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N-ISOPROPYL-N-METHYL FORMAMIDINE, A REAGENT FOR THE SYNTHESIS OF BIOACTIVE AMINO-ALCOHOLS.

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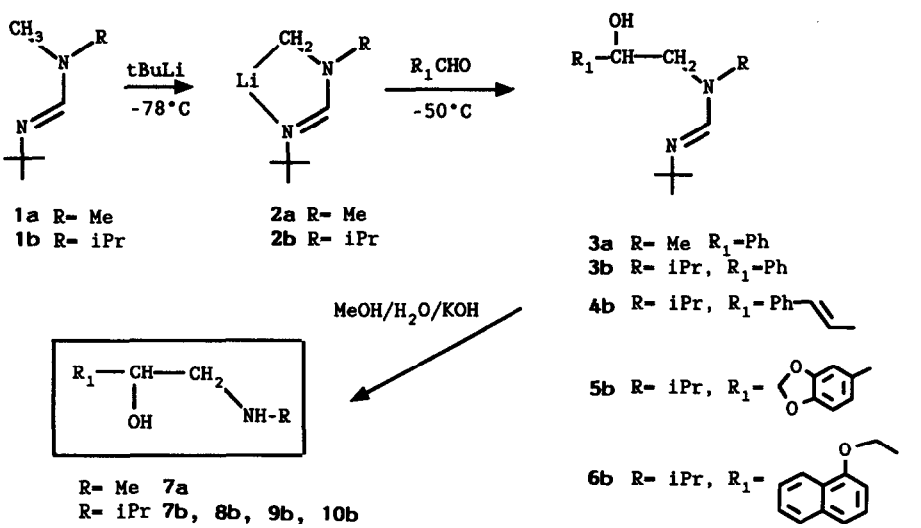
Abstract : The lithium anion of N-isopropyl-N-methyl formamidine 1b reacts with aldehydes in yields up to 95% leading to the less-substituted addition-products, and thus provides a short synthesis (3 steps) of propranolol, an important bioactive amino-alcohol .

Since their introduction by Meyers in 1980, formamidines have proved to be powerful reagents for C-C bond formation (1,2) and have been successfully used for the synthesis of alkaloids (3) or heterocycles (4,5).

Carbanion **2a** of N,N-dimethyl formamidine **1a** was also shown (1) to give, in 75% yield, the corresponding N-methylamino-alcohol **7a** upon addition to benzaldehyde 11 (R_1=Ph).

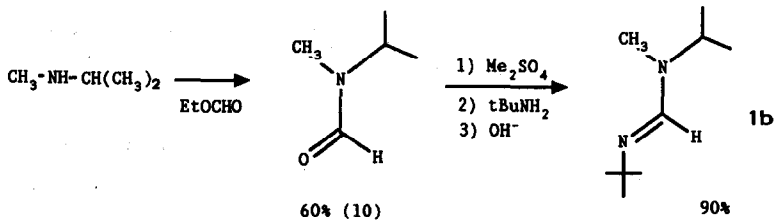


Scheme 1

A variety of N-alkyl amino-alcohols of type **7-10** such as isoproterenol, pindolol or propranolol (6) possess important α- or β- adrenergic activity, but, in those compounds, the N-alkyl group is an isopropyl group.

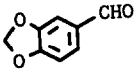
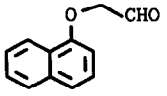
In the course of our work on such bioactive amino-alcohols (7,8), we started investigating the formamidine method. We report herein the synthesis and the use of formamidine **1b** which, as expected (1), leads to the less substituted addition-products, **3b-6b** and therefore to the desired amino-alcohols **7b-10b**.

Formamidine **1b** (9) is easily synthesized (1,4) from commercially available isopropylmethyl amine (10) and is purified by flash chromatography on silicagel (eluent : 7% NEt_3/hexane).



Addition of the corresponding carbanion **2b** on aldehydes **11** (11), **12**, **13** and **14** provides compounds **3b** (12), **4b**, **5b** and **6b** (13) in good to very good yields. the results are given on Table 1.

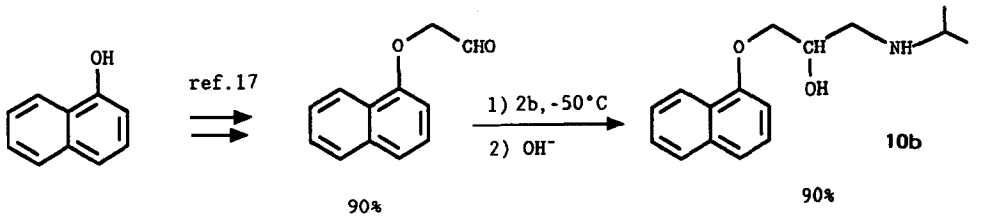
Table 1

	R_1-CHO	Solvent	Compound	Yield[a]
11	Ph-CHO	THF	**3b**	60%
12		THF	**4b**	65%
13		THF	**5b**	63%
11	Ph-CHO	Ether/THF (4/1)	**3b**	95%
14		Ether/THF (4/1)	**6b**	90%

a) in weight of isolated crude product and corrected from remaining starting material when necessary according to the 200MHz ^1H NMR of the crude product .

After the usual hydrolysis (14) the desired amino-alcohols **7b-10b** (15) are recovered in quantitative yields.

Therefore formamidine **1b** provides a 3-step and high overall yield (80%) synthesis of (±) propranolol.



Chiral analogs of formamidine **1b** are currently under investigation.

