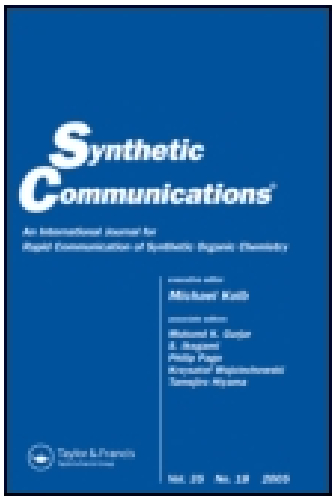

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A SIMPLE AND EFFICIENT SYNTHESIS OF 2-(N-PHENYLAMINO)- BENZOIC ACIDS

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A SIMPLE AND EFFICIENT SYNTHESIS OF 2-(*N*-PHENYLAMINO)-BENZOIC ACIDS

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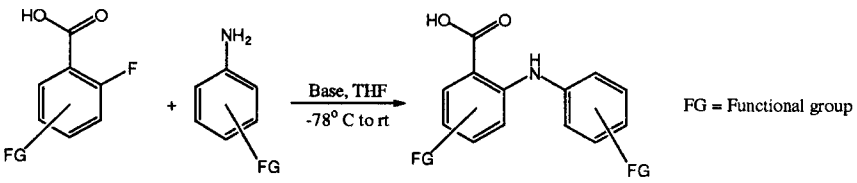
ABSTRACT

A new method for the synthesis of 2-(*N*-phenylamino)benzoic acids is presented, with 2-fluorobenzoic acids and anilines as starting materials. Several experimental conditions as well as the factors influencing the outcome of the reaction are described.

The reaction between aliphatic amines and both 2- and 4-fluorobenzoic acids to give 2- or 4-aminobenzoic acids has been reported in the literature.[1–8] However, much more scarcely found is the reaction between 2- and 4-fluorobenzoic acids and anilines.[1,9–13] The most likely reason for this is the less nucleophilic character of the latter. In the course of a research project undertaken in our laboratories, the need for the synthesis of variously substituted 2-(*N*-phenylamino)benzoic acids (**1**) as

*Corresponding author.

important intermediates arose. The yields we found in the literature were, in many cases, fair to low, and the need for synthesizing large amounts of these compounds demanded a more efficient method. We report an improved method which gives good to excellent yields of the desired products. The general reaction is shown in Scheme 1.



1

Scheme 1.

The reactions were run using 1 equivalent each of the fluorobenzoic acid and the aniline with 3 equivalents of lithium hexamethyldisilazide (LiHMDS), which was found to be the most suitable base for this type of reaction.

Three different methods to carry out the reaction were tested:

- Method A, or "two-pot procedure": In a first flask, base (1 eq) was added to a solution of the acid (1 eq) in tetrahydrofuran (THF) at -78°C. In a second flask, base (2 eq) was added to a solution of the aniline (1 eq) in THF at -78°C. The contents from the first flask were transferred into the second flask and the resulting mixture was allowed to reach ambient temperature overnight.
- Method B, or "one-pot procedure": Both the acid and the aniline were dissolved in THF, the mixture cooled to -78°C, the base added, and the mixture allowed to warm up to ambient temperature overnight. In Method B*, the base was added at -20 to 0°C, and then the mixture was warmed up at 40–50°C overnight.
- Method C is also a "two-pot procedure". The difference with respect to Method A is that the 3 equivalents of base are added to the aniline followed by a solution of the acid in THF.

A summary of the results from this study is shown in Table 1.

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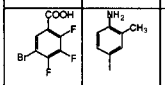
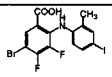
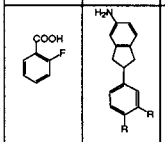
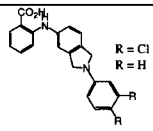
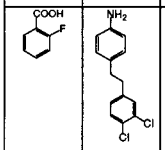
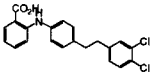
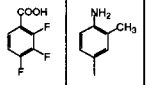
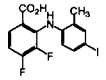
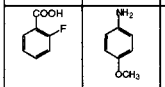
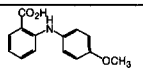
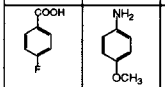
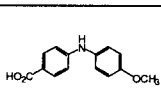
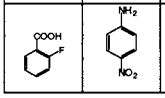
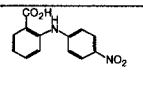
Table 1.

