Pergamon

Tetrahedron 54 (1998) 2763–2770

TETRAHEDRON

The Effect of an Alkoxy Group on the Kinetic and Thermodynamic Acidity of Benzene and Toluene

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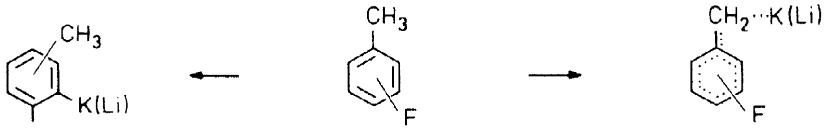
Received 23 October 1997; accepted 13 January 1998

Abstract : 2-, 3- and 4-Methoxytoluene can be selectively metalated at an *O*-adjacent *ortho* position when butyllithium or *tert*-butyllithium in the presence of sodium (potassium) *tert*-butoxide or *N,N,N',N'',N''*-pentamethyldiethylenetriamine are employed as reagents. In contrast, lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide deprotonate the benzylic α-position of 2- and 3-methoxytoluene exclusively and of 4-methoxytoluene preferentially. These relative reactivities can be rationalized by an interplay of transition state stabilizing and destabilizing forces (dipole matching and metal coordination *vs.* lone pair repulsion). © 1998 Elsevier Science Ltd. All rights reserved.

The superbasic mixture [1,2] of butyllithium and potassium *tert*-butoxide ("LIC-KOR") is powerful enough to promote a fast hydrogen/metal exchange at a halogen neighboring position of 2-, 3- and 4-fluorotoluene. The intermediates thus formed can be trapped with suitable electrophiles and the products isolated with good yields (60 - 65% after purification). [3] On the other hand, when lithium diisopropylamide in the presence of potassium *tert*-butoxide ("LIDA-KOR") is employed as the base, the *ortho* and *meta* isomers are exclusively deprotonated at their methyl groups. [3] However, proton abstraction from the *para* isomer occurs concomitantly at fluorine neighboring and benzylic sites in a ratio of 88 : 12 [3].



ortho, meta and *para* isomers

Fluorine and alkoxy substituents are electronically similar. Both withdraw electrons inductively and donate electrons mesomerically. This analogy prompted us to extend our study to the three methoxytoluenes (methylanisoles, cresyl methyl ethers). We expected to establish *optional site selectivity* once more by the proper matching of the substrates with the organometallic reagent, the additive and the solvent. The choice of the metal was to be made among lithium, sodium and potassium. By the fine-tuning of reaction conditions we

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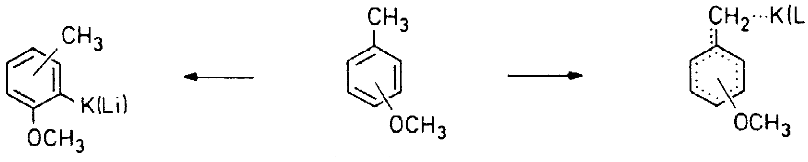
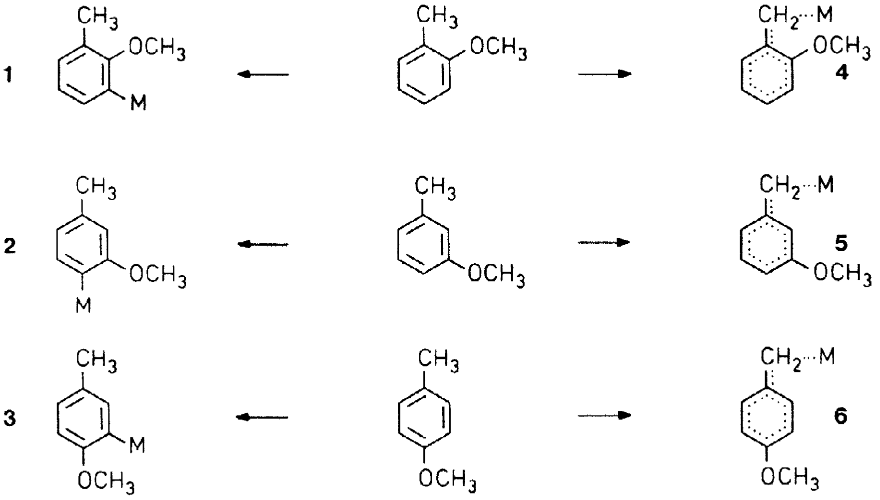
PII: S0040-4020(98)00052-0

