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Synthesis of New Sterically Hindered Anilines

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Ring-alkylated primary, secondary and tertiary anilines have been ethylated with ethylene at benzylic positions in a simple and inexpensive one-pot procedure which is mediated by the use of the superbase system *n*BuLi/LiK($OCH_2CH_2NMe_2$)$_2$ in the presence of Mg(OCH_2CH_2OEt)$_2$. Primary and secondary anilines are ethylated readily at *ortho*-benzylic positions but with difficulty or not at all at other positions. Tertiary anilines are ethylated at all positions. Mono- or diethylation occurs depending on the steric constraints present.

Introduction

Aromatic molecules containing sterically demanding alkyl groups feature in a number of important areas of chemistry, such as homogeneous catalysis, materials chemistry, medicinal chemistry, unsaturated and low-coordination compounds of the heavier main group elements. Of the various classes of aromatic compounds, the 2,6-dialkylanilines feature widely as starting materials for the synthesis of Schiff bases, N-heterocyclic carbenes, and related ligands for metal complexes, particularly those with applications in homogeneous catalysis. Because of their ready availability, apart from anilines with *ortho*-methyl substituents, those with isopropyl or *tert*-butyl groups are particularly popular. Examples where they have been used as building blocks for the synthesis of ligands include the imino ligands used in post-metallocene olefin polymerisation catalysis,[1a] such as salicylaldimine[1b] and bis(iminopyridine) ligands,[1c] the anilide supporting ligands for Schrock's olefin metathesis catalysts,[1d] many of the N-heterocyclic carbene ligands now widely used in olefin metathesis and palladium-catalysed coupling reactions,[1e] and diimino ligands for the catalytic borylation of vinylarenes.[1f] Other significant recent applications are as structural elements in dye materials,[2a,2b] and biologically active compounds.[3a,3b] We have recently reported the one-step conversion of a range of methyl-substituted aromatic molecules to the corresponding 1-ethylpentyl derivatives by means of the superbase system[4,5] *n*BuLi/LiK($OCH_2CH_2NMe_2$)$_2$ in the presence of Mg(OCH_2CH_2OEt)$_2$,[6,7] and we have also reported on the chemistry of the compounds obtained.[8–10] We now report an adaptation of this methodology to the ethylation of methyl- and ethyl-substituted primary, secondary and tertiary anilines to new compounds which demonstrate a range of steric hindrance around the amino group and complement other bulky primary ring-alkylated anilines that we have reported recently, and which were prepared in two steps from the corresponding hydrocarbons by nitration and subsequent reduction.[9]

Results and Discussion

The route used to synthesise the amines reported here is similar to that previously reported for hydrocarbons and phenols,[6,7] and involves the addition of benzylic organometallic reagents to ethylene. The methodology is synthetically quite convenient since it generally provides one major product which can be readily isolated in good yield. It constitutes a development of previous work reported for aromatic hydrocarbons and heteroaromatic compounds but which was synthetically less attractive, not only due to the more severe conditions normally required, but also because of the difficulty of obtaining pure compounds from the mixtures produced.[11] As for the phenol series,[7] it was first necessary, in the case of the primary and secondary anilines, to perform an initial stoichiometric deprotonation to the corresponding anilide and this was most conveniently done by using *n*BuLi. For the 2,6-dialkylanilines examined, 1 equiv. of *n*BuLi was used to achieve this. With the addition of further *n*BuLi alone there were no observable signs of further reaction such as a second deprotonation at the nitrogen atom occurring; but in the presence of LiK($OCH_2CH_2NMe_2$)$_2$, yellow or yellow-orange suspensions, which are a characteristic indication of metalation at the benzylic position, developed immediately. If only one *ortho* position is occupied, however, as in the case of *o*-toluidine,

