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Unexpected behavior of the methoxymethoxy group in the metalation/formylation reactions of 3-methoxymethoxyanisole

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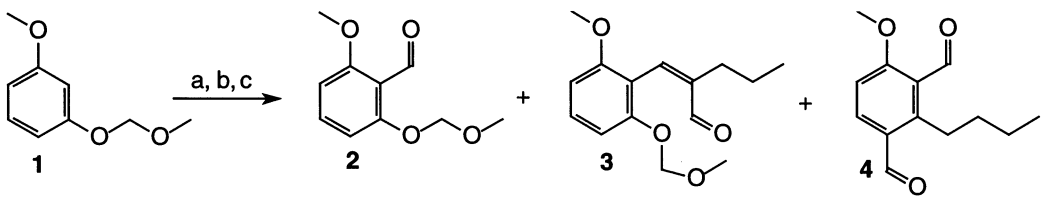
Abstract—The formation of tetrasubstituted benzenes and doubly lithiated intermediates in metalation/formylation reactions of 3-methoxymethoxyanisole has been observed with the methoxymethoxy group acting as a leaving group in some cases.

Our research activity on inhibition of enzymes of the copper-containing amine oxidase class led to the first selective, fully reversible inhibitors of benzylamine oxidase with benzylamine[1] or 4-aminomethylpyridine[2,3] structures containing alkoxy groups and to polyaminated pyridines[4] which are very active as inhibitors of diamine oxidase. To exploit some of these results for setting up new biospecific separations of benzylamine oxidase based on bioactive insoluble macromolecular systems containing inhibitor residues able to form stable complexes with the enzyme, we directed our attention to styrene monomers bearing 3,5-dialkoxybenzylamine functions through various linkers obtainable from 3-methoxymethoxyanisole **1**[5] by *ortho*-metalation reactions[6] of the known benzaldehyde derivative **2**.[7]

The methoxymethoxy group attached to an aromatic ring is known to direct hydrogen–metal exchange with alkyllithiums to the *ortho*-position,[8] and to undergo easy acid hydrolysis to give a phenol[9] useful for further transformations. In our hands the metalation/formylation of **1** gave rise to new, interesting results which are the subject of the present work.

When **1** was allowed to react in Et_2O with *n*-BuLi, and then with DMF according to the literature,[7] a reaction mixture was obtained which was more complex than that reported: together with the expected benzaldehyde derivative **2**[10] (65%) two aldehydic components **3**[11] (12%) and **4**[12] (8%) (Scheme 1) were produced, which were characterized by ^1H and ^{13}C NMR spectra, COSY, COLOC and NOE experiments, GC–MS and FTIR data. The structure of **2** was also confirmed by its transformation into the crystalline 2-hydroxy-6-methoxybenzaldehyde using aqueous methanolic HCl.[7]

The formation of **3** clearly occurs during the basic hydrolysis of the reaction mixture and involves an aldol condensation between **2** and pentanal produced from DMF and the excess of *n*-BuLi. In fact the formation



Scheme 1. (a) *n*-BuLi (2 equiv.), rt, 90 min; (b) DMF (3 equiv.), rt, 30 min; (c) H_2O.

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of **3** could be restricted by carrying out the hydrolysis by pouring the mixture into a stirred saturated aqueous solution of NH_4Cl. A sample of **2**, allowed to react with commercial pentanal in 1 M aqueous NaOH at 80°C afforded **3** in 60% yield.

