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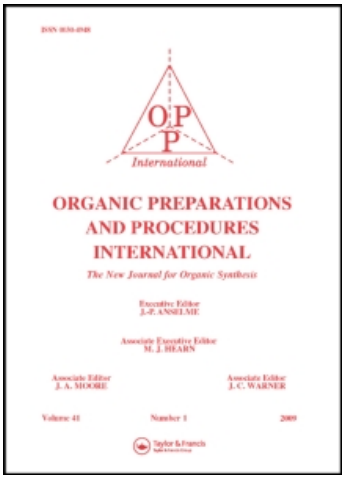

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AN ALTERNATE METHOD FOR THE SYNTHESIS OF SECONDARY NITRAMINES

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The mechanism of the nitramine rarrangement has been the subject of much controversy for several years.[1] Although heavy atom kinetic isotope effect studies (KIE) indicate that migration of the nitro group is a non-concerted process[2] and a free radical path has been established for sterically hindered nitramines;[3] nevertheless, the problem of the mechanism is far from being resolved and a simple and effective route to model compounds is needed for further investigations. Arylnitramines may be prepared either by the oxidation of precursors containing N-N bonds (diazoates,[4] N-nitrosamines[5]) or by nitration of amines under proper conditions.[6] Since typical arylnitramines are sensitive to acids and elevated temperature, N-nitration of aniline derivatives with nitric acid or anhydride is limited to amines of low basicity, *e. g.* N-methyl-2,4-dinitroaniline.[7] Nitration with alkyl nitrates in the presence of phenyllithium seems to be the most effective route to phenyl- and naphthylnitramines although the yields usually do not exceed 40%.[8,9]

We now report that secondary arylamines (**1**, R = Ar) and related compounds can be easily converted into corresponding nitramines (**3**) by the action of *n*-butyl nitrate on the organomagnesium compounds:

1 **2** **3**

The yields generally ranged from 40% to 77%; significant loss of the material during crystallization resulted in low yields of nitramines having melting points below 50° (Table 1). Methanesulfonyl derivatives which could not be prepared according to the method of White and Klink[9] were obtained without any difficulties. The procedure is rapid and simple. The nitramines are isolated by crystallization or vacuum distillation and contain no traces of the rearranged products. Although the syntheses may be carried out in an ethereal solvent (tetrahydrofuran or diethyl ether), we have found it advantageous to dissolve the substrates in a non-polar solvent such as benzene or hexane. After addition of the dilute ethereal solution of the Grignard reagent, the anilinomagnesium bromides remained in solu-

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tion. Addition of *n*-butyl nitrate caused a slightly exothermic reaction which was completed in 0.5-1 hr. The reaction mixture was extracted with water containing an excess of acetic acid which facilitated removal of the magnesium salts, then dried and evaporated *in vacuo*. In spite of the large excess (50%) of the reagents and protection of the reaction vessel from moisture, some of the starting amines remained unchanged. Transformation of esters into amides is usually a reversible process, as may also be the case for the nitrate ester to nitramine reaction. The equilibrium was not studied in detail but the reaction mixture obtained from N-methylaniline under conditions described in the Experimental Section, contained, according to GC analyses, ca. 90% of N-methyl-N-phenylnitramine (RT = 22.0 minutes) and 10% of the substrate (RT = 10.0). It was also found that magnesium butoxide reacts with the nitramine forming *n*-butyl nitrate (RT = 2.7) and N-methylaniline. The amines can be removed from the crude product by extraction with petroleum ether, but with liquid or low-melting nitramines

TABLE 1. Ring Substituted N-Methyl-N-arylnitramines (R = Me)

