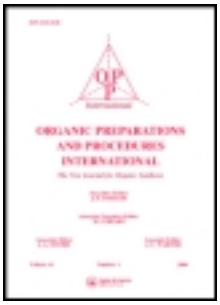

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A CONVENIENT PROCEDURE FOR INDIRECT OXIDATION OF AROMATIC METHYL GROUPS TO ALDEHYDES AND CARBOXYLIC ACIDS

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The oxidation of methyl groups attached to aromatic rings, to give aldehydes and/or carboxylic acids, is a common reaction in organic chemistry. The classic way to obtain the acids is the direct oxidation with a strong oxidant and has been performed under many conditions.[1] There are limitations, however, and our experience with methyl groups attached to polycyclic heterocycles is that much decomposition of the ring systems accompanies the targeted oxidation. Among various indirect methods for the conversion to aldehydes, the previously reported[2] sequence shown below has attractive features.

$$ArCH_3 \longrightarrow ArCH_2Br \longrightarrow ArCH_2ONO_2 \longrightarrow ArCHO$$

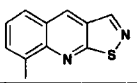
Although the intermediate aldehydes could also be obtained by the Kornblum oxidation of the benzyl bromides,[3] our primary interest was in the development of a one-pot process for the conversion of the benzyl bromides to the carboxylic acids. The key step in the above sequence involved the formal elimination of nitrous acid from the nitrate ester in aqueous ethanolic hydroxide under mild conditions. The oxidation reaction was not subject to steric effects suffered by the traditional Sommelet reaction of benzyl halides[4] and could be combined with the nitrate ester forming step in one pot. There were limitations, however; the reaction failed with nitro- and cyano-substituted aryl rings,[2] and in our hands, substitution of the nitrate ester by solvent-derived nucleophilic species was a problem the procedure was applied to polycyclic systems.

We have found that the use of triethylamine as base in non-aqueous conditions solves these problems for such systems. The range of substituted bromomethyl aromatic compounds that can be handled is thereby extended and the system worked for our prime candidates, polycyclic heterocycles. *Table 1* lists yields of products from some representative examples chosen to test the scope of the reaction. The first step was carried out essentially under the conditions previously reported.[2] Reaction of the highly hindered dinitro compound (entry 3) required more mercury (I) nitrate and two recharges. Triethylamine was then added (10 mol equiv. was routinely used) and the mixture was refluxed until reaction was complete (^{1}H NMR analysis). The aldehyde could be isolated at this stage. The method is least successful when the acidity of the α-methylene protons is reduced by the presence of an electron donating ring substituent. Thus, for the *p*-methyl substituted compound (entry 4), side-reactions competed and the isolated aldehyde contained an approximately equal amount of the *p*-methylbenzyl alcohol.

The original aim was to accomplish formation of carboxylic acids and the method also allows this goal to be realized by addition of a second oxidation step in the same one-pot reaction. A known procedure for oxidation of aldehydes with chlorite[5] was adapted to produce the correponding carboxylic acid in all but one example. This final step was not satisfactory for 2,6-dinitrobenzyl bromide (entry 3); in both the one-pot procedure and with the isolated aldehyde, chlorite oxidation gave the desired acid accompanied by an equal amount of dinitrobenzyl alcohol. A Cannizzaro aldehyde disproportionation reaction had apparently occurred. In this case, the aldehyde was isolated and then oxidized with aqueous permanganate according to a literature procedure.[6] Although the yields of entry 6 are modest, it is reasonable since this ring system is very sensitive to hydrolytic and basic conditions.

The required bromomethyl starting materials were prepared by standard *N*-bromosuccinimide/benzoyl peroxide reaction of the corresponding methyl compounds in refluxing carbon tetrachloride. Known aldehydes and acids were characterized by comparison of their mp's and ^{1}H NMR spectra with literature data, while data for the new compounds in entry 6 are reported in the Experimental Section.

