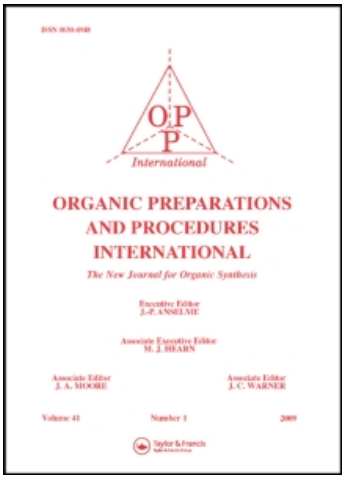

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THE VON BRAUN REACTION BETWEEN N-t-BUTYLAMIDES AND PHOSPHORUS OXYCHLORIDE. A CONVENIENT NITRILE SYNTHESIS

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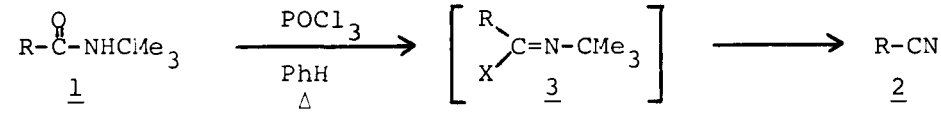
The reaction of N-alkylamide (or N,N-dialkylamide) with a phosphorus pentahalide, known as the von Braun reaction[1], has been used to prepare alkyl halides[2] but only rarely[3] nitriles, the other product of this reaction. Nitriles are then only formed under vigorous conditions (200-285°C). We here describe an adaption of the von Braun reaction that provides a convenient synthesis of nitriles under mild conditions.

Thus, treatment of an N-t-butylamide 1 with phosphorus oxychloride in refluxing benzene for 4-6 hrs gives the corresponding nitrile 2 in generally excellent yield. Our results are summarized in Table 1. The amides are easily prepared from the appropriate acid chloride and t-butylamine.



a) X = $OPOCl_2$ b) X = Cl

The mechanism of this transformation likely involves the formation of the imidoyl species 3, similar to those intermediates that have been implicated in the Vilsmeier Haack reaction.[4] Subsequent E1 or E2 type fragmentation would lead to

the nitrile and isobutylene[5] (or t-butyl chloride).

Table 1. Preparation of Nitrile 2 from N-t-Butylamides 1 and Phosphorus Oxychloride in Benzene

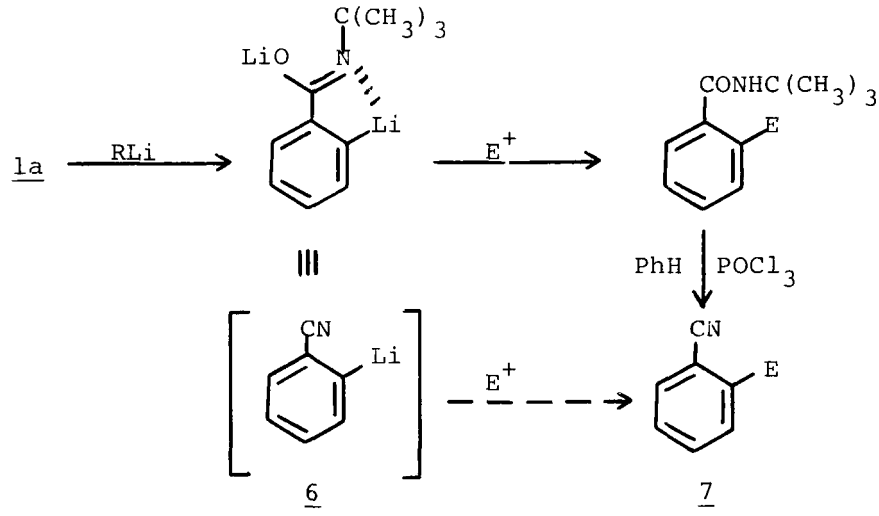
Amide	R	Nitrile[a]	Temp (°C)	Time	Yield[b] (%)	Purity[c] (%)
1a	Ph	2a	reflux	6h	81	100
1b	$CH_3(CH_2)_{14}$	2b	reflux	4h	94	97
1b	$CH_3(CH_2)_{14}$	2b	20°	240h	71[d]	--
1c	$(CH_3)_3CNHC(=O)(CH_2)_4$	2c[e]	70°	14h	51	89
1d	PhCH=CH	2d	reflux	5h	81	96
1e	indolyl-3-CH_2	2e	reflux	5h	94	--

a) Nitriles exhibited satisfactory ^{1}H-NMR and IR spectra which were in agreement with published spectra. b) Yields refer to column chromatographed product. c) By gas chromatography. d) A mixture of 2b (71%) and 1b (29%) by GC. e) Adiponitrile.

Indeed, Ugi has noted[6] the instability of imidoyl chloride 3b (R = phenyl), which fragments to benzonitrile (2a) and t-butyl chloride upon attempted isolation, and Merritt and Johnson[7] have reported that the anti isomer of $PhC(F)=NCMe_3$ fragments to 2a, isobutylene, and hydrogen fluoride in less than five minutes at 25°, perhaps intramolecularly since the syn isomer is stable at 25°.