R'	Yield (%)	mp. (°) (solvent)	lit. mp. (°C)	IR:NO_2 ν_{sym}	stretch ν_{asym}
C_6H_5	47	44-45 (*n*-hexane)	44.5[8]	1288	1524
4-MeC_6H_4	60	80-81 (petrol)[a]	74-75[9]	1289	1524
4-*t*-BuC_6H_4	65	80-81 (Et_2O-petrol)	[b]	1299	1517
4-$PhCH_2C_6H_4$	49	48-49 (*n*-hexane)	[c]	1287	1525
4-PhC_6H_4	77	147-148 (PhH)	137-138[9]	1292	1528
4-$PhN_2C_6H_4$	66	118-120 (MeOH)	[d]	1286	1534
4-$MeOC_6H_4$	52	73-74 (*n*-hexane)	69-69[8]	1290	1522
4-$MeSO_2C_6H_4$	45	157-159 (PhMe)	158-159[9]	1289	1522
4-BrC_6H_4	61	82-83 (*n*-hexane)	84.5-85[8]	1287	1522
4-IC_6H_4	70	94-95 (Et_2O-petrol)	[e]	1285	1528
3-MeC_6H_4	73	bp.85/0.4 mm Hg	liquid[9]	1291	1531
3-$MeSO_2C_6H_4$	68	102-104($CHCl_3$ -petrol)	[f]	1293	1519
3-FC_6H_4	41	24-25 (Et_2O-petrol)	24-25[9]	1288	1536
3-ClC_6H_4	65	54-55 (petrol)	48-49[9]	1288	1533
3-BrC_6H_4	55	41-42 (petrol)	43-44[9]	1284	1530
2-MeC_6H_4	65	bp.75-79/0.5 mm Hg	liquid[10]	1277	1522
2,6-Me_2C6H_3	10	95-97 (petrol)	[g]	1288	1513

a) Petroleum ether (bp. 45-50°) was used for crystallization.
b) *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.43; H, 7.74. Found: C, 63.49; H, 7.74
c) *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.45; H, 6.00
d) *Anal.* Calcd for $C_{13}H_{12}N4O_2$: C, 60.93; H, 4.72. Found: C, 61.06; H, 4.78
e) *Anal.* Calcd for $C_7H_7IN_2O_2$: C, 30.02; H, 2.52. Found: C, 30.52; H, 2.50
f) *Anal.* Calcd for $C_8H_{10}N_2SO_4$: C, 41.73; H, 4.38. Found: C, 41.79; H, 4.40
g) *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71. Found: C, 60.21; H, 6.75

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extraction of the reaction mixture with aqueous hydrogen potassium sulfate gives better results. Most of the crude nitramines can be crystallized from light petrol containing 5-10% of ether or methylene chloride which increase solubility. Vacuum distillation when carried out from a boiling water bath causes no decomposition.

Steric hindrance retards the reaction (Table 2). Thus, N-methyl-2,6-dibromoaniline could not be N-nitrated in this way and N-*t*-butyl- and N,2,6-trimethyl-N-phenylnitramines have been obtained in low yields. Crystalline N,N-diphenylnitramine rearranges when stored at room temperature; after two weeks it contains significant amounts of C-nitro compounds. Its preparation must be carried out at ca.-15° and four low-temperature crystallizations are necessary to obtain pure nitramine, hence the yield is very poor. The method is not applicable to nitramines containing nitroso or nitro groups attached to an aromatic ring. The corresponding anilinomagnesium bromides do not react with the nitrate; moreover, excess of the Grignard reagent attacks these groups. Our attempts to prepare N-nitroazoles in this way were also unsuccessful; pyrazole, imidazole, indazole and benzotriazole were recovered unchanged.

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TABLE 2. Secondary Aromatic and Aliphatic Nitramines.

Nitramine	Yield (%)	mp. (°) (solvent)	lit. mp. (°C)	IR:NO_2 stretch ν_{sym}	ν_{asym}
N,N-Diphenyl	11	83-85 (petrol)	81-83[5]	1286	1530
N-Benzyl-N-phenyl	62	57-58 (*n*-hexane)	[a]	1275	1518
N-*n*-Butyl-N-phenyl	54	65-67/0.6 mm Hg	[b]	1279	1524
N-*t*-Butyl-N-phenyl	21	39-40 (petrol)	[c]	1287	1526
		69-72/0.4 mm Hg			
N-Allyl-N-phenyl	43	64-67/0.4 mm Hg	[d]	1277	1526
N-Methyl-N-(1-naphthyl)	54	80-82 (Et_2O-petrol)	72-74[6]	1291	1521
N-Methyl-N-(2-naphthyl)	53	110-112 (Et_2O-petrol)	109[10]	1295	1592
N-Methyl-N-(2-pyridyl)	43	28-29 (Et_2O-petrol)	30-31[14]	1276	1534
N-Methyl-N-(3-pyridyl)	54	62-63 (Et_2O-petrol)	60[11]	1287	1530
N,N-Diisobutyl	63	78-80 (petrol)	79-80[12]	1274	1500
N,N-Dimethyl	20	55-56 (petrol)	57-58[12]	1335	1502
N-Nitropiperidine[e]	49	63-65/2 mm Hg	-6[13]	1282	1510
N-Nitropyrrolidine[f]	14	49-51 (petrol)	55-57[11]	1381	1495

