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Synthesis of *N*-Aryl and *N*-Alkyl Anthranilic Acids via S_NAr Reaction of Unprotected 2-Fluoro- and 2-Methoxybenzoic Acids by Lithioamides

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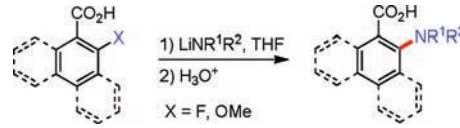
ABSTRACT



Substitution of the fluoro or methoxy group in *unprotected* 2-fluoro- and 2-methoxybenzoic acids to afford *N*-aryl and *N*-alkyl anthranilic acids occurs upon reaction with lithioamides under mild conditions in the absence of a metal catalyst.

N-Aryl and *N*-alkyl anthranilic acids are very important synthetic intermediates which have been marketed as anti-inflammatory agents for the treatment of dysmenorrhea and rheumatic pain and as candidates for the therapy of neurodegenerative and amyloid diseases.[1] *N*-Aryl anthranilic acids are also synthetic precursors of acridines, which have been utilized as antimalarial and anticancer drugs.[2] Traditionally, these compounds have been prepared by the copper-mediated coupling of amines with halobenzoic acids (the Ullmann reaction).[3] The success of this reaction often requires strongly activated aryl halides and forcing reaction conditions. Anthranilic acids have also been prepared by Buchwald−Hartwig amination with alkyl 2-halobenzoates in the presence of base and palladium catalyst and subsequent ester cleavage.[4]

Due to potentially toxic contamination of pharmaceutical products, effective removal of Pd or Cu in active pharmaceutical ingredients (API) poses acute problems inasmuch as the limits set by health authorities are very low. Guidelines from the European Medicines Agency have set the permitted

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daily exposure of patients to palladium, 100 μg·day^{-1} for oral doses and 10 μg·day^{-1} for parenterally administered drugs.[5] On the basis of these guidelines, the pharmaceutical industry generally needs to achieve less than 10 and 1 ppm, for oral and parentral drug substances, respectively. For large scale synthesis, it is best to avoid the use of Pd during the last three steps and place Pd-coupling reactions early in the process in hopes of reducing the amount of metal throughout the synthesis. On a practical level, when a synthetic scheme requires the use of a metal such as Pd at the end of a synthesis and the standards of metal content permitted in the API are exceeded, it is necessary to find empirically a disposal method such as nanofiltration or use scavenging agents, which is costly in time and money.[6]

Conventional wisdom indicates that the nucleophilic aromatic substitution (S_NAr) reaction of benzoic acids requires steps of protection and deprotection of the carbonyl which acts as an essential carbon anchor group for subsequent chemical transformations. Although there have been numbers of reports using aryloxazolines[7] and 2,6-dialkylphenyl arylcarboxylates[8] to dictate the S_NAr reaction course, these methods have suffered from several limitations, the most severe being most certainly the difficulty of removal of the protecting carbonyl group. 2,6-Disubstituted benzamides and benzoates are especially inert to hydrolysis except in cases where anchimeric assistance by *ortho*-introduced electrophiles is capable of forming five- or six-membered-ring tetrahedral intermediates, which greatly enhances amide hydrolytic rates.[9,10] Therefore, there is still a need to explore more efficient and concise methodologies.

While carrying out earlier work involving the coupling reactions of alkyllithium with unprotected fluoro-substituted benzoic acids,[11] we became aware that surprisingly only very few studies investigated the fluoro displacement reaction of 2-fluorobenzoic acid derivatives with lithioamides.[12,13] Herein we report that this process is general, affords anthranilic acids, and does not require the use of a catalyst. It is also shown that subjecting 2-methoxy benzoic acids to lithioamides results in methoxide displacement.

The amino substituent was directly introduced in place of the *ortho*-fluoro/methoxy group in fair-to-excellent yields (Table 1).