The formation of the interesting tetrasubstituted benzene derivative **4**, in which substitution of the methoxymethoxy group by the *n*-butyl moiety of the metalating agent has occurred, attracted our attention and was further investigated with different metalating reagents. Besides *n*-BuLi, other alkyllithiums such as MeLi, *sec*-BuLi and *tert*-BuLi, which possess different deprotonation abilities and steric hindrance, were examined. MeLi proved to be unreactive under the conditions in Scheme 1 and was abandoned; *sec*-BuLi produced **2** in good yields (88%) together with small amounts (9%) of **5**,[13] which was identified from its ^1H and ^{13}C NMR spectra, COSY, COLOC and NOE experiments, GC–MS and FTIR data. The more hindered *tert*-BuLi yielded a mixture which, by GC–MS and GC–FID analyses, was shown to be composed of **2** (73%) and a non-purified isomer of **2** (11%) probably having the formyl group *ortho* to the methoxymethoxy group and *para* to the methoxy.

This reaction was repeated with the same butyllithiums at 0°C and gave the following yields of **2**: *n*-BuLi (82%), *sec*-BuLi (81%) and *tert*-BuLi (80%). The addition of TMEDA to the reaction mixture had no significant effects. As the first positive result of our investigation, the synthesis of the desired compound **2** was significantly improved using *sec*-BuLi with a molar ratio of 2:1 at rt.

To encourage the formation of the tetrasubstituted benzenes **4**, **5** and **8**, a 6:1 molar excess of the metalating reagent was used at rt. With *n*-BuLi, the product mixture showed complex GC–FID and GC–MS chromatograms, with **2** (23%), **3** (3%) and **4** (10%) being isolated. *sec*-BuLi afforded a mixture including **5** (50%), but which did not include any **2** (Scheme 2). With *tert*-BuLi the reaction mixture showed GC–FID and GC–MS chromatograms with well distinct peaks for the aldehydes **6** (2%), **7** (24%) and **8** (20%), which were separated by column chromatography (Scheme 2).

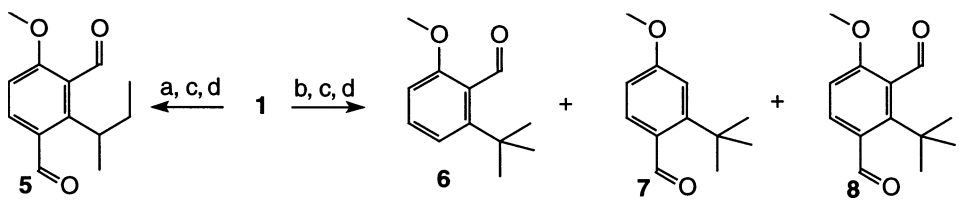
The spectroscopic data of **7**[14] and **8**[15] (^1H and ^{13}C NMR spectra, COSY, COLOC and NOE, GC–MS and FTIR) confirmed their structures. The structure of **6** was deduced from GC–MS data. The formation of the tetrasubstituted benzenes **4**, **5** and **8** was improved by using an excess of metalating agent and *sec*-BuLi was confirmed to be the most effective.

The reaction of the lithium derivative obtained from **1** using an excess of *sec*-BuLi with 1,2-diiodoethane yielded 2,4-diiodo-3-*sec*-butylanisole, which was characterized by GC–MS, FTIR and ^1H NMR spectra.[16] Decomposition with CH_3OD or H_2O of the lithium derivative obtained from **1** with an excess of *tert*-BuLi or *n*-BuLi respectively afforded 2,4-dideutero-3-*tert*-butylanisole fully characterized by spectroscopic analysis[17] or *n*-butylanisole identical to that prepared according to Durrani and Tyman.[18] Such results, as well as the production of **4**, **5** and **8**, are accounted for by a reaction pathway (Scheme 3) in which 3 mol of metalating reagent give displacement of the methoxymethoxy group and the dilithiated product **9**, which is converted into **10** in which E is equal to hydrogen or deuterium or iodine or formyl group after reaction with the proper electrophile.