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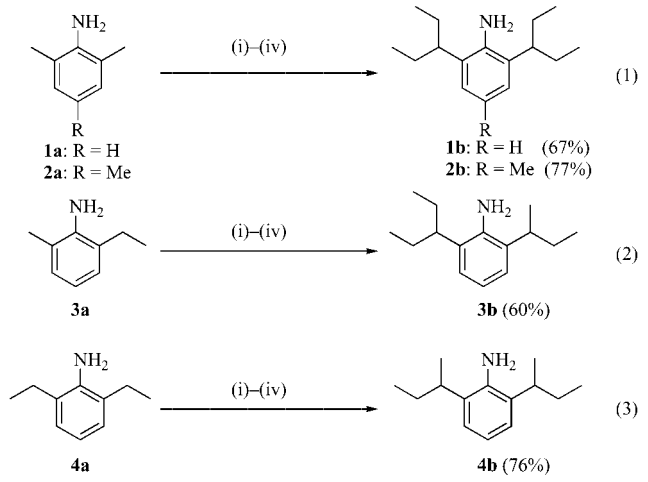
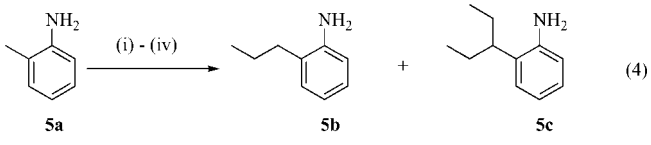
this yellow colour does not develop until an excess of 2 equiv. of *n*BuLi is added, implying that double metalation of the amino group occurs first before any metalation of the methyl group. It thus appears likely that for the 2,6-dialkylanilines steric effects favour the second metalation step to occur at the benzylic position. Subsequent addition of 5 mol-% of $Mg(OCH_2CH_2OEt)_2$ and reaction with ethylene under pressure at 80 °C for 24 h gives clean addition of ethylene at the benzylic position. For the primary anilines examined, i.e. 2,6-dimethylaniline (**1a**), 2,4,6-trimethylaniline (**2a**), 2,6-diethylaniline (**3a**), and 2-ethyl-6-methylaniline (**4a**), the reaction stops when the alkyl group is converted to a secondary benzylic substituent. Thus, two molecules of ethylene add to *ortho*-methyl groups, but just one to *ortho*-ethyl groups [Equation (1)].



(i) *n*BuLi (1 equiv.); (ii) *n*BuLi/LiK$(OCH_2CH_2NMe_2)_2$ (20 mol-%); (iii) $Mg(OCH_2CH_2OEt)_2$ (5 mol-%), C_2H_4 (10 atm), 80 °C, 24 h; (iv) H_2O.

As observed for similar compounds in the phenol series, no addition was observed to the *para*-methyl group of **2a**.

The corresponding reaction with *o*-toluidine (**5a**), was also examined. Using, as stated above, 2 equiv. of *n*BuLi for the initial deprotonation of the amino group, a mixture of the monoethylated and diethylated products, **5b** and **5c**, was obtained together with unreacted starting material and some insoluble material which was not characterized [Equation (4)].

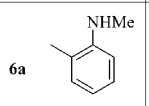
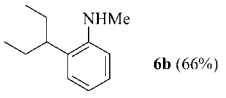
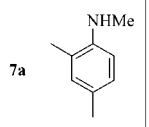
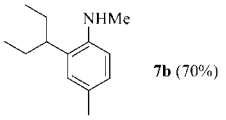
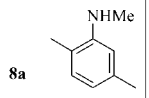
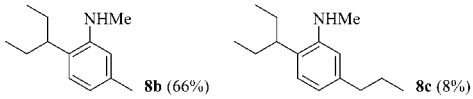
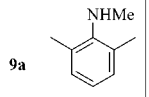
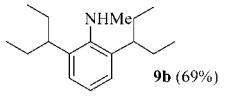
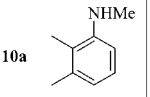
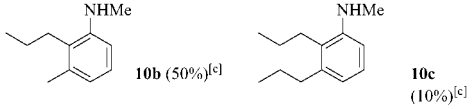


(i) *n*BuLi (2 equiv.); (ii) *n*BuLi/LiK$(OCH_2CH_2NMe_2)_2$ (20 mol-%); (iii) $Mg(OCH_2CH_2OEt)_2$ (5 mol-%), C_2H_4 (10 atm), 80 °C, 24 h; (iv) H_2O.