$LiNEt_2$, $LiN(CH_2CH_2)_2NMe$, LiNMeBn, and $LiNBn_2$ readily displaced the fluorine of the lithium salt of 2-fluorobenzoic acid (**1**) at −50 °C to give anthranilic acids **3**−**6** (entries 1−4). Lithium arylamides and diarylamides entered into the displacement reaction with benzoate **1** under somewhat forcing conditions (50−60 °C, entries 5 and 6). This may be attributed to lower pK_a values in comparison to dialkylamines.[14] Most striking are those examples using so-called "nonnucleophilic" bases such as LDA and LiNH*t*-Bu, indicating that there are virtually no steric effects to inhibit fluoro displacement (entries 7 and 9). LDA which is commonly used as a strong base of scarce nucleophilicity due to steric congestion reacted with lithium benzoate **1** to afford the aminated product **9** in appreciable amount.[15] In an attempt to introduce an *ortho*-NH_2 unit, **1** was treated with a THF solution of $LiNH_2$ (3.5 equiv) (entry 8). However, the amidation product **11** was the only isolable product from this reaction. LiNH*t*-Bu also led to **11** by rapid degradation of **12** during acidic workup.

In view of the efficiency of lithioamides in this reaction and the unlikelihood of their ability to proceed by electron transfer (ET) mechanisms, this reaction presumably proceeds through an addition−elimination sequence.[16,17]

The closely related lithium 2,2,6,6-tetramethylpiperidide (LTMP) exhibited a totally different behavior when exposed to **1** (entry 10 and Scheme 1). LTMP metalated the position adjacent to fluorine affording dianion **14** which partly

(5) Note for guidance on specification limits for residues of metal catalysts, 2002. The European Agency for the Evaluation of Medicinal Products Web site. http://www.emea.europa.eu/pdfs/human/swp/444600en.pdf (accessed April 21, 2010).

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(10) Deprotection of 2-aminated aryloxazolines requires acidic conditions (3 M HCl, 12−24 h, reflux) which are not compatible with delicate structures. Yields do not exceed 70%, and in many instances the deprotection only leads to degradation products. See: Meyers, A. I.; Gabel, R. *J. Org. Chem.* **1977**, *42*, 2653–2654.

(11) The reaction of 2-fluorobenzoic acid with *s*-BuLi and *t*-BuLi affords the the *ipso*-attack product arising out of substitution of the fluorine atom by the alkyl group: (a) Gohier, F.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2003**, *5*, 1919–1922. Metalation reactions, recent references: (b) Nguyen, T. H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765–768. (c) Nguyen, T. H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419–3429. (d) Tilly, D.; Fu, J.-m.; Zhao, B.-p.; Alessi, M.; Castanet, A.-S.; Snieckus, V.; Mortier, J. *Org. Lett.* **2010**, *12*, 68–71.

(12) Two recent papers described LiHMDS-promoted coupling of primary and *N*-substituted anilines with 2-fluorobenzoic acid (or amide) to give *N*-arylanthranilic acids and *N*-arylanthranilamides: (a) Chen, M. H.; Beylin, V. G.; Iakovleva, E.; Kesten, S. J.; Magano, J.; Vrieze, D. *Synth. Commun.* **2002**, *32*, 411–417. (b) Davis, E. M.; Nanninga, T. N.; Tjiong, H. I.; Winkle, D. D. *Org. Process Res. Dev.* **2005**, *9*, 843–846.

(13) Nucleophilic displacements of 2-fluorobenzoic acid derivatives are well known to occur readily in the presence of strong electron-withdrawing substituents (NO_2, CF_3, CN, F_x. .). See: Crampton, M. R. *Organic Reaction Mechanisms*; A. C. Knipe, W. E. W., Ed.; John Wiley & Sons: UK, 2004; p 189.

(14) Lithium arylamides have weaker nucleophilic strengths than lithium dialkylamines but are more stable at higher temperature (50−60 °C).

(15) The synthesis of anthranilic acids using sterically hindered amines via a three-component coupling with arynes and CO_2 has been reported: Yoshida, H.; Morishita, T.; Ohshita, J. *Org. Lett.* **2008**, *10*, 3845–3847.

(16) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 6th ed.; Wiley- Interscience: New York, 2007; pp 853−864, and references cited therein. Addition of radical scavengers (tetraphenylhydrazine or 2-methyl-2-nitrosopropane dimer) to a mixture of **1** and $LiNEt_2$ gave only a slight decrease of yield of the substitution product **3**.

