Tetrahedron Letters 53 (2012) 388–391

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nucleophilic ring-opening reaction of benzoxazinones—access to *o*-amino-2,2,2-trifluoroacetophenones

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ARTICLE INFO

Article history:
Received 20 April 2011
Revised 29 October 2011
Accepted 4 November 2011
Available online 18 November 2011

Keywords:
Fluorine
Trifluoromethylation
Benzoxazinones
Ruppert's reagent

ABSTRACT

Organofluorine compounds are of high interest in modern drug discovery and material sciences. We herein report a new synthetic access to *o*-amino-2,2,2-trifluoroacetophenones starting from commercially available *o*-amino benzoic acids, which can easily be converted into the corresponding benzoxazinones. In a second step the trifluoromethylated ketone is formed via addition of Ruppert's reagent following acidic work up.

In current drug discovery and material sciences organofluorine chemistry has become an important tool. The unique properties of fluorine like the strong electronegativity, small size and the low polarizability of the C–F bond enhance for example the lipophilicity of biological active molecules.[1–7]

Especially trifluoromethylated compounds like CF_3–ketones are of synthetic interest due to their exceptional properties and applicability as building blocks.[8] Recently, trifluoromethyl-acetophenones with an additional amino substituent in *ortho*-position have become useful precursors for selective colorimetric sensing of anions, fluorinated benzoxazinones and quinolines.[9–11] These molecules can also be used in anion recognition, which is stabilized by hydrogen bonding.[12] A well established method to form CF_3–ketones is the nucleophilic addition of TMS–CF_3 (Ruppert's reagent) to esters[13] or aldehydes,[14] whereas the second reaction requires the oxidation of the intermediate trifluoromethylated alcohol.[15] To the best of our knowledge, the addition of Ruppert's reagent to aromatic aldehydes in the presence of an amino group is unknown.[16] Other methods like Friedel–Crafts-acylation,[17] *ortho*-lithiation,[18] Barbier-procedure,[19] trifluoromethylation of acid chlorides[20] or electrochemical reactions[21] are also established but often require harsh reaction conditions and functional groups are not always tolerated. In our studies we also examined substrates bearing methyl groups in *ortho*-position to the amino functionality. These methylated derivatives are not accessible using for example the recently published *ortho*-lithiation by Zhu et al. due to the lithiation of the benzyl group instead of the aromatic ring.[18] For that reason our work is a complement to the already existing methods.

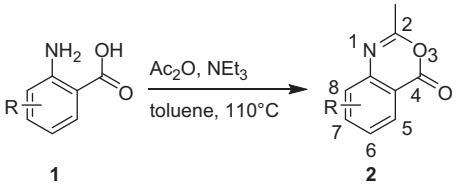
Herein, we present a novel method to generate CF_3–ketones bearing an amino functionality in *ortho*-position. Therefore, *o*-amino benzoic acids[22] were converted into the corresponding benzoxazinones using triethylamine and acetic anhydride (Scheme 1).[23,24]

All benzoxazinones, shown in Table 1, could be isolated in excellent yields (79–99%). The spectroscopic data of known compounds (Table 1, entries 1–3, 7) were in accordance to the literature.[25] Thus, derivatives substituted with halides, nitriles, methyl-, and methoxy-groups were accessible.

The general structure of benzoxazinones was confirmed by conducting an X-ray structural determination on **2d** (Fig. 1, see Supplementary data for details).

These benzoxazinones were then reacted with TMS–CF_3 and a catalyst to form the corresponding keto-compounds (Scheme 2).

Depending on the reaction conditions, we observed the free amino compound **3** or the corresponding acetylated derivative **4**.



Scheme 1. Synthesis of benzoxazinones **2** starting from anthranilic acids **1**.

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doi:10.1016/j.tetlet.2011.11.014

Table 1
Synthesized benzoxazinones **2**

Entry	Acid	Substituents R[a]	Product	Yield (%)
1	**1a**	6-Cl	**2a**	79
2	**1b**	8-Me	**2b**	92
3	**1c**	6,8-Cl	**2c**	92
4	**1d**	6-Cl, 8-Me	**2d**	>99
5	**1e**	6-I, 8-Me	**2e**	>99
6	**1f**	6-CN, 8-Me	**2f**	>99
7	**1g**	6,7-OMe	**2g**	98

[a] Numbering based on the product.