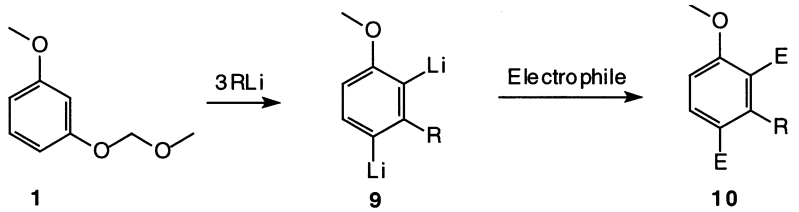
Substitution of the methoxymethoxy group by the alkyl moiety of the metalating reagent may involve the formation of intermediates of the benzyne type which undergo attack of a further molecule of alkyllithium, by analogy to fluoroanisoles,[17,19] *N*,*N*-dialkylbenzamides[20] and oxazoline derivatives.[21] Nevertheless, even if this can explain the formation of **6** or **7**, the production of the more important dilithiated product **9** is not satisfactorily explained, because double lithiation of **1** followed by elimination should give a lithiated benzyne which is unprecedented. A sequential step with progress of monolithiation of **1**, elimination, addition of alkyl lithium, and a further lithiation seems an arduous way of rationalizing the second lithiation. In conclusion, the formation of **9** represents an interesting short route for the synthesis of various functionalized arenes of type **10**, and stimulates mechanistic consideration to clarify whether lithiation and substitution in the benzene ring gives an initial double lithiation of **1** or not.

Experimental

Bruker DPX 300 NMR (^1H and ^{13}C NMR recorded in $CDCl_3$ at 300 and 75 MHz, respectively, chemical shifts δ in ppm referred to TMS), Perkin–Elmer System 2000 FTIR–GC Perkin–Elmer Autosystem equipped with an FID detector and a DB-5 (J&W) capillary column, and GC–MS Ion Trap Varian Saturn 2000 (EI mode) equipped with a DB-5MS (J&W) capillary column, were used. Column chromatography was on Merck 60 silica gel (0.040–0.063 mm) (eluent benzene/ethyl acetate 70/30 for **2**, petroleum ether 40–60°C/acetone 95/5 for **3** and **4**, and 92/8 for **5**, **7** and **8**).



Scheme 2. (a) *sec*-BuLi (6 equiv.), rt, 90 min; (b) *tert*-BuLi (6 equiv.), rt, 90 min; (c) DMF (9 equiv.), rt, 30 min; (d) H_2O.



Scheme 3.

