Tetrahedron Vol 43, No 18, pp 4221 to 4226, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00

ONE-POT CHEMOSELECTIVE REDUCTIVE ALKYLATION OF NITROARENES: A NEW GENERAL METHOD OF SYNTHESIS OF ALKYLANILINES.

GIUSEPPE BARTOLI,[a*] MARCELLA BOSCO,[b] RENATO DAL POZZO,[b] MARINO PETRINI[a]

a. Dipartimento Scienze Chimiche,
Via S. Agostino 1, 62037 Camerino (MC) Italy

b. Dipartimento di Chimica Organica
Viale Risorgimento 4, 40136 Bologna, Italy

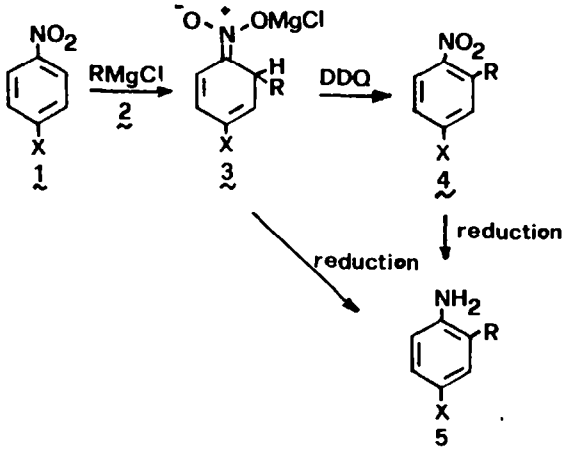
(*Received in UK* 6 *July* 1987)

Abstract - A New facile and general synthesis of alkylanilines by one-pot reductive alkylation of nitroarenes is reported. This method is based on the "in situ" reduction by hydrides ($LiAlH_4$ or $NaBH_4$) in the presence of catalytic amounts of Pd/C, of nitronate adducts arising from the conjugate addition of Grignard reagents to mononitroarenes. $LiAlH_4$ showed to be a more efficient but less selective reducing agent than $NaBH_4$. The reaction can be successfully applied to mono, homo and hetero bicyclic systems and allows to introduce a large variety of alkyl chains without isomerisation phenomena.

Alkylanilines are undoubtedly a class of topical interest in organic synthesis, mainly due to the easy conversion of the aromatic amino group into a large variety of organic functions. For example, **ortho**-alkylanilines are the usual building-blocks in several methods of synthesis of indole nucleus.[1]

Anilines are generally obtained by reduction of the corresponding nitro-derivatives. For this purpose, it seems very useful the recently reported alkylation of nitroarenes[2] based on the ability of certain organometallic reagents ($RMgX$[2], RLi[3], $RSiMe_3/F^-$[4]) to give an irreversible conjugate addition to nitroarenic systems, which leads to nitronate adducts like 3 (scheme 1).

Scheme 1



The "in situ" oxidation of 3 with the appropriate oxidizing agent (generally DDQ) affords alkyl nitroarenes 4[3a,4]. The high usefulness of this method as a source of precursors of ortho-alkylanilines lies in the possibility of introducing chemoselectively[5] long alkylic chains without isomerisation phenomena.

A very recent ingenious method of indole synthesis[6] follows a synthetic pattern similar to the 1→4→5 sequence depicted in scheme 1.

The direct conversion of 3 into 5 with the appropriate reducing agent could represent undoubtedly an actual improvement to the above described synthetic strategy, since, besides obtaining a much more immediate procedure, it could avoid the use of a very expensive reagent such as DDQ, necessary to ensure selectivity in the oxidation of 3 to 4.[5b]

Previous attempts to convert 3 into 5 were made using a large excess of Grignard reagent in the presence of catalytic amounts of CuI.[7] However this method seems to be of restricted applicability, as incompatible with substrates having functions, which do not survive a large excess of Grignard reagent for long contact times. In addition, the request of five moles of organomagnesium compound per mole of substrate makes this way not-profitable with very expensive or sophisticated RMgX.

