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A HIGHLY EFFICIENT AND GENERAL N-MONOMETHYLATION OF FUNCTIONALIZED PRIMARY AMINES VIA FORMYLATION--BORANE METHYL SULFIDE REDUCTION

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Abstract Formylation of functionalized primary aromatic and aliphatic amines with acetic formic anhydride (AFA) followed by borane methyl sulfide reduction in the same pot affords the corresponding N-methylamines in excellent isolated yields, uncontaminated by bis alkylation, the reaction sequence is applicable to even very weakly basic and sterically hindered amines

N-Monomethylation (or N-monoalkylation) of primary amines is a key functional group transformation often encountered in organic synthesis Although numerous methodologies[1] are available for the N-monomethylation (or N-monoalkylation), none are without limitations [2] Consequently, a general, convenient and high-yield procedure under mild conditions is still a highly desirable goal An efficient and general one-pot procedure for the N-monomethylation of primary amines, compatible with a wide range of functional groups, is presented here The strategy involves formylation of the amino group followed by in situ reduction of the generated formamide to the corresponding N-methylamine derivative

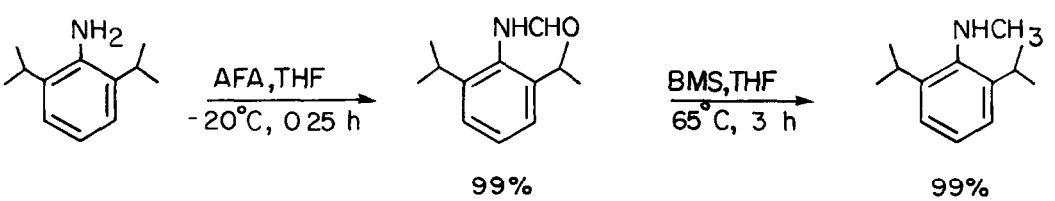
Primary aromatic and aliphatic amines react with excess acetic formic anhydride[3] (acetic anhydride and formic acid, 0 °C, 50-60 °C, 2 h) regioselectively Evaporation of the reaction mixture (to remove the acetic acid and other volatiles) provides the corresponding N-aryl- and N-alkylformamides respectively in quantitative yields The reaction is clean and rapid and proceeds under extremely mild conditions Thus, formylation of aniline at -20 °C is complete in less than 0 25 h, yielding essentially pure formanilide (mp 46 °C) in 99% isolated yield [4,5] The reaction is applicable even to very weakly basic amines (4-nitroaniline, 0 °C, 0 25 h, 100%) and highly hindered amines (2,6-diisopropylaniline, -20 °C, 0 25 h, >99%)

Conversion of the formamide intermediate to the corresponding N-methylamine is conveniently achieved by selective reduction with borane methyl sulfide (BMS) [6,7] Accordingly, the formamide intermediate was dissolved in tetrahydrofuran (THF) and reduced with 2-2 5 mol equiv[8] of BMS under a gentle reflux The reductions were complete in less than 3 h, providing the corresponding N-methylamines in excellent isolated yields (80-100% based on the starting primary amine) The products were completely free from bis-alkylated products, frequently encountered unwanted side products observed with a number of previous methods [1] The reaction sequence is applicable to both aromatic and aliphatic primary amines (Table I) Especially significant is the successful conversion of the sterically hindered amines 2,6-dimethylaniline and 2,6-diisopropylaniline to their corresponding N-monomethyl derivatives in excellent isolated yields (eq 1)

Table I N-Monomethylation of Representative Primary Amines via Formylation--Borane Methyl Sulfide Reduction[a]