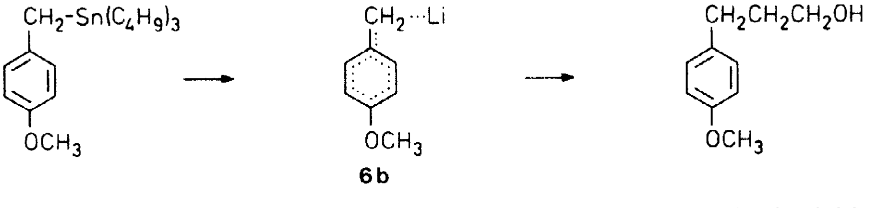
hoped not only to direct the attack either to the benzylic or to an oxygen neighboring aromatic position, but also to deprotonate the *meta* isomer exclusively at the sterically less hindered 4-position when the reaction occurs at the nucleus.



Previous attempts to metalate such kind of substrates did not meet more than limited success. Both, 2- and 3-methoxytoluene invariably afforded mixtures of regioisomeric products [4, 5]. Solely the 4-isomer was found to be amenable to a clean lithiation at a position *ortho* with respect to the methoxy group [6]. We have now identified reaction conditions that permit to accomplish selective *ortho* metalation of all three isomers and selective deprotonation of the benzylic position in the case of 2- and 3-methoxytoluene giving rise to intermediates **1**, **2** and **3** (M = Li, Na, K) and **4** and **5** (M = Li, Na, K), respectively (see Table 1). The 4-methoxybenzylmetal (M = Li, K) **6** can only be generated concomitantly with its aryl-metalated isomer **3** (see Table 1).

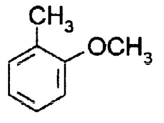
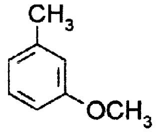
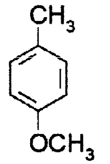


Although pure 4-methoxybenzyllithium **6b** (M = Li) will hardly ever become accessible by the hydrogen/metal permutation route, this species can be easily generated by treatment of tributyl(4-methoxybenzyl)tin with methyllithium in tetrahydrofuran at -75 °C. It was trapped with oxirane to give 3-(4-methoxyphenyl)propan-1-ol (79%). If a more polar reagent is required, it can be formed by the addition of potassium *tert*-butoxide [7].



The more intriguing problem is how to rationalize the observed reactivities and selectivities. In particular, why does the α-deprotonation of 2-methoxytoluene take place considerably more slowly than that of the 3-isomer but considerably more rapidly than that of the 4-isomer ? At the same time we would like to understand what factors facilitate the *o*-metalation of the three methoxytoluenes and the α-metalation of the isomeric benzyl methyl ether.

Table 1. Consecutive treatment of 2-, 3- and 4-methoxytoluene with a variety of metalating reagents, carbon dioxide and diazomethane : yields of carboxylic acid methyl esters and *o* : α ratios (substitution of an *O*-adjacent *ortho* position or the benzylic α-position).