In this work, we wish to describe a new general and chemoselective method of reduction of nitronate adducts 3 into anilines 5 by means of hydrides ($LiAlH_4$ or $NaBH_4$) in the presence of activated palladium on charcoal.

Cyclohexadienic nitronates like 3 cannot be isolated owing to the instability of their conjugate acids. Therefore, the reduction must be performed by adding the hydride to a THF solution of 3 as soon as formed from RMgX and nitroarene. The preparation of 3 was generally carried out at -30°C except for some particular cases (4-nitrobenzonitrile and 4-nitrobenzoate) for which milder conditions (-78°C) were necessary to ensure chemoselectivity.[5a]

As shown in table 1, very satisfactory yields were generally obtained with various nitroarenic systems and a large variety of Grignard reagents. In fact, only 6-nitrobenzothiazole and 6-nitroquinoline led to the respective amines in moderate yields. However, this is mainly due to decomposition phenomena occurring in the work-up of the reaction especially during the separation on silica gel column, as demonstrated by the significantly higher g.l.c. yields calculated on the crude of the reaction.

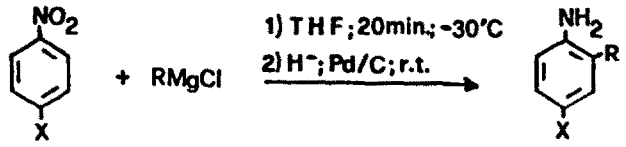
In several cases, we observed the formation of N-alkyl anilines as by-products. However, their amounts did not generally exceed the 3-4% yields, except in the cases where benzylmagnesium chloride was involved (12-18%).

Lithium aluminum hydride is a more efficient but less selective reducing agent than sodium borohydride. The choice of the hydride, therefore, essentially depends on the presence of easy reducible substituents in the nitronate system. In fact, cyano and ester groups bound to 4-position of the phenyl ring (entries 7,8,9) are unaffected only utilizing $NaBH_4$ at room temperature. In an analogous manner, $NaBH_4$ is able to reduce nitronate function without affecting thiazole nucleus in appreciable extent, by carrying the reaction at -30°C for 4 hours.

On the other hand, when reducible functions are not present in the substrate, the use of $LiAlH_4$ is much more convenient, requiring much shorter reaction times

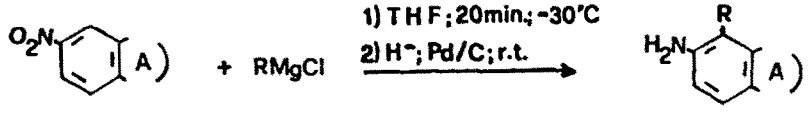
Table 1: One-pot Reductive Alkylation of Nitroarenes to Alkylanilines[a]

a)

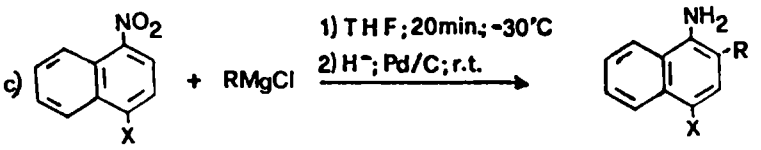


Entry	X	R	Hydride	Reaction[a] time (h)	Yield[b] (%)
1	MeO	Me	$LiAlH_4$	2	60
2	MeO	i-Pr	$LiAlH_4$	6	59
3	MeO	Me_3SiCH_2	$LiAlH_4$	2	70 (75)
4	Cl	Me	$LiAlH_4$	2	72
5	Cl	Me	$NaBH_4$	7	68 (71)
6	Cl	i-Pr	$LiAlH_4$	8	57
7	CN[c]	Me	$NaBH_4$	6	75 (82)
8	CN[c]	$CH_2=CH(CH_2)_3$	$NaBH_4$	12	73 (81)
9	COOMe[c]	Me	$NaBH_4$	8	71 (79)
10	Me_3SiO[d]	C_8H_{17}	$LiAlH_4$	4	63

b)