(17) If it is assumed that these reactions proceed via an addition−elimination sequence, then the σ complex B allows the carboxylate to orientate itself in a coplanar fashion with the aromatic ring while Li^+ forms a strong complex with the fluoro/methoxy group and the carboxylate. For the complex-induced proximity effect, CIPE, see: Whisler, M. N.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225. The transition state leading to **B** may be envisioned as forming from **A**, where the NR^1R^2 group enters from the side almost perpendicular to the aromatic ring (to the π cloud). This is consistent with the lack of steric inhibition to addition by large groups.

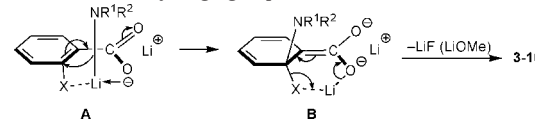
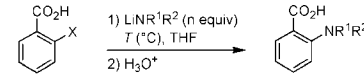


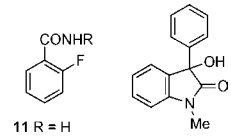
Table 1. Amination Reactions of 2-Fluoro- and 2-Methoxybenzoic Acids (**1** and **2**)



1 X = F
2 X = OMe

3-10

entry	**1**, **2**	$LiNR^1R^2$ (equiv)[a]	temp (°C)	**3**−**10** %[b]	others
1	**1**	$LiNEt_2$ (2.2)	−50	87 (73*) [**3**]	—
2	**1**	$LiN(CH_2CH_2)_2NMe$ (2.2)	−50	95 (88*) [**4**]	—
3	**1**	LiNMeBn (2.2)	−50	95 (85*) [**5**]	—
4	**1**	$LiNBn_2$ (2.2)	−50	93 (80*) [**6**]	—
5	**1**	LiNMePh (2.2)	50	100 (64*) [**7**]	—
6	**1**	$LiNPh_2$ (2.2)	60	72 [**8**]	—
7	**1**	LDA (2.2)	−50	33 (28*) [**9**]	—
8	**1**	$LiNH_2$ (3.5)	60	0	50 (40*) [**11**]
9	**1**	LiNH*t*-Bu (2.2)	0	60 (36*) [**10**]	30 (15*) [**11**][c]
10	**1**	LTMP (2.2)	−50	0	[d]
11	**2**	$LiNEt_2$ (2.2)	−50 → 0	97 (93*) [**3**]	—
12	**2**	$LiN(CH_2CH_2)_2NMe$ (2.2)	0	87 (70*) [**4**]	—
13	**2**	LiNMeBn (2.2)	−50 → 0	90 (65*) [**5**]	—
14	**2**	LiNMeBn (5)	−50 → 0	5 [**5**]	95 (51*) [**13**][e]
15	**2**	$LiNBn_2$ (2)	0 → rt	50 (45*) [**6**]	—
16	**2**	LiNMePh (2.2)	60	14 [**7**]	—
17	**2**	$LiNPh_2$ (2.2)	60	0	—
18	**2**	LDA (2.2)	0	5 [**9**]	—
19	**2**	LTMP (2.2)	−50	0	[d]



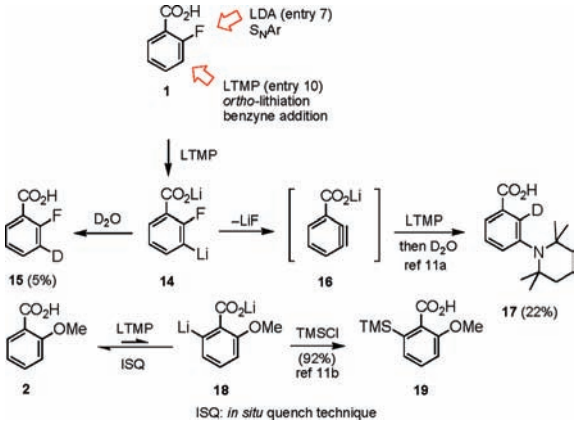
11 R = H
12 R = *t*-Bu

13

[a] The lithioamides $LiNR^1R^2$ were prepared in situ by deprotonation of the corresponding amines with *n*-BuLi. [b] NMR yields (%). Isolated yields (recrystallized or chromatographed) are followed by an asterisk (*). All new compounds gave correct analytical data. See Supporting Information. [c] Deterbutylation of **12** led to amide **11**. [d] See Scheme 1. [e] See Scheme 2.

eliminated LiF to give the transient lithium benzyne-3-carboxylate (**16**). Electrophilic quenching of **14** with D_2O provided **15**, whereas reaction of benzyne **16** with the excess of LTMP followed by quench with D_2O gave **17**.