substrate	reagent [a)]	conditions [b)]	yield	*o* : α ratio [c)]
	$LiC_4H_9 + NaOC(CH_3)_3$ [d)]	THF (10 h -75 °C)	52%	100 : 0
	LIDA + $KOC(CH_3)_3$	HEX (10 h 25 °C)	67%	0 : 100
	$LiC(CH_3)_3$ + PMDTA	HEX (16 h 25 °C)	64%	95 : 5 [e)]
	$LiC_4H_9 + NaOC(CH_3)_3$ [f)]	HEX (6 h 25 °C)	71%	0 : 100
	$LiC_4H_9 + KOC(CH_3)_3$	THF (15 h -50 °C)	78%	100 : 0
	LITMP + $KOC(CH_3)_3$	THF (3 h -50 °C) [g)]	43%	40 : 60

a) The reagent was used in a 1 : 1 stoichiometry relative to the substrate, unless stated otherwise. Abbreviations : PMDTA = *N,N,N',N'',N''*-pentamethyldiethylenetriamine, LIDA = lithium diisopropyl-amide, LITMP = lithium 2,2,6,6-tetramethylpiperidide.

b) Solvent and, in parentheses, metalation time and temperature. Abbreviations : THF = 3 : 1 (v/v) mixture of tetrahydrofuran and hexane, HEX = hexane.

c) In this context, "*o*" means an oxygen neighboring position.

d) Employing a slight excess (1.2 equiv.) of the 1 : 1 reagent mixture.

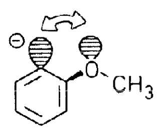
e) The main component is 2-methoxy-4-methylbenzoic acid, no trace of the other *ortho* substituted derivative, 2-methoxy-6-methylbenzoic acid, being detected.

f) Two molar equivalents of each component of the reagent mixture were used.

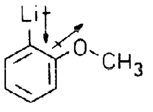
g) After 2 h of reaction time, a yield of 72% and an *o* : α ratio of 65 : 35 was found.

The selective replacement of a hydrogen atom at the *ortho* position of anisole by sodium [8] or lithium [9] was a milestone in the evolution of organometallic methods and, by extension, of modern organic synthesis. Soon two hypotheses confronted each other concerning the nature of the neighboring group participation. Was it the inductive electron-withdrawing effect of the heteroatom that "acidified" the CH bonds in the vicinity [10] or was it rather the electron donor capacity of the methoxy group that complexed the metal and guided it to the nearest reaction center [11] ? As we believe [12], both effects operate simultaneously although their description needs some refinement.

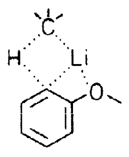
We shall evaluate the energy profiles of the given reactions in a stepwise approach, beginning with metal-free ("naked") carbanions, next turning to the realistic organolithium intermediates and finally addressing the rate determining transition states. The gas phase basicity of anisole has not yet been reported. Therefore we have to rely again [12] on a comparison with the isoelectronic nitrogen species (see Table 2). The 2-methoxy-pyridinium ion being only slightly more acidic than the pyridinium ion itself ($\Delta\Delta G^{\circ}_{deprot}$ 0.9 and 2.1 kcal/mol in the gas phase [13] and aqueous medium [14], respectively), we assume a similar relationship to hold for anisole and benzene. The small difference in basicity between the 2-anisyl anion (**7a**) and the phenyl anion appears to reflect a lone pair/lone pair repulsion of excess charge density by the electronegative heteroatom that compensates much of the inductive effect of the methoxy group. The picture changes profoundly when 2-anisyl*lithium* (**7b**) is compared to phenyl*lithium*. As evidenced by their heats of neutralization, the methoxy bearing compound is 9 kcal/mol more stable than the unsubstituted one [15]. Obviously the combination of a carbanion with a lithium counterion to form an organometallic bond attenuates the electronic repulsion of neighboring lone pairs and, in addition, leads to a favorable compensation of local dipoles. At the four-center type [16] transition state (**7c**), all these factors are operational to some extent but are largely dominated by the intra-complex coordination of the methoxy group to the lithium atom. Although this kind of interaction may also play a significant role at the ground state of the organolithium compound, there are two reasons why it must be considerably stronger at the level of the transition state generating this intermediate. The spatial arrangement is more favorable and, on the other hand, the lithium atom when switching from one organic moiety to another is only weakly linked to either carbon center and in this emergency situation requires efficient coordination by electron donor ligands to counterbalance the temporary loss of ordinary binding forces [17]. Thus, it is well intelligible that the difference in metalation rates of anisole and benzene amounts to several orders of magnitude.



