A Practical Method for the Preparation of 4-Nitrogen-substituted Benzoic Acids

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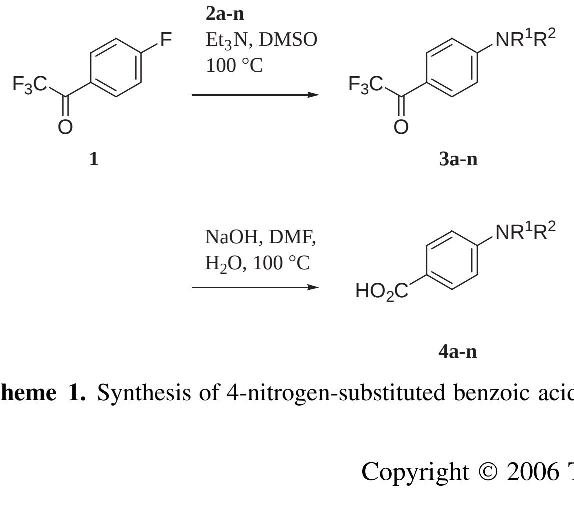
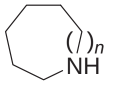
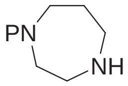
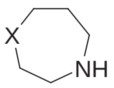
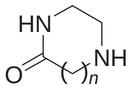
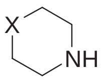
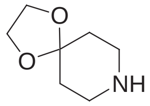
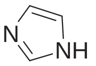
An efficient and practical method for the preparation of 4-nitrogen-substituted benzoic acids is described. Our method consists of the aromatic substitution of 2,2,2,4′-tetrafluoroacetophenone with amines, followed by haloform reaction to the benzoic acids. In this method, even though for the less nucleophilic 7-, 8-, and 9-membered amines 1 equiv. was used, corresponding benzoic acids were obtained in moderate to excellent yield. As the experimental procedure including purification is simple, this method is applicable to large-scale syntheses.

4-Nitrogen-substituted benzoic acids are utilized as building blocks for drug research.[1] They are also useful precursors of several heteroaromatic compounds such as oxazoles,[2] thiazoles,[3] triazoles,[4] and thiadiazoles.[5] In a research program, we needed a variety of 4-aminobenzoic acids, which would be derived from synthetically elaborated amines. One of the conventional methods for the preparation of 4-nitrogen-substituted benzoic acids is a nucleophilic aromatic substitution of 4-flurobenzonitriles or 4-fluorobenzoates with amines followed by hydrolysis.[6] This method requires large amounts of amines and long reaction times to achieve good yields. Alternatively, a recent development of palladium-catalyzed coupling reactions of aryl halides with amines can be applied to the preparation of 4-nitrogen-substituted benzoates.[7] However, more complicated amines gave poor results.[8] Herein, we wish to report an efficient and practical 2-step reaction for the preparation of 4-nitrogen-substituted benzoic acids.



Scheme 1. Synthesis of 4-nitrogen-substituted benzoic acids.

Table 1. Structures of **2**, and isolated yields (%) of **4**[a]

Entry	HNR^{1}R^2 (**2**)		**4**	Yield/%[b]
1	HNEt$_2$	(**2a**)	**4a**[14]	71
2		n = 1 (**2b**)	**4b**[15]	90 (81)[c]
3		n = 2 (**2c**)	**4c**	86
4		n = 3 (**2d**)	**4d**	67
5		P = Boc (**2e**)	**4e**	87 (87)[d]
6		P = Cbz (**2f**)	**4f**	83 (84)[e]
7		X = O[f,g] (**2g**)	**4g**	77
8		X = S[f,g] (**2h**)	**4h**	77
9		n = 1 (**2i**)	**4i**	99
10		n = 2[f,g] (**2j**)	**4j**	83
11		X = O (**2k**)	**4k**	99
12		X = S (**2l**)	**4l**	83
13		(**2m**)	**4m**[16]	81
14		(**2n**)[h]	**4n**	74[i]

[a] All reactions were carried out on a 10-mmol scale unless otherwise noted. [b] Isolated yield over 2 steps. [c] 1,4-Dioxane was used as a solvent. [d] 50-mmol scale. [e] 100-mmol scale. [f] HCl salt. [g] 2.0 equivalents of Et$_3$N were used. [h] 2.0 equivalents of **2n** were used. [i] Purified by reverse phase column chromatography.