Scheme 1. Reactions of Benzoic Acids **1** and **2** with LTMP



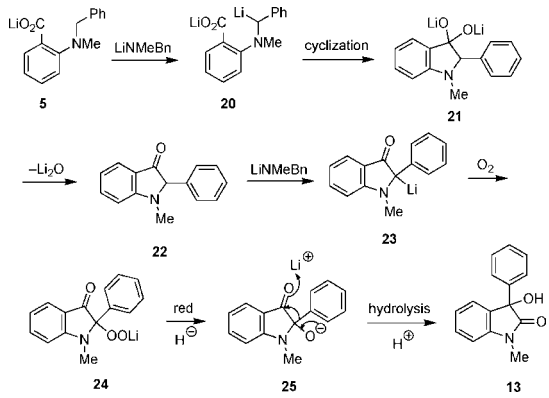
To our delight, the methoxy group was also found to be an efficient leaving group. Reaction of 2-methoxybenzoic acid (**2**) with $LiNEt_2$, $LiN(CH_2CH_2)_2NMe$, and LiNMeBn gave anthranilic acids **3**−**5** in good yields (entries 11−13). Increasing the amount of LiNMeBn to 5 equiv modified dramatically the course of the reaction (entry 14). The dioxindole **13** resulted as the main product.[19]

An attractive rationale for the formation of dioxindole **13** would involve initial benzylic deprotonation of **5** by the excess of LiNMeBn leading to **20** as outlined in Scheme 2. In an experiment to probe this question, **5** was allowed to react with 5 equiv of LiNMeBn to give a red solution which was hydrolyzed to **13**. It can be assumed that the benzylic lithiation of **5** is followed by an intramolecular nucleophilic addition of the carbanion to the carboxylate leading to indolin-3-one **22** by way of the geminal dilithio dialkoxide **21**.[20] Deprotonation by the excess of base in the presence of molecular oxygen contained in the nondegassed

(18) The base and TMSCl were premixed prior to addition of the acid. The deprotonation which produces a small concentration of the trappable aryllithium **18** is sufficiently rapid to make the process competitive with reaction of the hindered base with the in situ electrophile (TMSCl). See ref 11b.

(19) Structure of **13** was confirmed by NOESY and HMBC (see Supporting Information).

Scheme 2. Postulated Mechanism for the Formation of Dioxindole **13**



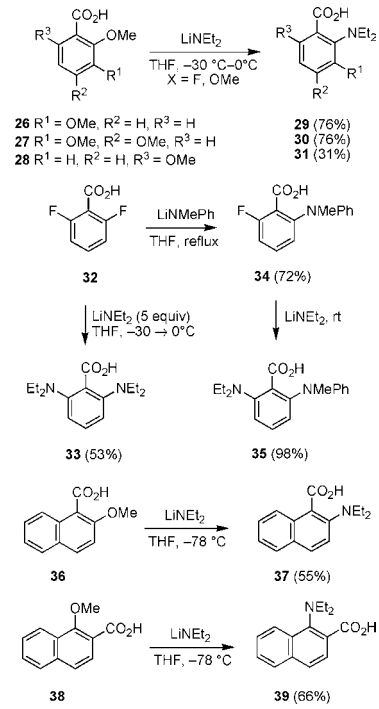
THF solution[21] provides an organolithium peroxide species **24**.[22] Reduction by a hydride ion transferred by LiNMeBn[23] affords alkoxide **25** which undergoes subsequent 1,2-phenyl shift[24] to dioxindole **13** after acidic hydrolysis.[25]