7a

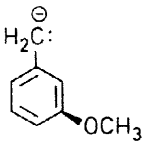


7b

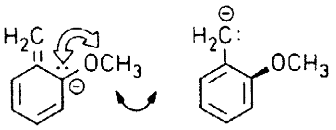


7c

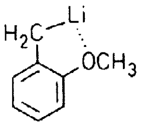
If we turn now to the 2-, 3- and 4-methoxybenzyl anions (**4a**, **5a** and **6a**), all of them benefit from inductive electron withdrawal. However, only the *meta* isomer can be assumed to be as "stable" as or slightly more stable (*i.e.*, less basic) than the parent benzyl anion whereas the two others suffer from lone pair/lone pair repulsion (as manifestly illustrated by representative resonance structures). Compared with the *para* isomer, the *ortho* isomer has nevertheless an advantage since the proximity between the center of deprotonation and the methoxy group permits an intramolecular coordination of the metal at the ground state (**4b**) and, more importantly, at the transition state (**4c**). Competition kinetics of deprotonation performed with lithium 2,2,6,6-tetramethylpiperidide (LITMP) in tetrahydrofuran at -50 °C nicely reflect the relative anion stabilities. 3-Methoxytoluene which was found to be twice as reactive as toluene itself undergoes deprotonation one and two powers of ten (exactly 9.12 and 100.1 times) faster than 2- and 4-methoxytoluene, respectively.



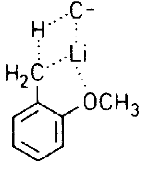
5a



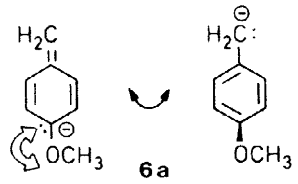
4a



4b



4c



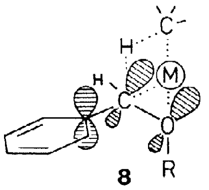
6a

The expected relative stabilities of benzyllithium and its three alkoxy substituted congeners are paralleled by the basicities of the isoelectronic anilines. The 4-methoxyanilinium ion is less acidic than the parent compound in both an aqueous medium [14] (see Table 2) as in the gas phase [18, 19].

Table 2. Relevant pK_a values of pyridinium and anilinium ions in aqueous solution [14].

corresponding base	pK_a
4-methoxypyridine	6.5
pyridine	*5.2*
3-methoxypyridine	4.9
4-chloropyridine	3.8
2-methoxypyridine	3.1
3-fluoropyridine	3.0
3-chloropyridine	2.8
2-chloropyridine	0.6
2-fluoropyridine	- 0.4
4-methoxyaniline	5.3
4-fluoroaniline	4.7
2-methoxyaniline	4.5
aniline	*4.2*
3-methoxyaniline	4.2
3-fluoroaniline	3.5
2-fluoroaniline	3.2

A last possible objection needs to be addressed. If lone pair/lone pair repulsion is really at the origin of all the difficulties encountered with the deprotonation of 4-methoxytoluene at the benzylic position, should the same phenomenon not manifest itself even much more drastically when the isomeric benzyl methyl ether is the substrate ? As one knows, however, benzyl ethers can be α-metalated with extreme ease at very low temperatures, much faster than diphenylmethane or any dialkoxymethane (formaldehyde acetal). Examining the presumable transition state structure (**8**), one recognizes two major differences between methoxytoluenes and benzyl ethers at the moment of α-deprotonation.