Table 1. Conversion of Bromomethyl Aromatic Compounds to Aldehydes and Acids

	$ArCH_2Br$[a]	Reflux With NEt_3 (hrs)	Yield[b] ArCHO (%)	mp. (°C)	lit.[7] mp. (°C)	Yield[b] $ArCO_2H$ (%)	mp. (°C)	lit.[7] mp. (°C)
1	4-$NO_2C_6H_4$-	2	86[c]	103–104	106	65[c]	238–240	241.5
2	4-NCC_6H_4-	2	87[c]	93–94	92	64[c]	217–219	219
3	2,6-$(NO_2)_2C_6H_3$-[d]	1.5	40[e]	120–121	123	–[f]	200–201	202–203
4	4-MeC_6H_4-	2	28[g]		–	14[c]	173–175	181
5	8-quinolinyl	4	86[h]	91–92	94–95	46[c]	186–187	187
6		3	37[i]	193–194	–[j]	19[k]	260–262	–[j]

a) Except for entry 3, 1.5 equiv. of $Hg_2(NO_3)_2 \cdot 2H_2O$ was used with reflux time of 2 hrs for entries 1, 2, 5 and 3 hrs for entries 4 and 6. b) Yields for one-pot reaction. c) Recrystallized from water. d) 3.0 equiv. of $Hg_2(NO_3)_2 \cdot 2H_2O$ was used with reflux time of 2.5 hrs and this was repeated two further times. e) Recrystallized from acetic acid/water (1:2). f) See text; acid obtained in 65% yield by oxidation of isolated aldehyde with aqueous permanganate according to *ref 5*. g) Not purified. Yield estimated from the crude product which contained an approximately equal amount of *p*-methylbenzyl alcohol. h) Chromatography [silica; ethyl acetate:hexane (1:1)]. i) Recrystallized from acetonitrile. j) See Experimental Section. k) Recrystallized from ethanol.

Thus, from the examples investigated, the conditions devised are expected to be generally applicable to aromatic bromomethyl compounds, except those with diminished acidity of the methylene protons and with rings bearing functional groups such as amino and hydroxy which

cannot survive the conditions of the various steps, to give either aldehydes or acids in a convenient one-pot reaction.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker Avance AM-300 spectrometer operating at 300.13 MHz (^{1}H) and chemical shifts are reported as δ values (ppm), relative to tetramethylsilane. Microanalyses were carried out at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

Typical Procedure.- To a solution of bromomethyl compound (1 mmol) in 1,2-dimethoxyethane (10 mL) was added mercury (I) nitrate dihydrate (generally 1.5 mmol—see Table) and the whole was heated under reflux, with stirring, for the required time to give the intermediate nitrate ester (^{1}H NMR: CH_2 peak shifts from *ca* δ 5 (CH_2Br) to 6 (CH_2ONO_2). Triethylamine (10 mmol) was added to the mixture and reflux was continued for the time stated in the Table. The reaction mixture was then treated in either of two ways:

(a) Aldehyde Workup. The residual mercury salts were filtered off and the filtrate was concentrated, poured onto crushed ice and extracted with dichloromethane (3 × 10 mL). The extracts were dried ($MgSO_4$) and the solvent was evaporated to afford the desired aldehyde.

(b) Oxidation to Acids. Water (5 mL), acetic acid (2.5 mL), and 2-methyl-2-butene (a chlorine scavenger) (0.25 mL) were added to the reaction mixture, followed by dropwise addition of sodium chlorite (3 mmol) in water (5 mL). The mixture was stirred for 16 h at room temperature, then filtered and the filtrate was evaporated to dryness at reduced pressure. Water (10 mL) was added to the residue and the whole was taken to pH 12 with 10% sodium hydroxide, then filtered. The filtrate was acidified to pH 2 to precipitate the acid, except for the *p*-toluic and 8-quinolinic acids which were extracted into dichloromethane.

Isothiazolo[5,4-*b*]quinoline-8-carbaldehyde, a brown solid, mp. 193–194°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (t, *J*=7.7 Hz, H-6); 8.31 (dd, *J*=8.3, 1.5 Hz, H-5); 8.49 (dd, *J*=7.1, 1.4 Hz, H-7); 8.96 (s, H-4); 9.14 (s, H-3).

Anal. Calcd for $C_{11}H_6N_2OS$: C, 61.67; H, 2.82; N, 13.08. Found: C, 61.34; H, 2.73; N, 12.98.

Isothiazolo[5,4-*b*]quinoline-8-carboxylic Acid. Basification of the reaction mixture required short exposure to 10% sodium carbonate at 0°C to avoid breakdown of the product. Also for this compound, some of the product was trapped in the first filtered mercury salts and was extracted by boiling in acetonitrile, followed by a hot filtration. The acid was a brown solid, mp. 260–262°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.84 (t, *J*=7.7 Hz, H-6); 8.56 (d, *J*=7.7 Hz, 2H, H-5,7); 9.47 (s, H-4); 9.54 (s, H-3).

Anal. Calcd for $C_{11}H_6N_2O_2S$•0.25H_2O: C, 56.28; H, 2.79; N, 11.93. Found: C, 56.39; H, 2.82; N, 11.76.

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