987**, 318:1-3, 1-28.

3. Borane-pyridine was stable for up to two weeks in ethanol with no evident decomposition. The borane-pyridine was easily visualized with I_2 or UV and the progress of the reaction was easily monitored using tlc. In contrast to $NaCNBH_3$, borane-pyridine can be titrated thus decreasing the chances for aldehyde reduction, through inadvertant use of excess hydride.

4. Hutchins, R.O.; Learn, K.; Nazer, B.: Pytlewski, D.; Pelter, A. *Organic Preparations and Procedures Int.*, **1983**, 337-372.

5. In separate reactions BAP and an aldehyde were added as needed until the 3- or 4- piperidone was consumed. Substantial reduction of the piperidone to the corresponding hydroxypiperidine and aldehyde to the alcohol occured under these conditions. The reductive amination products were the same as those obtained from piperidines **D** & **E**.

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