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The metal is penetrating in the area in between the incipient carbanionic orbital and one of the lone pairs of the oxygen atom, thus acting like an insulator. In this way, the heteroatom provides coordination to the metal but does not produce repulsive interactions. A second rate-enhancing effect can be attributed to the known predisposition of oxygen to tolerate small valence angles formed with neighbors attached to the same carbon atom [20]. The shrinking of OCC and OCH angles facilitates the assembling of the substrate and reagent to a transition state structure characterized by a pentavalent α-carbon atom.

The oxygen supported angle compression and metal coordination can also explain the ease with which purely aliphatic ethers such as dimethyl ether or tetrahydrofuran undergo the hydrogen/potassium interconversion [21]. The naked methoxymethyl anion appears to be at best 5 kcal/mol less basic than its hydrocarbon counterpart, the 1-propanide ion [22], while the basicity difference at the level of the corresponding monomeric organolithium species, methoxymethyllithium and propyllithium, has been predicted to be twice as large [23].

EXPERIMENTAL PART

1. Generalities

For practical routine and technical details, see previous articles [24] from this laboratory.

2. Products

2-Methoxy-3-methylbenzenecarboxylic acid [25] : mp 83 - 84 °C methyl ester [26] : bp 86 °C/3mmHg; n_D^{20} 1.5162; 2-methoxy-6-methyl-benzenecarboxylic acid [27] : mp 138 - 139 °C; methyl ester [28] : 95 - 96 °C/0.5 mmHg; 2-methoxy-4-methylbenzenecarboxylic acid [27] : mp 103 - 104 °C; methyl ester [29] : bp 263 - 265 °C; 2-methoxy-5-methylbenzenecarboxylic acid [30] : mp 68 - 69 °C; methyl ester [31] : 143 - 146 °C/14 mmHg; n_D^{17} 1.5311; (2-methoxyphenyl)acetic acid [32] : mp 123 - 124 °C; methyl ester [33] : bp 132 - 136 °C/9 mmHg; (3-methoxy-phenyl)acetic acid [34] : mp 67 °C; methyl ester [35] : bp 87 - 90 °C/0.3 mmHg; n_D^{15} 1.5137; 4-methoxyphenyl)acetic acid [36] : mp 85 - 86 °C; methyl ester [35] ; bp 96 - 99 °C/0.2 mmHg; n_D^{15} 1.5125.

3. Hydrogen/Metal Exchange ("Metalation") Reactions

At -75 °C, precooled tetrahydrofuran (19 mL) and sodium *tert*-butoxide (1.1 g, 10 mmol) were added to butyllithium (10 mmol in hexane (6 mL). After 15 min of vigorous stirring, the substrate (12 g, 10 mmol) was introduced into the reaction mixture which had become homogeneous. It was kept (without further stirring) 5 h at -75 °C before being poured on an excess of freshly crushed dry ice. After evaporation of the solvents, the residue was treated with water (15 mL), washed with diethyl ether (2 × 15 mL), acidified (to pH 1) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were shaken with brine (2 × 10 mL) and dried. One tenth of this solution was withdrawn and treated with an ethereal solution of diazomethane until the yellow color persisted. After addition of octadecane as a reference compound ("internal standard"), the solution was analyzed by gas chromatography using capillary columns (30 m, DB-Wax, 150 °C; 50 m, OV-1701, 180 °C). The products were identified by comparison of their retention times with those of authentic samples and were quantified by comparison of their peak areas with that of a reference compound of known amount using calibration factors. The main part of the extract was evaporated to dryness and the acid left behind purified by crystallization.

The reactions in the presence of potassium *tert*-butoxide were carried out in the same way except that the temperature was raised to -50 °C. Lithium diisoproprpylamide (LIDA) and lithium 2,2,6,6-tetramethylpiperidide were instantaneously formed when diisopropylamine (1.4 mL, 1.0 g, 10 mmol) and, respectively, 2,2,6,6-tetramethylpiperidine (17 mL, 14 g, 10 mmol) were added to the solution of butyllithium in tetrahydrofuran or hexane. When hexane was used as the only solvent, the components (*tert*-butyllithium in hexane and PMDTA or butyllithium in hexane, diisopropylamine and potassium *tert*-butoxide) were mixed at °C and stirring was continued over the entire reaction time.