Acknowledgements

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10. *2-Methoxy-6-methoxymethoxybenzaldehyde* (**2**)[7]: IR (film) cm^{-1} 2847, 2779, 1691, 1597, 1475, 1253, 1107, 1072; ^1H NMR 3.50 (s, 3H, $\underline{CH_3}OCH_2$), 3.90 (s, 3H, CH_3OAryl), 5.26 (s, 2H, $CH_3O\underline{CH_2}$), 6.63 (d, 1H, $J=8.5$ Hz, H(3)), 6.79 (d, 1H, $J=8.5$ Hz, H(5)), 7.43 (t, 1H, $J=8.5$ Hz, H(4)), 10.53 (s, 1H, CHO). ^{13}C NMR 56.1 (CH_3OAryl), 56.5 ($\underline{CH_3}OCH_2$), 94.8 ($CH_3O\underline{CH_2}$), 104.9 (C(5)), 107.4 (C(3)), 115.2 (C(1)), 135.8 (C(4)), 159.8 (C(6) or C(2)), 161.8 (C(2) or C(6)), 189.3 (CHO). MS (*m*/*z*, relative%) 196 (M^+, 24), 195 (M^+-1, 24), 167 (81), 150 (64), 45 (100).
11. *3-[2-Methoxy-6-(methoxymethoxy)phenyl]-2-propylpropen-2-al* (**3**): IR (film) cm^{-1} 2837, 2712, 1630, 1595, 1468, 1253, 1155, 1104, 1072. ^1H NMR 0.76 (t, 3H, $J=7.4$ Hz, H(3″)), 1.38 (m, 2H, H(2″)), 2.20 (m, 2H, H(1″)), 3.44 (s, 3H, $\underline{CH_3}OCH_2$), 3.82 (s, 3H, CH_3OAryl), 5.16 (s, 2H, $CH_3O\underline{CH_2}$), 6.63 (d, 1H, $J=8.4$ Hz, H (3′)), 6.82 (d, 1H, $J=8.4$ Hz, H(5′)), 7.20 (s, 1H, H(3)), 7.28 (t, 1H, $J=8.4$ Hz, H(4′)), 9.63 (s, 1H, CHO). ^{13}C NMR 14.1 (C(3″)), 20.7 (C(2″)), 28.4 (C(1″)), 55.6 (CH_3OAryl), 56.2 ($\underline{CH_3}OCH_2$), 94.7 ($CH_3O\underline{CH_2}$), 104.5 (C(3′)), 107.1 (C(5′)), 114.1 (C(1′)), 130.3 (C(4′)), 143.7 (C(3)), 145.9 (C(2)), 155.1 (C(6′)), 157.3 (C(2′)), 195.6 (CHO). MS (*m*/*z*, relative%) 264 (M^+, 1), 203 (100), 45 (27).
12. *2-n-Butyl-4-methoxybenzene-1,3-dicarboxaldehyde* (**4**): IR (film) cm^{-1} 2779, 1691 (broad), 1579, 1465, 1276, 1246, 1116, 1071. ^1H NMR 0.96 (t, 3H, $J=7.2$ Hz, H(4′)), 1.44–1.61 (m, 4H, H(2′)+H(3′)), 3.33 (m, 2H, H(1′)), 3.99 (s, 3H, CH_3O), 6.97 (d, 1H, $J=8.8$ Hz, H(5)), 8.08 (d, 1H, $J=8.8$ Hz, H(4)), 10.30 (s, 1H, CHO(3)), 10.60 (s, 1H, CHO(1)). ^{13}C NMR 13.8 (C(4′)), 23.0 (C(3′) or C(2′)), 26.8 (C(1′)), 35.0 (C(2′) or C(3′)), 56.2 (CH_3O), 109.3 (C(5)), 123.7 (C(1)), 127.8 (C(3)), 136.7 (C(4)), 149.9 (C(2)), 166.5 (C(6)), 190.0 (CHO), 192.0 (CHO). MS (*m*/*z*, relative%) 220 (M^+, 84), 219 (M^+-1, 22), 205 (86), 191 (100).
13. *2-sec-Butyl-4-methoxybenzene-1,3-dicarboxaldehyde* (**5**): IR (film) cm^{-1} 2768, 1682, 1580, 1471, 1274, 1237, 1085, 1059. ^1H NMR 0.88 (t, 3H, $J=7.4$ Hz, H(3′)), 1.44 (d, 3H, $J=7.4$ Hz, H(1″)), 1.72–1.88 (m, 2H, H(2′)), 3.77–3.93 (m, 1H, H(1′)), 3.96 (s, 3H, CH_3O), 6.96 (dd, 1H, $J_1=8.8$ Hz, $J_2=0.5$ Hz, H(5)), 8.11 (d, 1H, $J_1=8.8$ Hz, H(4)), 10.51 (d, 1H, $J=0.5$ Hz, CHO(3)), 10.57 (s, 1H, CHO(1)). ^{13}C NMR 11.9 (C(3′)), 22.0 (C(1″)), 31.6 (C(2′)), 35.2 (C(1′)), 56.2 (CH_3O), 109.2 (C(5)), 126.3 (C(1)), 129.2 (C(3)), 135.7 (C(4)), 152.7 (C(2)), 164.8 (C(6)), 190.3 (CHO(3)), 194.2 (CHO(1)). MS (*m*/*z*, relative%) 220 (M^+, 88), 219 (M^+-1, 25), 205 (89), 191 (100).
14. *2-tert-Butyl-4-methoxybenzaldehyde* (**7**): IR (film) cm^{-1} 2773, 1677, 1596, 1482, 1254, 1232, 1075, 1047. ^1H NMR 1.50 (s, 9H, H(2′)), 3.87 (s, 3H, CH_3O), 6.82 (ddd, 1H, $J_1=8.6$ Hz, $J_2=2.5$ Hz, $J_3=0.6$ Hz, H(5)), 6.98 (d, 1H, $J=2.5$ Hz, H(3)), 8.00 (d, 1H, $J=8.6$ Hz, H(6)), 10.66 (d, 1H, $J=0.6$ Hz, CHO). ^{13}C NMR 32.7 (C(2′)), 35.9 (C(1′)), 55.4 (CH_3O), 110.0 (C(5)), 113.6 (C(3)), 128.6 (C(1)), 133.7 (C(6)), 154.9 (C(2)), 163.5 (C(4)), 191.1 (CHO). MS (*m*/*z*, relative%) 192 (M^+, 66), 191 (M^+-1, 100), 177 (65), 159 (70).
15. *2-tert-Butyl-4-methoxybenzene-1,3-dicarboxaldehyde* (**8**): IR (KBr) cm^{-1} 2773, 1707, 1677, 1571, 1459, 1285, 1266, 1151, 1053. ^1H NMR 1.51 (s, 9H, H(2′)), 3.86 (s, 3H, CH_3O), 6.87 (dd, 1H, $J_1=8.7$ Hz, $J_2=0.6$ Hz, H(5)), 7.94 (d, 1H, $J=8.7$ Hz, H(4)), 10.63 (d, 1H, $J=0.6$ Hz, CHO(3)), 10.64 (s, 1H, CHO(1)). ^{13}C NMR 34.8 (C(2′)), 37.8 (C(1′)), 56.0 (CH_3O), 108.3 (C(5)), 130.1 (C(3) or C(1)), 130.7 (C(1) or C(3)), 133.6 (C(4)), 152.4 (C(2)), 161.3 (C(6)), 190.8 (CHO(3)), 198.1 (CHO(1)). MS (*m*/*z*, relative%) 220 (M^+, 4), 219 (M^+-1, 16), 205 (34), 187 (100).