In accord with an E1 or E2 type reaction for 1→2 is our observation that N-cyclohexylbenzamide is only slowly converted to 2a under the usual conditions (10% of 2a after 5 hrs at reflux). Likewise, N-benzylhexadecanamide gave 2b in about 15% yield after refluxing with phosphorus oxychloride in benzene for 4 hrs. These amides are expected to be less reactive than the N-t-butylamides (1) in E1 and E2 elimination reactions.

It should be noted that, in at least one case, thionyl chloride (refluxing benzene, 6 hrs) works equally well, i.e., 1b→2b (95% yield). Finally, this new methodology provides a synthetic equivalency for ortho-metalated benzonitriles, such as 6, since the directed ortho lithiation of N-t-butylbenzamides (e.g., 1a) has been reported.[8] These transformations are summarized below. This approach to ortho-substituted benzonitriles 7 is potentially significant since ortho metalation of benzonitrile itself proceeds in low yield.[8b,9]



EXPERIMENTAL

Amide Preparation. General Procedure. - To a magnetically stirred solution of t-butylamine (10-20 mmol) and triethylamine (20-40 mmol) in dichloromethane (50 ml) at 0° was added the acid chloride (10-20 mmol) in portions over 5 min. The reaction was stirred and allowed to warm to room temperature overnight. Water (50 ml) was added and the layers were separated. The organic layer was washed with 5% aqueous HCl (1 x 50 ml) and water (1 x 50 ml), dried (Na_2SO_4), and concentrated in vacuo to afford colorless amide as listed below and suitable

for use in the von Braun reaction.

N-t-Butylbenzamide (1a), obtained by the above procedure in 98% yield, mp.128-130°, lit.[10] 135-136° IR (KBr): 3310, 2960, 1630, 1535, 1308, 1210 cm^{-1}.

N-t-Butylhexadecanamide (1b), obtained by the above in 94% yield, mp.60-62°, lit.[11] 63-64° IR (KBr): 3225, 3010, 1640, 1542, 1360, 1218 cm^{-1}.

N-t-Butylcinnamamide (1d), obtained by the above in 97% yield, mp.142-144°, lit.[12] 143° IR (KBr): 3270, 1655, 1626, 1556, 1342, 1220 cm^{-1}.

N,N-Di-t-Butyladipamide (1c). - The usual reaction conditions were used but the workup was modified. The reaction mixture was concentrated to dryness in vacuo and water was added to the residue. The aqueous suspension was suction filtered and the solid was dried in vacuo to afford 1c in 89% yield. Two recrystallizations from aqueous ethanol gave the analytical sample, mp.206-210° IR (KBr): 3300, 2960, 2920, 1645, 1604 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.37 (s, 18H), 1.45-1.78 (m, 4H), 1.97-2.30 (m, 4H), 6.55 (broad s, 2H)ppm. ^{13}C-NMR ($CDCl_3$): δ 25.0, 28.8, 37.1, 51.0, 172.0ppm.

Anal. Calcd for $C_{14}H_{28}N_2O_2$: C, 65.59; H, 11.01; N, 10.93; Found: C, 65.43; H, 11.04; N, 10.70.

Indole-3-(N-t-butyl)acetamide (1e). - The usual procedure afforded crude 1e as an orange foam. Chromatography over Florisil (ether) gave 1e as a white solid in 63% yield, mp.115-117°. Recrystallization from ether-hexane gave the analytical sample, mp.116-117° IR (KBr): 3410, 3305, 1640, 1542 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.27 (s, 9H), 3.60 (s, 2H), 5.61 (broad s, 1H), 6.75-7.52 (m, 5H), 9.13 (broad s, 1H). ^{13}C-NMR (CDCl3):

δ 28.6, 34.6, 50.9, 109.0, 111.4, 118.4, 119.6, 122.1, 123.6, 126.8, 136.5, 170.9.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17; Found: C, 72.88; H, 7.90; N, 12.11.

N-Cyclohexylbenzamide. - The usual procedure using cyclohexylamine gave this amide in 84% yield, mp.145-147°, lit.[13] 151-152° IR (KBr): 3330, 2925, 2850, 1627, 1530 cm^{-1}.

N-Benzylhexadecanamide. - The usual procedure using benzylamine gave this amide in 98% yield, mp.89.5-91°, lit.[11] 93-94° IR (KBr): 3315, 2925, 2870, 1642 cm^{-1}.

Nitrile Synthesis. General Procedure. - A magnetically stirred solution of N-t-butylamide (10 mmol) in benzene (40 ml) at room temperature was treated with phosphorous oxychloride (ca. 5 ml, 50 mmol). The solution was refluxed for 4-14 hrs (see Table 1) and then concentrated in vacuo. Dichloromethane (50 ml) and saturated aqueous sodium bicarbonate solution (50 ml) were added to the residue and the mixture was stirred overnight or until gas evolution ceased. The organic layer was separated, washed with water (50 ml), dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed over Florisil to give the nitrile generally as an oil in the yield shown in the Table. Nitrile 2b is a solid, mp.27-29°, lit.[14] mp.31°.

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