The details of the 2-step reaction are summarized in Scheme 1 and Table 1. The reactions were carried out on a 10-mmol scale unless otherwise noted. The first step of this reaction is the aromatic substitution of 2,2,2,4′-tetrafluoroacetophenone (**1**)[9] with amines. The reaction proceeded quantitatively within 30 min in DMSO at 100 °C to provide substituted trifluoroacetophenones **3**.[10] In this reaction, 1 equivalent each of amines **2** and Et$_3$N were sufficient for the complete consumption of **1**, even when less nucleophilic 7-, 8-, and 9-membered amines were employed. Under the same reaction condition, the reaction of 4-flurobenzonitrile with **2b** provided the product in only 31% yield and 60% of starting 4-flurobenzonitrile was recovered. Thus, the use of 2,2,2,4′-tetrafluoroacetophenone (**1**) is more practical than 4-flurobenzonitrile in terms of the reactivity. This increase of reactivity can be ascribed to stronger electron deficiency of the aromatic ring in **1** compared to 4-fluorobenzonitrile and 4-fluorobenzoate. Nevertheless, in the reaction of **1** with imidazole (**2n**), 2 equivalents of **2n** and a longer reaction time of 2 h were required to consume the starting **1** because of its low nucleophilicity.

The second step was haloform reaction.[11] Treatment of **3a** with 8 M NaOH in DMF at 100 °C provided **4a** in 71% yield calculated from **1**.[12] The product precipitated after the addition of 1 M HCl to the reaction mixture. Similarly, most of the other carboxylic acids **4** were also isolated by this workup procedure.

Azepane **4b** was isolated in 90% yield,[13] whereas 8-membered **4c** and 9-membered **4d** were isolated in 86 and 67% yields, respectively. Then, the conversion of several 7-membered amines to the corresponding 4-substituted benzoic acids was examined. *N*-Boc-diazepane (**2e**) and *N*-Cbz-diazepane (**2f**) provided desired products **4e** and **4f** in 87 and 83% yields, respectively. Oxazepane **4g**, thiazepane **4h**, and diazepanone **4j** were isolated in 77, 77, and 83% yields, respectively. In these reactions, the starting amines **2g**, **2h**, and **2j** were HCl salts, and 2 equivalents of Et_3N were used. Nucleophilic 6-membered amines gave excellent results, in particular, piperazinone (**2i**) and morpholine (**2k**) provided **4i** and **4k**, respectively, in quantitative yields. Acetal **4m** was obtained in 81% yield without the cleavage of the acetal group by 1 M HCl treatment. Imidazole **4n** was isolated by reverse phase column chromatography as it was water soluble.

Preparation of **4e** and **4f** was also carried out on a larger scale, and the products were obtained in as good yields as the reactions on a 10-mmol scale.

As described above, DMSO was a suitable solvent in the aromatic substitution reaction, and DMF was preferred in the haloform reaction. To avoid the aqueous workup after the aromatic substitution, one-pot reaction was examined in the reaction with azepane **2b**. Neither DMSO nor DMF gave a satisfactory result, but 1,4-dioxane gave a tolerable result. In 1,4-dioxane, a reaction time of 2 days was required for the nucleophilic aromatic substitution reaction, but the subsequent haloform reaction completed within 1 h to provide **4b** in 81% yield.

In summary, an efficient and practical method for the preparation of 4-nitrogen-substituted benzoic acids was established. 2,2,2,4′-Tetrafluoroacetophenone (**1**) reacted with various amines including less nucleophilic amines. The adduct **3** was treated with NaOH to afford 4-nitrogen-substituted benzoic acids **4** in moderate to excellent yields. This method is superior to the conventional method, especially in the case where the amine being introduced is precious, as one equivalent of amine is sufficient in most reactions. In addition, the experimental procedure including purification is simple; therefore, this method would be suitable for large-scale syntheses.

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