Thus, although this demonstrates the feasibility of the reaction for the production of mono-*ortho*-substituted anilines, the poor yields and the need for careful separation of the products indicate that indirect routes to these compounds may be preferable.

Secondary anilines react similarly to primary anilines; in this case the reaction works quite well for mono-*ortho*-methyl-substituted substrates, and the chemoselectivity closely resembles the behaviour found for the analogous phenols (Table 1).[7]

Table 1. Ethylation of secondary anilines.[a]

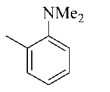
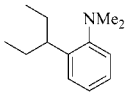
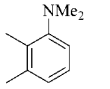
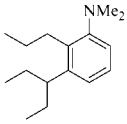
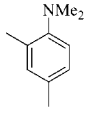
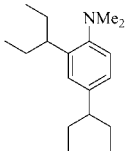
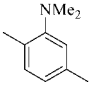
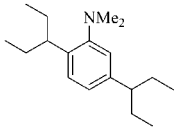
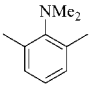
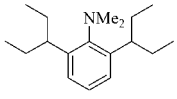
Reagent	Product (Yield)[b]
 **6a**	 **6b** (66%)
 **7a**	 **7b** (70%)
 **8a**	 **8b** (66%) **8c** (8%)
 **9a**	 **9b** (69%)
 **10a**	 **10b** (50%)[c] **10c** (10%)[c]

[a] Reaction conditions: (i) *n*BuLi (1 equiv.); (ii) *n*BuLi/LiK-$(OCH_2CH_2NMe_2)_2$; (iii) $Mg(OCH_2CH_2OEt)_2$, C_2H_4 (10 atm), 80 °C, 24 h; (iv) H_2O. [b] Yield of isolated product except where otherwise indicated. [c] Yield estimated by GC of isolated product mixture.

For both the primary and the secondary aniline series, consideration was given to the possibility of products arising from the hydroamination of ethylene. The base-catalysed hydroamination of unactivated olefins is now a well-established reaction; while initial studies used very forcing conditions,[12] later work has led to the development of systems which catalyse the reaction under relatively mild conditions.[13–16] Indeed, recent systematic studies have shown that the addition of diethylamine to ethylene can be efficiently catalysed by $LiNEt_2$ in the presence of TMEDA at 20–60 atm and 80 °C.[17] Anilines are reported to be less reactive, but aniline itself does add to ethylene in the presence of $NaNH_2$ as catalyst at 40–60 atm and 275 °C.[18] We therefore examined the initial crude extracts from all our reactions for the presence of *N*-ethylated products, but none were detected nor were such products detected when substoichiometric amounts of the superbase reagent were employed.

Tertiary anilines react similarly, and since the need for initial deprotonation of the amino group is, of course, now dispensed with, reactions can also be carried out on a larger scale with ease. Mono-*ortho*-methyl-substituted tertiary anilines are readily ethylated using the above procedure, and again, steric effects are evident in some cases. For example, the *ortho*-methyl group of *N*,*N*,2,3-tetramethylbenzeneamine (**12a**), which is flanked by other substituents, is only monoethylated, as was observed for similar cases in the hydrocarbon and phenol series (Table 2).

Table 2. Ethylation of tertiary anilines.[a]

Reagent	Product (Yield)[b]
 **11a**	 **11b** (68%)
 **12a**	 **12b** (86%)
 **13a**	 **13b** (80%)
 **14a**	 **14b** (74%)
 **15a**	 **15b** (73%)

[a] Reaction conditions: (i) *n*BuLi/LiK($OCH_2CH_2NMe_2$)$_2$; (iii) Mg(OCH_2CH_2OEt)$_2$, C_2H_4 (10 atm), 80 °C, 24 h; (iv) H_2O. [b] Yield of isolated product except where otherwise indicated.