Entry	A	R	Hydride	Reaction[a] time (h)	Yield[b] (%)
11	 [e]	C_4H_7	$NaBH_4$	5	35. (71)
12		CH_3	$LiAlH_4$	20	60
13	"	$PhCH_2$	$LiAlH_4$	20	61[f]
14	"	$PhCH_2$	$NaBH_4$	48	63[f]
15		$PhCH_2$	$LiAlH_4$	20	66[f]
16	"	$CH_2=CH(CH_2)_2$	$LiAlH_4$	20	66
17	 [g]	$CH_2=CH(CH_2)_2$	$NaBH_4$	12	30 (67)



Entry	X	R	Hydride	Reaction time (h)[a]	Yield (%)[b]
18	OCH_3	CH_3	$LiAlH_4$	36	60

[a] Refers to contact time between the hydride and the nitronate. [b] Yields in pure isolated product, values in parenthesis refer to g.l.c. yields detected on the crude of the reaction. [c] In order to ensure chemoselectivity (see ref. 4), the formation of nitronate adducts from RMgX and the nitroarene was carried at -78°C. [d] 4-amino-3-octyl phenol was isolated, being the trimethylsilyl group hydrolized during the work-up. [e] The reduction of the nitronate was carried out at -30°C. [f] An appreciable amount of N-benzyl-derivatives (see experimental) was also isolated (12.18%). In all other cases the amount of these by-products does not exceed 4%. [g] The reduction of the nitronate was carried out at 0°C.

with comparable results. For example, the reduction of nitronate arising from 4-chloronitrobenzene went to completion in two hours against the seven hours required by the $NaBH_4$.

The presence of palladium as a catalyst is essential to warrant complete and profitable reduction of nitronate to amino function. In fact the attempted reaction of nitronate adduct from CH_3MgX and p-chloronitrobenzene with $LiAlH_4$ alone led to the formation of appreciable amounts of 4,4'-dichloro-2,2'-dimethylazobenzene as by-product of uncomplete reduction, while it resulted to be sluggish when $NaBH_4$ was used as the reducing agent in the absence of Pd/C.

Finally, we wish to outline that in all investigated cases no possible products arising from the reduction of the cyclohexadienic system were observed, although $LiAlH_4$ is known to reduce activated conjugate carbon-carbon double bonds.

In conclusion, a new, facile and general method to synthetize alkyl anilines by on-pot reductive alkylation of nitroarenes is now available.

EXPERIMENTAL

^1H - N.m.r. spectra were recorded with a Varian EM360L instrument. Chemical shifts are given in p.p.m. from Me_4Si in $CDCl_3$ solutions. IR spectra were recorded with a Perkin-Elmer 983 spectrometer. Mass spectra were recorded with an HP59970 workstation formed by an HP-5890 gas-chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. Melting points are uncorrected and were determined with a Büchi apparatus. THF was dried by refluxing it over sodium wires until the blue colour of benzophenone ketyl persisted and then distilling it into a dry receiver under nitrogen atmosphere. Commercial nitrocompounds were recrystallized before use. 4-Nitrophenoxytrimethylsilane[8] and 1-methyl-5-nitroindole[5b] were prepared by the reported methods. Grignard reagents were titrated before use.[9]

Preparation of alkylanilines (5) from the corresponding nitroarenes (1). General Procedure.

A 100 mL three-necked round-bottom flask equipped with a magnetic stirrer and a dropping funnel was charged under nitrogen atmosphere with the appropriate nitrocompound (5 mmol) dissolved in dry THF (20 ml).