16. *2,4-Diiodo-3*-sec-*butylanisole*: IR (film) cm^{-1} 2961, 2927, 2871, 1460, 1423, 1058. ^1H NMR 0.83 (t, 3H, $J=7.5$ Hz, H(4′)), 1.38 (d, 3H $J=7.5$ Hz, H(1′)), 2.15–2.34 (m, 2H, H(3′)), 3.72–3.87 (m, 1H, H(2′)), 3.87 (s, 3H, CH_3O), 6.38 (d, 1H, $J=9.0$ Hz, H(4) atropoisomer), 6.44 (d, 1H, $J=9.0$ Hz, H(4) atropoisomer), 7.82 (d, 1H, $J=9.0$ Hz, H(5) atropoisomer), 7.88 (d, 1H, $J=9.0$ Hz, H(5) atropoisomer). MS (m/z, relative%) 416 (M^+, 100), 385 (45), 260 (87).
17. *2,4-Dideutero-3*-tert-*butylanisole*: IR (film) cm^{-1} 2956, 2870, 1595, 1463, 1433, 1272, 1248, 1066. ^1H NMR 1.31 (s, 9H, $C(CH_3)_3$), 3.80 (s, 3H, CH_3O), 6.72 (d, 1H, $J=8.2$ Hz, H(6)), 7.22 (broad d, 1H, $J=8.2$ Hz, H(5)). ^{13}C NMR 31.3 ($(\underline{CH}_3)_3C$), 34.7 ($\underline{C}(CH_3)_3$), 55.1 (CH_3O), 110.0 (C(6)), 128.8 (C(5)), 152.8 (C(3)), 159.4 (C(1)). MS (m/z, relative%) 166 (M^+, 39), 151 (100).
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