To optimize the reaction conditions several parameters like solvent, catalyst, equivalents, or work-up procedure were varied. The chlorinated benzoxazinone **2a** was used as model system due to its use as precursor in the synthesis of *efavirenz*; a drug used in HIV-therapy.[26]

The first optimization was based on a solvent screening (Table 2). The benzoxazinone **2a** was reacted with 1.5 equiv Ruppert's reagent, 0.1 equiv TBAF as initiator and HCl as acidic work up at room temperature. The results indicate that the reaction is favored in polar solvents like DMF and DMSO (entries 4 and 5). Further studies concerning the amount of Ruppert's reagent have shown that DMSO is the solvent of choice and that the reaction can be accomplished with 2.0–3.0 equiv of the trifluoromethylating reagent (entries 12 and 13). Furthermore, various catalysts were investigated in the ring-opening reaction. The use of $TiCl_4$ or NaOAc[27] did not succeed (entries 14 and 15). For that aspect, TBAF was chosen as best initiator for the trifluoromethylation. Another attempt to optimize the reaction conditions was the screening of different reaction temperatures (entries 16–18). Higher temperatures did not lead to higher amounts of the trifluoromethylated ketone **4**. Next, we investigated a range of various work-up procedures to remove the acetyl group at the amino function. Different HCl concentrations led to an increased amount of products with a free amino group. In the case of 6 M HCl the conditions were probably too harsh and led to the decomposition of the substrates. Slightly acidic 2 M HCl can be used at room temperature to remove the acetyl group (rt, 24 h, quant). Due to this fact, a 2 M HCl solution was used for the substrate screening to cleave the amide bond. If the work up was carried out with 2 M HCl at 100 °C, a complete decomposition occurred. Additional attempts to remove the acetyl

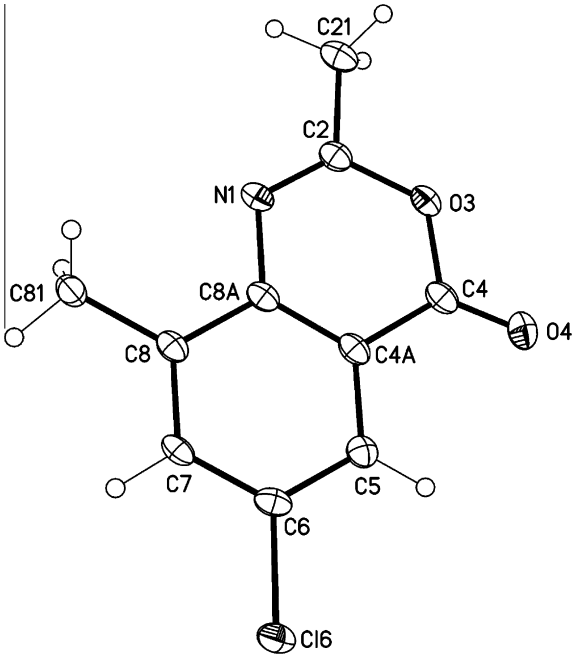
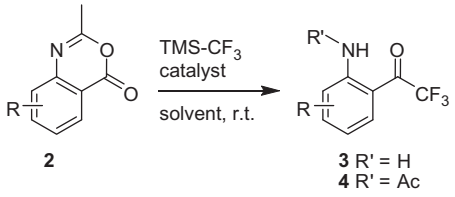


Figure 1. Molecular structure of **2d** (displacement parameters are drawn at 50% probability level).



Scheme 2. Trifluoromethylation of benzoxazinones **2**.

Table 2
Optimization studies on model system **2a**

Entry	Solvent	T (°C)	Catalyst	Equiv TMS–CF_3	Work up	**2**[a] (%)	**3**[a] (%)	**4**[a] (%)
1	Et_2O	rt	TBAF	1.50	1 M HCl	22	10	68
2	CH_2Cl_2	rt	TBAF	1.50	1 M HCl	60	13	28
3	$CHCl_3$	rt	TBAF	1.50	1 M HCl	89	11	0.0
4	DMF	rt	TBAF	1.50	1 M HCl	3	27	70
5	DMSO	rt	TBAF	1.50	1 M HCl	3	40	56
6	Hexane	rt	TBAF	1.50	1 M HCl	57	18	26
7	Toluene	rt	TBAF	1.50	1 M HCl	43	4	53
8	MeCN	rt	TBAF	1.50	1 M HCl	14	21	65
9	THF	rt	TBAF	1.50	1 M HCl	17	7	76
10	DMSO	rt	TBAF	1.50	3 M HCl	0	54	46
11	DMSO	rt	TBAF	1.50	6 M HCl	0	70	30
12	DMSO	rt	TBAF	2.00	6 M HCl	0	63	37
13	DMSO	rt	TBAF	3.00	6 M HCl	0	89	11
14	DMSO	rt	$TiCl_4$	1.50	6 M HCl	76	24	0
15	DMSO	rt	NaOAc	1.50	6 M HCl	>99	0	0
16	DMSO	40	TBAF	1.50	6 M HCl	0	68	32
17	DMSO	80	TBAF	1.50	6 M HCl	0	62	39
18	DMSO	120	TBAF	1.50	6 M HCl	0	69	31
19	DMSO	rt	TBAF	1.50	2 M HCl 100 °C	0	0	0
20	DMSO	rt	TBAF	1.50	TFA	41	0	59
21	DMSO	rt	TBAF	1.50	$[(CH_3CH_2)_3O]BF_4$	41	0	59

In each case, 10 mol % of the catalyst was used.
[a] Ratios determined by GC–MS analysis with *n*-dodecane as internal standard.