The solution was cooled at -30°C and the Grignard reagent (5.5 mmol) was added

dropwise. When nitroarenes were 4-nitrobenzonitrile and 4-nitrobenzoate methyl ester, the reaction was cooled at -78°C[4] before adding the Grignard reagent. After 20 minutes $LiAlH_4$ (10 mmol) or $NaBH_4$ (10 mmol) and 10% palladium on charcoal (0.45 g) were added. Stirring was continued at 20°C for the right time except for the reduction of 6-nitrobenzothiazole (reaction carried out at -30°C) and 6-nitroquinoline (reaction carried out at 0°C). Then a NH_4Cl solution was very cautiously added, the mixture was filtered, extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4, evaporated under reduced pressure.

The crude of the reaction was submitted to a flash-chromatographic purification on a short silica gel column using light petroleum: diethyl ether 7:3 to separate **ortho**-alkyl amines from the corresponding N-alkyl derivatives generally present in negligible amounts (0-4%). In the case of reaction of $PhCH_2MgCl$ with 2-nitronaphthalene and with 1-methyl-5-nitroindole, a 12% of N-benzyl-2-naphthylamine and a 18% of 1-methyl-5-benzylaminoindole respectively, was recovered besides the expected anilines.

Yields and reaction times are reported in table 1.

2-Methyl-4-anisidine (entry 1) and 4-chloro-2-toluidine (entry 4) were identified by comparison with authentic commercial samples (Aldrich); 6-amino-7-n-butylbenzothiazole[7] (entry 11) and 2-methyl-4-methoxy-1-naphthylamine[10] (entry 18) showed physical data identical with those previously reported.

Physical data for other synthetised anilines follow:

2-iso-propyl-4-anisidine: oil, ^{1}H-n.m.r. δ : 1.20 (d, 6H, CH_3, J_{CH_3-CH} = 6.0 Hz); 3.30-4.00 (m, 6H, $CH+NH_2$ + OCH_3); 6.50-7.10 (m, 3H, arom); IR (film)ν3381 and 3229 (NH_2) cm^{-1}; m/z: 165 (M^+); 150, 135, 122, 108. Anal calcd for $C_{10}H_{15}NO$: C, 72.73; H, 9.09; N, 8.48% found: C, 72.60; H, 9.10, N, 8.50%

2-trimethylsilylmethyl-4-anisidine: oil, ^{1}H-n.m.r. δ : 0.00 (s, 9H, Me_3Si); 1.50 (s, 2H, CH_2); 3.00 (bs, 2H, NH_2); 3.67 (s, 3H, OMe), 6.47 (bs, 3H, arom); m/z: 209 (M^+); 194, 178, 163, 73; IR (film)ν3368 and 3225 (NH_2), 1247 (C-Si) cm^{-1}. Anal calcd for $C_{11}H_{29}NOSi$: C, 63.16; H, 9.09; N, 6.70%; found C, 63.20; H, 9.00; N, 6.60%.

4-chloro-2-isopropylaniline: oil, ^{1}H-n.m.r. δ : 1.23 (d, 6H, CH_3, J_{CH_3CH} = 7.0 Hz); 2.78 (hep. 1H, CH), 3.60 (bs, 2H, NH_2); 6.40-7.23 (m, 3H, arom); IR (film) 3387 and 3239 (NH_2) cm^{-1}; m/z 169-171 (M^+), 154, 140, 119; Anal calcd for $C_9H_{12}NCl$: C, 63.91; H, 7.10; N, 8.28; Cl, 20.71%; found C, 64.00; H, 7.10; N, 8.25; Cl, 20.65.

4-amino-3-methylbenzonitrile mp 94-5°C (lit[11] 95°C), ^{1}H-n.m.r.δ: 2.06 (s, 3H, CH_3); 6.50 (bs, 2H, NH_2); 6.95-7.75 (m, 3H, arom); IR (CCl_4) ν 3300 and 3290 (NH_2); 2220 (CN) cm^{-1}.