4. Tin/Lithium Interconversion Reaction

Precooled (-75 °C) tetrahydrofuran (0.20 L) and tributyl-4-methoxyphenyltin [37] (8.2 g, 20 mmol) were consecutively added to butyllithium (20 mmol) from which the commercial solvent hexane had beforehand been stripped off. After 3 h at -75 °C, oxirane (1.0 mL, 0.88 g, 21 mmol) was added. The mixture was kept 2 h at

25 °C, before the solvent was evaporated and the residue dissolved in diethyl ether (25 mL) and water (10 mL). The organic layer was absorbed on silica gel (10 mL). The powder, when dry, was placed on top of a column filled with more silica (90 mL). Elution with hexane afforded a fraction containing some starting material (5%) and 1,2-bis(4-methoxyphenyl)ethane (2%), with ethyl acetate a second one containing *3-(4-methoxyphenyl)-propanol* [38]; bp 164 - 167 °C /18 mmHg; 61%. The 1,2-bis(4-methoxyphenyl)ethane was purified by crystallization from diethyl ether; mp 123 - 125 °C. - ^{1}H-NMR (250 MHz, $CDCl_3$) : δ 7.08 (2 H, dt, *J* 8.5, 2.7), 6.82 (2 H, dt, *J* 8.5, 2.7), 3.79 (3 H, s), 2.84 (2 H, s). - MS : 242 (15%, M^+), 121 (100%). - Analysis : calc. for $C_{16}H_{18}O_2$ (242.32) C 79.31, H 7.49; found C 78.93, H 7.56%.

5. Competition Reactions

Pairs of substrates (4.0 mmol each) were conjointly dissolved in tetrahydrofuran (5.0 mL) : 2-methoxytoluene and toluene; 3-methoxytoluene and toluene; 4-methoxytoluene and 4-*tert*-butyltoluene; 4-*tert*-butyltoluene and toluene. At -50 °C, lithium 2,2,6,6-tetramethylpiperidide (4.0 mmol) and potassium *tert*-butoxide (4.0 mmol) were added to each of the four solutions. The mixtures were stirred until homogeneous and then kept 2 h at -50 °C before being poured on dry ice. After addition of water (25 mL), the mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with 2 M hydrochloric acid (2 × 10 mL), a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and brine (10 mL). The amounts of unconsumed methoxytoluenes, 4-*tert*-butyltoluene and toluene were determined by gas chromatography (2 m, 5% C-20M, 50 → 200 °C [5 °C/min]; 2 m, 5% Ap-L, 60 → 220 °C [7 °C/min]) using nonane as an internal reference ("standard"). The aqueous layers were acidified to pH 3, extracted with diethyl ether (3 × 10 mL), washed with brine (10 mL) and treated with diazomethane until persistence of the yellow color. The methyl esters formed were identified and quantified by gas chromatography (conditions as specified above). The correlation between the toluenes consumed and the esters formed was quantitatively satisfactory. The concentrations of toluene and its various congeners before and after the reaction were used to calculate [39, 40] the rates of deprotonation of 2-methoxytoluene 0.229, 3-methoxytoluene 2.09, 4-*tert*-butyltoluene 0.125, relative to the parent compound toluene, and of 4-methoxytoluene 0.167 relative to 4-*tert*-butylbenzene.

These competition experiments were repeated twice and the reproducibility of the rate ratios found was excellent. On this basis, one can estimate the probable error deviation to be ±3%.

Acknowledgment : This work was financially supported by the *Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung*, Bern (grants 20-36'385-92 and 20-41'887-94).

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