The reaction of $LiNBn_2$ yielded anthranilic acid **6** (45%) (entry 15). LiNMePh, $LiNPh_2$, and LDA were almost unreactive toward **2**. Whereas 2-methoxybenzoic acid (**2**) did not react with LTMP after MeI addition (−50 °C) under external quench conditions (entry 19), in situ quenching (ISQ) with LTMP in the presence of TMSCl at −78 °C led to **19** (via **18**) free of any isomers (92%) (Scheme 1).[18] It is well demonstrated that the fluoro group is a better leaving group and smaller in bulk than the methoxy.[7,8]

Reaction of commercially available 2,3-dimethoxy, 2,3,4-trimethoxy, and 2,6-dimethoxybenzoic acids (**26**−**28**) with $LiNEt_2$ led to *ortho*-substituted derivatives **29**−**31** (Scheme 3).[26] Introduction of $LiNEt_2$ to the 2,6-dimethoxybenzoic acid **28** proceeded with less efficiency presumably due to steric effects. In an attempt to introduce two substituents *ortho* to the acid **32**, 5 equiv of NEt_2 was used, and a good yield of the 2,6-disubstituted product **33** was obtained (THF, −30 to 0 °C). In the presence of a weaker nucleophile such as LiNMePh (vide supra), the monosubstitution product **34** was formed exclusively, even in refluxing THF. These results suggest that it should be feasible to introduce two different amino groups. This indeed proved to be the case by the clean conversion of **34** to **35**.

In the literature, examples of direct amination reactions of a naphthalene are very scarce.[7,8] Reaction of 2-methoxy-

Scheme 3. Amination Reactions of Methoxybenzoic Acids **26**−**28**, 2,6-Difluorobenzoic Acid **32**, and Naphthoic Acids **36** and **38**



1-naphthoic acid (**36**)[27] and 1-methoxy-2-naphthoic acid (**38**)[28] with $LiNEt_2$ provided the naphthalenes **37** and **39**.

We believe that the chemistry reported herein might become rapidly a preferable alternative to the oxazoline and BHA−ester systems. The carboxylic acid substituent which is one of the most reliable resources for introduction of various functionalities does not require protection/deprotection steps or the use of metal catalysts. These preliminary results indicate that the amination of *ortho*-fluoro- and *ortho*-methoxybenzoic acids may provide additional methodology to aromatic substitution, and further studies in this respect are in progress.[29] The biaryl skeleton can be reached by a process involving unprotected benzoic acid derivatives and aryllithium and aryl Grignard reagents. This work will be reported soon.

Acknowledgment. Helpful discussions with Dr. Sven Taylor and Dr. Gérard Moine (Hoffmann-La Roche Ltd., Basel) are gratefully acknowledged. M.B.R., T.T.L., and R.A. are indebted to the French Ministry of Research and Technologies, the Algerian Ministry of Research, and Soprema for doctoral fellowships. We also express appreciation to Patricia Gangnery (Université du Maine) for technical assistance.

Supporting Information Available: Details of compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The geminal dimetallo dialkoxide $C(OM)_2$ (M = Li, K) group is a good director of *ortho*-metalation: Tilly, D.; Samanta, S. S.; De, A.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2005**, *7*, 827–830.

(21) Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3059–3062.

(22) Rappoport, Z. *The Chemistry of Peroxides*; Wiley-Interscience: New York, 2006; Vol. 2, part 1.

(23) Majewski, M.; Gleave, D. M. *J. Organomet. Chem.* **1994**, *470*, 1–16.

(24) Observations of a similar rearrangement, leading to dioxindoles, have been reported: Kafka, S.; Klasek, A.; Kosmrlj, J. *J. Org. Chem.* **2001**, *66*, 6394–6399.

(25) In deoxygenated medium, the reaction of **2** with LiNMeBn (5 equiv) led to **5** (> 90%). It is assumed that the reduction step leading to **25** is the first irreversible step in the pathway.

(26) All new compounds gave correct analytical data. See Supporting Information.

(27) (a) Fuson, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 5409–5413. (b) Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010–1015.

(28) Castagnetti, E.; Schlosser, M. *Chem.—Eur. J.* **2002**, *8*, 799–804.

(29) A patent application was filed: Mortier, J.; Castanet, A.-S.; Belaud-Rotureau, M. patent pending, filing number FR201051226 (2010).