4-amino-3-(5-penten-1-yl)-benzonitrile: m.p. 130-1°C; ^{1}H-n.m.r δ : 1.50-2.65 (m, 6H, CH_2); 4.85-5.17 (m, 2H, $=CH_2$); 5.30 (bs, 2H, NH_2); 5.60-6.15 (m, 1H, CH=) 7.10-7.70 (m, 3H, arom) IR (CCl_4)ν3300 and 3290 (NH); 2220 (CN) cm^{-1}.Anal calcd for $C_{12}H_{12}N_2$: C, 77.42; H, 7.53; N, 15.05%; found C, 77.50; H, 7.50; N, 15.00%.

4-amino-3-methyl-benzoate methyl ester: mp 115-118°C (lit[12] 118°C); ^{1}H-n.m.r. δ : 2.15 (s, 3H, CH_3); 3.83 (s, 3H, OMe); 4.05 (bs, 2H, NH_2); 6.55-6.73 (m, 1H, arom); 7.67-7.88 (m, 2H, arom); IR (CCl_4)ν3320 and 3295 (NH); 1735 (CO) cm^{-1}.

4-amino-3-octylphenol: oil; ^{1}H-n.m.r.δ: 1.05-1.80 (m, 15H, aliph); 3.66 (t, 2H, CH_2, J_{CH-CH} = 6.0); 4.50 (bs, 3H, NH_2 + OH); 6.50-6.90 (m, 3H, arom); m/z: 221 (M^+), 122; 93, 77. Anal Calcd for $C_{14}H_{23}NO$: C, 76.02; H, 10.41; N, 6.33% found C, 76.10; H, 10.40; N, 6.30%

1-methyl-2-naphthylamine: p.f. 49-51°C (lit[13] 51°C); ^{1}H-n.m.r. δ : 2.33 (s, 3H, Me); 3.67 (bs, 2H, NH_2); 6.80-8.03 (m, 6H, arom), m/z: 157 (M^+), 156, 139, 128, 115.

1-benzyl-2-naphthylamine: p.f. 72-3°C; ^{1}H-n.m.r. δ : 3.40 (bs, 2H, NH_2); 4.37 (s,

2H, CH_2); 6.97-8.27 (m, 11H, arom); m/z: 233 (M^+), 215, 156, 128. Anal calcd for $C_{17}H_{15}N$: C, 87.55, H, 6.44, N, 6.01%; found C, 87.60; H, 6.40; N, 6.00%

5-amino-4-benzyl-1-methylindole: p.f. 63-4°C; ^{1}H-n.m.r. δ : 3.07 (bs, 2H, NH_2); 3.43 (s, 3H, CH_3) 4.00 (s, 2H, CH_2), 6.10-7.10 (m, 9H, arom); m/z: 236 (M^+), 218; 159, 117, 110. Anal calcd for $C_{16}H_{16}N_2$: C, 81.36; H, 6.78; N, 11.86%; found C, 81.40; H, 6.80; N, 11.80%.

5-amino-4-(4-buten-1-yl)-1-methylindole: oil; ^{1}H-n.m.r.δ: 2.13-3.10 (m, 4H, CH_2CH_2); 3.40 (bs, 2H, NH_2); 3.60 (s, 3H, CH_3); 4.90-5.33 (m, 2H, $=CH_2$); 5.53-6.10 (m, 1H, CH=); 6.33-7.15 (m, 4H, arom); m/z: 200 (M^+): 159, 132, 117. Anal calcd for $C_{13}H_{16}N_2$; C, 78.00; H, 8.00; N, 14.00%; found C, 78.10; H, 8.00; N, 13.90%.