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9) **1b** : Colorless oil.
200 MHz ^{1}H NMR ($CDCl_3$/TMS) δ(ppm) : 7.39 (1H, s, H-C=), 3.64 (1H, septuplet, J=6.7Hz, CH iPr), 2.69 (3H, s, CH_3N), 1.15 (9H, s, tBu), 1.12 (6H, d, J=6.7Hz, CH_3 iPr).
IR (film) : (CCl_4) : 2960-2800 cm^{-1} CH, 1640 cm^{-1} C=N
10) The 60 % yield in the formylation step, limited by the low boiling point of isopropylmethylamine, is under optimization.
11) To a 0.5M solution of formamidine **1b** in ether/THF (4/1) at -78 °C and under argon are added 1.1 equiv of t-butyl lithium. A precipitate appears which disappears on warming to -50 °C for 0.5hr. Then 1.3 equiv. of benzaldehyde are added dropwise. After stirring at -50 °C for 12hrs, 2.1 equiv of HCl (10 %) are added. After ether extraction the aqueous phase is made basic and extracted with CH_2Cl_2. The combined organic phases are dried over Na_2SO_4 and concentrated under vacuum. The colorless oil obtained, **3b**, is analyzed by 200MHz ^{1}H NMR prior to purification. No starting material is detected (no signal at 2.69 ppm, see above ref. 9).

12) **3b** : 200MHz ^{1}H NMR ($CDCl_3$/TMS) : 7.5 (1H, s, H-C=), 7.4 (5H, m, H arom.), 4.8 (1H, X part of an ABX, d.d, J=7Hz and 1.5Hz, CH), 3.4 (2H, AB part of an ABX, J_{AB}=14Hz, J=7Hz and 1.5Hz $_{AB}$=10Hz, CH_2), 3.44 (1H, sept, CH iPr), 1.22 (9H, , tBu), 1.13 (3H, d, J=6Hz, CH_3 iPr), 0.95 (3H, d, J=6Hz, CH_3 iPr).

13) **6b** : 200MHz ^{1}H NMR ($CDCl_3$/TMS) : 8.2 (1H, m, H arom.), 7.8 (1H, m, H arom.), 7.5 (5H, m, H arom. and H-C=), 6.9 (1H, m, H arom.), 4.1 (3H, m, OCH_2CH-O), 3.6 (2H AB type CH_2-N), 3.45 (1H, sept., CH/iPr), 1.2 (9H, s, tBu), 1.15 (6H, d, CH_3).

14) A solution of 1 mmole of **3b** (**4b**, **5b** or **6b**) in 5 ml of MeOH, 3 ml of H_2O and 0.4 g of KOH is heated at 60°C for 12h. The amino-alcohol is extracted with CH_2Cl_2, the organic layers are combined, dried over Na_2SO_4 and concentrated under vacuum. The crude product is analyzed by 200MHz ^{1}H NMR.

15) **7b** : white solid, mp=75-76°C.
200MHz ^{1}H NMR : δ 7.36 (5H, m, H arom.), 4.69 (1H, X part of an ABX, d.d, J=9Hz and 3.5Hz, CH), 2.95 (1H, A part of an ABX, J_{AB}=12Hz, J=3.5Hz), 2.86 (1H, sept, CH iPr), 2.67 (1H, B part of an ABX, J_{AB}=12Hz, J=9Hz), 1.09 (6H, d, J=6Hz, CH_3 iPr).
^{13}C NMR ($CDCl_3$/TMS) : δ 22.9, 23.2, 48.7, 54.6, 72.0, 128.8 (m or o), 127.4 (p), 128.4 (o or m), 142.8 (quat.).

8b : δ 7.35 (5H, m, H arom.), 6.67 (1H, A1 part of an A1B1XA2B2, d, J_{AB}=15.8Hz, HC=, trans isom.), 6.18 (1H, B1 part of an A1B1XA2B2, J_{AB}=15.8Hz, J=6Hz, =C-H, trans isom.), 4.29 (1H, m, X part of an A1B1XA2B2, CH), 2.85 (1H, A2 part of an A1B1XA2B2, J_{AB}=11.5Hz, J=4Hz), 2.84 (1H, sept, CH iPr), 2.64 (1H, B2 part of an A1B1XA2B2, J_{AB}=11.5, J=8Hz), 1.09 (6H, d, CH_3 iPr).

9b : δ 6.89 (1H, s, H arom.), 6.82 (2H, AB, H arom., J=9Hz), 5.97 (2H, s, O-CH_2-O), 4.61 (1H, d.d, X part of an ABX, J=7.5Hz and 3Hz), 2.9 (1H, A part of an ABX, J_{AB}=12Hz, J=3Hz), 2.85 (1H, sept, CH iPr), 2.64 (1H, B part of an ABX, J_{AB}=12Hz, J=7.5Hz), 1.08 (6H, d, CH_3 iPr).

10b : δ 8.25 (1H, m, H arom.), 7.80 (1H, m, H arom.), 7.45 (4H, m, H arom.), 6.85 (1H, m, H arom.), 4.32 (1H, X part of an A1B1XA2B2, CH), 4.2 (2H, A1B1 part of an A1B1XA2B2, JA1B1=9Hz, JA1X 5Hz, JB1X 0Hz, $\Delta\nu$AB=16Hz), 3.05 (2H, A2B2 part of an A1B1XA2B2, JA2B2=12.5Hz, JA2X 8Hz, JB2X 3.5Hz, $\Delta\nu$=27Hz), 1.25 (2d weakly non equivalent, 6H, CH_3).

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