a) *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30. Found: C, 63.42; H, 5.29
b) *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26. Found: C, 61.89; H, 7.35
c) *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26. Found: C, 61.87; H, 7.19
d) *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 60.66; H, 5.66. Found: C, 60.72; H, 5.59
e) Purified by crystallization from *n*-hexane with cooling in a Dry Ice bath.
f) 50% of the substrate was recovered unchanged.

Secondary aliphatic nitramines can be synthesized with the aid of acetone cyanohydrin nitrate[12] but both preparation of the reagent and work-up of the reaction mixture are hazardous due to evolution of HCN. The present method was also successfully applied to some aliphatic secondary nitramines (Table 2), although isolation of N,N-dimethylnitramine presented some problem due to its excellent solubility in water.

EXPERIMENTAL SECTION

The preparation of N-methylanilines was described previously.[15] *n*-Butyl nitrate was obtained according to a known procedure.[16] The purity of liquid products was determined with a Hewlett-Packard gas chromatograph using a capillary column 30 mX320 μm with silicone SPB-5 as the stationary phase. The temperature of the column was changed from 30° to 150° at the rate of 3°/min. The infrared spectra were recorded on an FTIR spectrometer PU 9804 (Philips) as KBr pellets. Electron-impact (70 eV) mass spectra were obtained on the MX 1321 instrument (Scientific Instruments, USSR).

***n*-Butyl Nitrate**.- To conc. sulfuric acid (140 mL, 96% H_2SO_4), maintained below 12° in an ice bath, nitric acid (80 mL, d = 1.52) and then methylene chloride (700 mL) were slowly added. *n*-Butanol (74 mL) was added dropwise at such a rate that the temperature remained 12o. The mixture was stirred at room temperature for 0.5 hrs and the layers were separated. The organic phase was extracted with water, 10% aqueous sodium carbonate (3x200 mL), 10% aqueous sodium azide (100 mL) and again with water. The solution was dried over magnesium sulfate and the solvent was evaporatedusing a water bath. Distillation of the residue *in vacuo* (the condenser was cooled to 18°) gave a forerun (10.7 g) which contained ca. 63% of *n*-butyl nitrate. The main fraction (86.0 g, 89%) was collected at 47°/10 mm Hg; the colorless liquid contained 98% of *n*-butyl nitrate according to GC analysis; $n_2^{D}{}_4$ = 1.4044. IR (neat): 874 cm^{-1} (N-O stretch), 1279, 1626 (nitro group stretching frequencies), 2879, 2940, 2967 (aliphatic C-H stretching vibrations).

Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.61. Found: C, 40.30; H, 7.80

N-Nitration of Secondary Amines. General Procedure.- Ethyl bromide (6.8 mL, 0.09 mole), diluted with 50 mL of anhydrous ether was added dropwise to a stirred suspension of 3.65 g (0.15 mole) of magnesium turnings in 100 mL of ether. The ethylmagnesium bromide mixture was filtered and added to a solution of 0.06 mole of the amine in 200 mL of dry benzene. The mixture was stirred for 15 minutes. Then *n*-butyl nitrate (10.72 g, 0.09 mole) was added and stirring continued for 0.5 hr. Water (100 mL) and acetic acid (12 mL) were added and the aqueous layer was separated and discarded. The solution was extracted twice with 5% aqueous potassium hydrogen sulfate, dried over anhydrous magnesium sulfate and evaporated under reduced pressure using a water bath maintained below 45°. The residue was distilled *in vacuo* from a boiling water bath or crystallized from a proper solvent system. The structure of the products was confirmed by their IR and mass spectra. GC analyses of liquid nitramines indicated that their purity exceeded 98%. The results are collected in the Tables.

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