6-amino-5-(4-buten-1-yl)quinoline: oil; ^{1}H-n.m.r. δ : 2.10-3.30 (m, 4H, CH_2CH_2), 3.60 (bs, 2H, NH_2); 4.90-5.43 (m, 2H, $=CH_2$); 5.60-6.23 (m, 1H, CH=); 7.10-9.10 (m, 5H, arom); IR (film) 3280 and 3180 (NH_2) cm^{-1}; m/z: 198 (M^+), 157, 130, 103, 77. Anal calcd for $C_{13}H_{14}N_2$: C, 78.79; H, 7.07; N, 14.14%; found C, 78.90; H, 7.00; N, 14.10%

1-methyl-5-benzylaminoindole: oil; ^{1}H-n.m.r. δ : 2.70 (bs, 1H, NH); 3.43 (s, 3H, Me); 4.13 (s, 2H, CH_2); 5.93-7.13 (m, 10H, arom); m/z: 236 (M^+), 145, 118, 91, 77. Anal. calcd for $C_{16}H_{16}N_2$: C, 81.36; H, 6.78; N, 11.86% found C, 81.39; H, 6.78; N, 11.83%.

N-benzyl-2-naphthylamine: oil, ^{1}H-n.m.r. δ : 3.43 (bs, 1H, NH); 4.66 (s, ZH, CH_2); 7.00-8.30 (m, 11H, arom); m/z: 233 (M^+); 122, 109, 91, 77. Anal calcd for $C_{17}H_{15}N$: C, 87.55; H. 6.44; N, 6.01%; found C, 87.58; H, 6.42; N, 6.00%.

REFERENCES AND NOTES

1. a. W.J. Houlihan, V.A. Parrino, Y. Uike, J.Org.Chem., 1981, **46**, 4511; b. R.L. Augustine, A.J. Gustavsen, S.F. Wanat, I.C. Pattison, K.S. Houghton, G. Koletar, J.Org.Chem., 1973, **38**, 3004; c. M. Le Corre, A. Herquet, H. Le Baron, J.Chem. Soc., Chem.Commun., 1981, 14; d. J.E. Nordlander, D.B. Catalane, K.D. Kotian, R.M. Stevens, J.E. Haki, J.Org.Chem., 1981, **46**, 778; e. Y. Ito, K. Kobayashi, N. Seko, T. Saegusa, Bull.Chem.Soc.Jap., 1984, **57**, 73; (f) A.B. Smith, M. Visnick, J. Haseltine, P.A. Sprengeler, Tetrahedron, 1986, **42**, 2957.
2. G. Bartoli, Acc.Chem.Res., 1984, **17**, 109.
3. a. F. Kienzle, Helv.Chim.Acta, 1978, **61**, 449; b. G. Bartoli, R. Dalpozzo, L. Grossi, P.E. Todesco, Tetrahedron, 1986, **42**, 2563.
4. T.V. Rajan Babu, G.S. Reddy, T. Fukunaga, J.Am.Chem.Soc., 1985, **107**, 5473.
5. a. G. Bartoli, M. Bosco, R. Dalpozzo, Tetrahedron Lett., 1985, **26**, 115; b. G. Bartoli, M. Bosco, R. Dalpozzo, P.E. Todesco, J.Org.Chem., 1986, **51**, 3694.
6. T.V. Rajan Babu, B.L. Chenard, M.A. Petti, J.Org.Chem., 1986, **51**, 1704.
7. G. Bartoli, A. Medici, G. Rosini, D. Tavernari, Synthesis, 1978, 436.
8. A.R. Bassindale, C. Eaborn, D.R.M. Walton, J.Chem.Soc. C, 1970, 1577.
9. D.E. Bergbreiter, E. Pendergrass, J.Org.Chem. 1981, **46**, 219.
10. G. Bartoli, M. Bosco, G. Cantagalli, R. Dalpozzo, Tetrahedron, 1984, **40**, 3437.
11. S. Gabriel, A. Thieme, Chem.Ber., 1919, **52**, 1079
12. V. Jürgens, Chem.Ber., 1907, **40**, 4409.
13. K. Fries, E. Hübner, Chem.Ber., 1906, **39**, 435.