It is also notable that, for the tertiary anilines, in contrast to the primary and secondary anilines, *meta*- and *para*-methyl groups are also ethylated easily. The metalation of benzylic protons in a position *para* to an electron-donating group has been studied by others; whereas, for example, the *para*-methyl group of *N*,*N*,4-trimethylaniline can be metallated using *n*BuLi/KO*t*Bu in THF at –75 °C,[19] metalation with TMEDA-activated *n*-butyllithium in hexane at room temperature occurs exclusively at the ring position *ortho* to the amino group.[20] Our system, which not only contains a tertiary amino group but also uses an inert hydrocarbon solvent, resembles the latter system; while this could be consistent with the lack of reaction that we observe at the *para*-benzylic position for the primary and secondary anilines, it is not consistent with the behaviour of the tertiary anilines. The lack of reactivity in previously reported cases has been ascribed to a strong interaction of the metalating reagent with the heteroatom which directs its reactivity almost exclusively to the *ortho* position.[19,21] A possible explanation in our case may lie in the nature of the alkali metal involved. For the primary and secondary anilines, where an initial stoichiometric deprotonation step has occurred, the second metalation would be expected to be energetically unfavourable except, perhaps, if strong *ortho* chelating interactions exist. Lithium ions generally coordinate much more strongly than the heavier alkali metal ions to first row donor atoms, and – if these *ortho* interactions are indeed a controlling factor – the nature of the metalated species becomes important. For the primary and secondary anilines, the metallated species will be quite lithium-rich, the Li/K ratio being about 13:1, and so ethylation at the *ortho*-benzylic position is, predominantly or exclusively, observed. For the tertiary anilines, where no stoichiometric deprotonation is required, the Li/K ratio is in the region of 3:1 and the relatively high proportion of the more weakly coordinating potassium ion may reduce the importance of any *ortho* effect. Further experiments are planned to investigate this behaviour.

It should be emphasised that, with the exception of compounds **8a** and **10a** where mixtures of compounds are obtained, the methodology described here provides only one major product. All the crude reaction products were examined by GC-MS for the presence of other products; although a number of minor products with *m*/*z* values corresponding to the possible addition of further ethylene were in evidence, extended reaction times did not cause an increase in the yield of these products. In particular, it is significant that products which could have derived from triethylation at the benzylic position were never observed in other than trace amounts. This may be a steric effect or it possibly may be metal-dependent, since it has been observed that allylic potassium species, for example, are able to add to three molecules of ethylene.[22] It should also be noted that there was also no evidence of ethylation directly onto the ring (cf. ref.[4a]).

A significant feature of many of the products is the very high apparent lipophilicity, not only of the anilines themselves, but also of their salts. It was notable that even the hydrochlorides of the primary amines were appreciably soluble in hexane, much more so than in water. Although we are reluctant to place too much weight on calculated values for the salts, simple estimates of CLogP values using ChemDraw® suggest that the lipophilicities of the anilinium ions derived from **1b**–**4b**, are comparable to those for the unprotonated anilines (CLogP = 5.5–6.5), and that those for the chloride salts should still be substantial (ClogP = 4–5).

Conclusions

We have developed simple routes to a range of ring-alkylated anilines, the nature of the products depending on the ring substitution of the starting materials used. The 1-ethylpropyl group is estimated from experimental observations[23] and computational studies to have a steric effect similar to that of the *tert*-butyl group[24] and many of the products reported have obvious potential as starting materials for bulky ligands. Schiff bases derived from these amines are currently being investigated by us as ligands in transition metal coordination complexes and in homogeneous catalytic applications.

Supporting Information (see footnote on the first page of this article): Procedures for the ethylation of compounds **1a**–**4a** and **6a**–**15a** and the isolation of the products, including spectroscopic and analytical data. Procedure for the metalation and derivatisation of benzene.

Acknowledgments

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[5] Although the term "superbase" is often used for any strongly basic system, organometallic superbases often refer to the organolithium/potassium alkoxide systems (ref.[4]). A potential definition of a superbase is a base that readily metalates benzene. In order to justify our use of this term for our system, we have confirmed that it does indeed readily metalate benzene under conditions similar to those described in ref.[4a] Experimental details are provided in the Supporting Information.

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