Benzoic Acid	Aniline	Compound #	Compound Structure	Entry #	Base	Method	Isolated Yield	M.P. °C
		**1**		1 2	LiHMDS LiHMDS	A B	89 70	>250
		**2** **3**	 R = Cl R = H	3 4	LiHMDS LiHMDS	B* B*	76 76	264-265
		**4**		5	LiHMDS	C	99	182-184
		**5**		6 7 8 9 10 11 12 13 14 15 16	LiHMDS NaHMDS KHMDS LDA NaH TEA LiHMDS (2 eq) LiHMDS (3.5 eq) LiHMDS (4 eq) LiHMDS LiHMDS	A A B B B A A A A B C	49 77 29 0 0 26 84 88 85 78 83	234-235
		**6**		17	LiHMDS	A	71	170-172
		**7**		18	LiHMDS	A	0	
		**8**		19	LiHMDS	A	0	

DISCUSSION

From the results that we have obtained, several conclusions can be drawn based on different factors that influence the outcome of the reaction:

1. Method employed (Entries 1–2): Method B provides somewhat lower yields than method A. The reason for this seems unclear at this

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point. A possible explanation is that having the acid in the presence of a very large excess of base (much more than what is needed to deprotonate it) may give rise to further side reactions through a benzyne intermediate.

2. Nature of the base (Entries 6–11): LiHMDS gives the best yields compared to other bases. For instance, in the reaction between 2,3,4-trifluorobenzoic acid and 4-iodo-2-methylaniline, the yields were 84% (LiHMDS), 28% (LDA) and no reaction was observed using NaH or triethylamine. With LDA, replacement of the F atom by a diisopropylamino group was detected in some cases, possibly occurring *via* a benzyne intermediate. Lower yields are also observed with bases such as NaHMDS and KHMDS.

3. Number of equivalents of base (Entries 12–14): Reducing the number of equivalents from 3 to 2 in the case of LiHMDS decreases the yield considerably. The most likely reason for this result is that the product is a diaryl amine which is much more acidic than the aniline. If a third equivalent of base is not present in the reaction medium to neutralize it, it may protonate the anilide anion that has not reacted, stopping the reaction. The use of more than 3 equivalents of base did not have a noticeable effect on the yield.

4. Position of the fluorine atom with respect to the carboxylic acid group in the ring (Entries 17–18): Only 2-fluorobenzoic acids react with anilines. Thus, the reaction between 2-fluorobenzoic acid and *p*-anisidine afforded 71% of the desired product under these reaction conditions; when 4-fluorobenzoic acid was employed, no reaction was observed. The proximity of the strongly electron-withdrawing carboxylic acid group plays a fundamental role. Even though its presence should influence both *ortho* and *para* positions, no effect seems to be observed in the latter. This is confirmed by the fact that when either 5-bromo-2,3,4-trifluorobenzoic (Entry 1) or 2,3,4-trifluorobenzoic (Entry 6) acids were used, the product resulting from attack at the 4-position was not observed.

5. Effect of the substituents on the aniline ring (Entries 17 and 19): The presence of electron-donating groups, such as methoxy, increases considerably the reactivity of the aniline. If strongly electron-withdrawing groups coexist on the ring, the reactivity decreases dramatically. This can be seen in the reaction between 2-fluorobenzoic acid and both *p*-anisidine and *p*-nitroaniline. In the first case, the yield was 71%, while no reaction was observed in the second one. This is to be expected, since it is well known that anilines are less nucleophilic than aliphatic amines due to the involvement of the lone pair on nitrogen in the conjugation with the ring, and additional deactivating groups make this conjugation even stronger.

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We are trying to extend the scope of this methodology to fluorinated substrates with electron-withdrawing groups other than carboxylic acids, such as nitro, carbonyl (both aldehyde and ketone), ester and nitrile. The most promising results so far have been obtained with fluorobenzonitriles and fluoronitrobenzenes, even though, in some cases, the yields still are quite modest.

CONCLUSION

We have developed a simple way to prepare 2-(*N*-phenylamino)benzoic acids and determined the best experimental conditions after considering important factors such as the nature of the base, steric and electronic effects and the influence of the substituents.