primary amine	formylation step[b] temp, °C	time, h	yield,[d] %	reduction step[c] N-methylamine	yield,[e] %
aniline	-20	0 25	100	N-methylaniline[f]	82[g]
2,6-dimethylaniline	-20	0 25	100	N,2,6-trimethylaniline[f]	99,[h] 83[g]
2,6-diisopropylaniline	-20	0 25	99	N-methyl-2,6-diisopropylaniline[f]	99,[h] 87[g]
o-aminophenol	-20	0 25	100	2-methylaminophenol[f]	98,[h] 76[g]
p-anisidine	-20	0 25	99	N-methyl-p-anisidine[f]	84[g]
p-bromoaniline	-20	0 25	99	N-methyl-p-bromoaniline[f]	80[g]
p-iodoaniline	-20	0 25	100	N-methyl-p-iodoaniline[f]	85[g]
2,4-dichloroaniline	-20	0 25	100	N-methyl-2,4-dichloroaniline[i]	97[h]
p-nitroaniline	0	0 25	100	N-methyl-p-nitroaniline[i]	91[h]
2-chloro-4-nitroaniline	25	3 0	100	N-methyl-2-chloro-4-nitroaniline[i]	97,[h] 88[g]
ethyl p-aminobenzoate	-20	0 25	97	ethyl p-N-methylaminobenzoate[i]	96[h]
4-amino-3-chloro-N,N-dimethylbenzenesulfonamide	25	2 0	99	4-methylamino-3-chloro-N,N-dimethylbenzenesulfonamide[i]	85[g]
benzylamine	-20	0 25	99	N-methylbenzylamine[f]	98,[h] 80[g]
n-octylamine	-20	0 5		N-methyloctylamine[i]	77[j]
3-aminopyridine	-20	0 25	99	3-methylaminopyridine[i]	87[j]

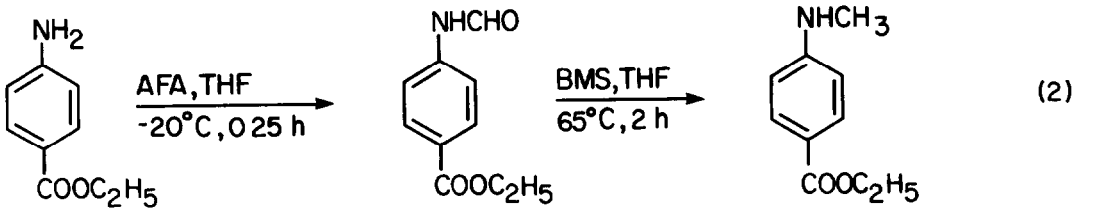
[a]Reactions were carried out in THF on 50-mmol scale (RNH_2) [b]Monitored by TLC [c]Reductions were carried out using 2-2 5 equiv of borane methyl sulfide in refluxing THF for 3 h [d]Isolated yield of the formamide [e]Isolated yield based on the starting primary amine [f]Isolated as amine hydrochloride [g]Yield after recrystallization [h]Essentially pure, crude yield [i]Isolated as the free amine [j]Yield after distillation



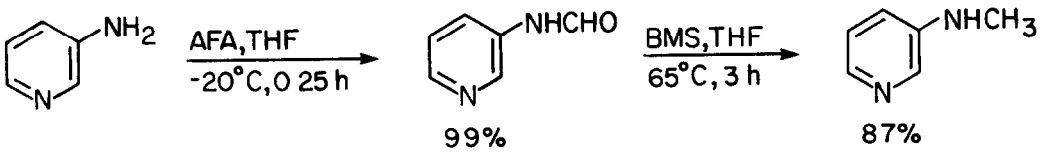
(1)

A reported attempt to use a number of the previously recorded N-monoalkylation procedures[1] for the synthesis of N,2,6-trimethylaniline and related derivatives has resulted in difficult to separate mixtures of mono- and dialkylated products in low yields [9]

The mildness of borane permits the presence of a large variety of functional groups including heteroaromatic rings (eq 2 and 3)



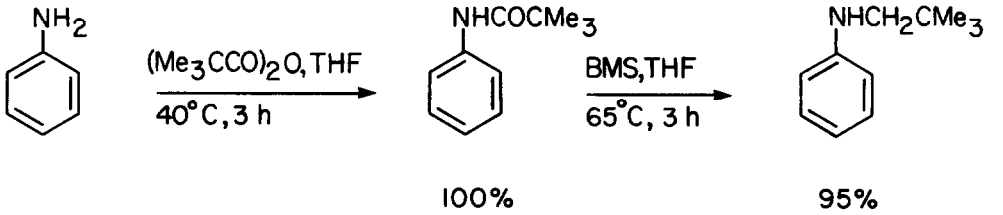
(2)