EXPERIMENTAL

A typical procedure for Method A is as follows:

Flask A: Into a three-necked-round bottomed flask equipped with a magnetic stirrer and a thermometer and under nitrogen atmosphere was placed 2-fluorobenzoic acid (1.00 g, 7.14 mmol, 1 eq) and dissolved in dry THF (35 ml). After cooling this solution to -70°C in a dry ice-acetone bath, LiHMDS (7.2 ml of a 1 M solution in THF, 7.20 mmol, 1 eq) was added *via* syringe over 10 min. The resulting suspension was stirred at this T for 15 min.

Flask B: Into a three-necked-round bottomed flask equipped with a magnetic stirrer and a thermometer and under nitrogen atmosphere was placed *p*-anisidine (0.88 g, 7.14 mmol, 1 eq) and dissolved in dry THF (35 ml). After cooling this solution to -70°C in a dry ice–acetone bath, LiHMDS (14.3 ml of a 1 M solution in THF, 14.30 mmol, 2 eq) was added *via* syringe over 15 min. The resulting suspension was stirred at this T for 15 min.

Then, the contents of Flask A were transferred by cannula into Flask B and the resulting mixture allowed to reach ambient temperature overnight. The dark brown solution was quenched with 1 N aqueous HCl to pH = 1 and extracted with diethylether (3×50 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$. Purification of the solid residue by flash chromatography (hexanes/ethyl acetate/acetic acid) afforded 1.23 g (71% yield) of the corresponding 2-(*N*-phenylamino)benzoic acid as a beige solid, m.p. 170–172°C.

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^{1}H-NMR and mass spectrometry data for new compounds:

Product **1**: (DMSO, 400 MHz): δ 2.37 (S, 3H), 6.80–6.84 (m, 1H), 7.53–7.55 (m, 1H), 7.70 (s, 1H), 8.11–8.13 (m, 1H), 9.17 (s, 1H). Mass (EI): 390 ($M^+ + 1$).

Product **2**: (DMSO, 400 MHz): δ 4.70 (d, J = 1.6 Hz, 4H), 6.75 (q, J = 2.6 Hz, J = 9.0 Hz, 1H), 6.93 (m, 2H), 7.30–7.35 (m, 2H), 7.39 (d, J = 1.6 Hz, 1H), 7.47–7.55 (m, 3H), 8.03 (q, J = 1.8 Hz, J = 7.8 Hz, 1H), 9.79 (s, 1H), 13.22 (s, 1H). Mass (EI): 387 ($M^+ + 1$).

Product **3**: (DMSO, 400 MHz): δ 4.53 (s, 4H), 6.63 (t, J = 9.2 Hz, J = 8.0 Hz, 3H), 6.74 (t, J = 7.2 Hz, J = 7.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.2 (t, J = 7.6 Hz, J = 8.0 Hz, 3H), 7.25 (s, 1H), 7.33–7.37 (m, 2H), 7.87 (d, J = 8.0 Hz, 1H), 9.63 (s, 1H), 13.04 (s, 1H). Mass (EI): 244 ($M^+ + 1$).

Product **4**: (DMSO, 400 MHz): δ 2.99 (t, J = 13.6 Hz, 4H), 6.86 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.8 Hz, 3H), 7.34 (t, J = 8.4 Hz, J = 8.8 Hz, 3H), 7.48 (t, J = 7.6 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 7.6 Hz, 1H), 9.69 (s, 1H), 13.15 (s, 1H). Mass (EI): 331 ($M^+ + 1$).

Product **5**: (DMSO, 400 MHz): δ 2.25 (s, 3H), 6.63 (q, J = 6.8 Hz, J = 8.0 Hz, 1H), 7.06 (q, J = 9.2 Hz, J = 16.4 Hz, 1H), 7.42 (q, J = 1.6 Hz, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.82 (t, J = 7.2 Hz, 1H), 9.05 (s, 1H). Mass (EI): 400 ($M^+ + 1$).

Product **6**: ($CDCl_3$, 400 MHz): δ 3.81 (s, 3H), 6.67 (t, J = 7.6 Hz, 1H), 6.89–6.94 (m, 3H), 7.17 (d, J = 8.8 Hz, 2H), 7.24–7.30 (m, 1H), 8.00 (d, J = 8.0 Hz, 1H), 9.11 (s, 1H). Mass (EI): 469 ($M^+ + 1$).

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