(3)

Even very weakly basic and multifunctional amines such as 2-chloro-4-nitroaniline and 4-amino-3-chloro-N,N-dimethylbenzenesulfonamide undergo this conversion smoothly

Finally, the present methodology appears to be readily adaptable for the introduction of a variety of other N-monoalkyl groups including the alkyl groups of very high steric requirements (eq 4) [10]



(4)

The following procedure for the N-monomethylation of 2-chloro-4-nitroaniline is representative An oven-dried 250-mL flask equipped with a sidearm fitted with a Teflon stopcock, a magnetic stirring bar, and a reflux condenser connected to a mineral oil bubbler was cooled to room temperature under a stream of dry nitrogen Acetic formic anhydride was generated in the flask by dropwise addition of 98% formic acid (7 5 g, 160 mmol) to 13 5 g (130 mmol) of acetic anhydride maintained at 0 °C followed by gentle heating (50-60 °C, 2 h) The mixture was cooled to room temperature, and 10 mL of THF was added The reflux condenser was temporarily removed, and 8 65 g (50 mmol) of 2-chloro-4-nitroaniline dissolved in 20 mL of THF was added The formylation was complete in 3 h, as shown by thin layer chromatography (TLC) The volatiles were removed in vacuo (ca 10 mm Hg) to provide 10 g (50 mmol, 100%) of essentially pure (TLC) 2-chloro-4-nitroformanilide, mp 174-175 °C The formanilide was dissolved in THF (25 mL), the solution was cooled to 0 °C, and 12 5 mL (125 mmol) of borane methyl sulfide complex was introduced dropwise After vigorous reaction ceased, the resulting mixture was brought to a gentle reflux and maintained at that temperature until completion (3 h, TLC) The reaction mixture was

cooled to 0 °C, 20 mL of methanol was added, and the mixture was stirred well (1 h) Anhydrous hydrogen chloride was bubbled through the mixture to attain a pH of ≤2, and the resulting mixture was gently refluxed for 1 h After the mixture was cooled, methanol (100 mL) was added and the solvents were removed on a rotary evaporator The solid residue obtained was made basic (water, NaOH pellets, pH >12) and extracted with three 100-mL portions of ether After the extracts were dried ($MgSO_4$), removal of the solvent gave 9 g (97%) of essentially pure (TLC) N-methyl-2-chloro-4-nitroaniline as an orange-yellow solid, mp 113-114 °C [lit [11] mp 116 °C] Recyrstallization from ethanol afforded 8 2 g (88%), mp 114 °C

In summary, formylation-reduction of primary amines provides a convenient route to the corresponding N-methylamine derivatives in nearly quantitative yields Further, all of the operations can be carried out in the same reaction vessel The mildness of the reaction sequence permits the presence of a variety of sensitive functional groups

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2 Limitations include competing bis alkylation (which results in mixtures that are difficult to separate), poor yields with sterically hindered amines, restricted applicability to aromatic primary amines, drastic reaction conditions, etc

3 Huffman, C W J Org Chem 1958, 23, 727-729

4 Examination of the reaction product by ^1H NMR and TLC showed only traces of acetanilide

5 Formylation at 0 °C is equally satisfactory

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7 (a) Brown, H C , Heim, P J Org Chem 1973, 38, 912-916 (b) Brown, H C , Narasimhan, S , Choi, Y M Synthesis 1981, 441-442

8 The reaction requires a minimum of 2 mol equiv of BH_3, one for the reaction with active hydrogen (N-H) and reduction and the other for complex formation with the resulting amine

9 McMaster, P D , Byrnes, E W , Feldman, H S , Takman, B H , Tenthorey, P A J Med Chem 1979, 22, 1177-1182

10 Aniline has been converted to a variety of N-monoalkyl derivatives in excellent isolated yields N-ethyl (100%), N-isobutyl (93%), N-benzyl (89%), and N-2-chloroethyl (92%)

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