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Journal of Fluorine Chemistry 103 (2000) 81–84

JOURNAL OF FLUORINE CHEMISTRY

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Short synthesis of 4-chloro-4′-(chlorodifluoromethoxy)benzophenone

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Received 10 September 1999; accepted 18 October 1999

Abstract

A one-pot, highly selective synthesis of 4-chloro-4′-(chlorodifluoromethoxy)benzophenone suitable for an industrial scale-up was developed. Fluorination of 4-(trichloromethoxy)benzoyl chloride at –20°C with HF to 4-(chlorodifluoromethoxy)benzoyl fluoride followed by an in situ Friedel–Crafts reaction with chlorobenzene in the presence of BF_3 at –5°C yielded the title compound in excellent yield.

Keywords: Chlorodifluorobenzene derivatives; Fluorination with HF/BF_3; Friedel–Crafts reaction

1. Introduction

In the course of our work on benzophenone hydrazone derivatives with insecticidal activity [1–6] we discovered the excellent biological properties of some acylated 4-(perhaloalkoxy)benzophenonehydrazones [7]. The interesting results obtained with derivatives in the chlorodifluoromethoxy series **1** (see Fig. 1) prompted us to seek a convenient synthesis of the crucial intermediate benzophenone **2** in view of a possible development process. Herein we present our work, which resulted in a short and easy synthesis of the hitherto unknown 4-chloro-4′-(chlorodifluoromethoxy)benzophenone **2**.

2. Results and discussion

We first tried a route suitable for small-scale synthesis starting from commercially available 4-chloro-4′-hydroxybenzophenone (**3**). Conversion of the OH group in simple phenols to the OCF_2Cl group is described in the literature (with HF in CCl_4 in [8], with HF and diphosgene in [9] and with $CHClF_2$ and consequent radical chlorination in [10]) essentially as a side reaction in the preparation of OCF_3 derivatives. For this reason another method, the reaction of **3** with CCl_2F_2 and $CBrClF_2$, was explored. After some optimisation work, we found the alkylation procedure outlined in Fig. 2. Importantly, the use of potassium *tert*-butylate as second base was essential to obtain **2** by this process. This method unfortunately showed serious drawbacks: the yields were never higher than 40% and not reproducible and the purification was tedious.[1]

To find an alternative to the above procedure we investigated the use of a Friedel–Crafts reaction. A notorious problem associated with Friedel–Crafts reactions on (haloalkoxy)benzenes is the halogen exchange reaction caused by the Lewis acid, which leads to mixtures of halogenated products.[2] The benzoylation of (trifluoromethoxy)benzenes has been attempted [11] using $AlCl_3$ as catalyst, conditions which cause halogen exchange and degradation reactions, and BF_3 in HF at 20–30°C, which gives excellent yields of the (trifluoromethoxy)benzophenones. These latter reaction conditions are nevertheless favourable to cause halogen exchange in a CF_2Cl group. Interestingly, Friedel–Crafts reactions using (chlorodifluoromethoxy)benzene have never been described in the literature.

On the other side, we expected acyl derivatives of type **6** (see Fig. 3) to react under milder conditions at lower

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[1] This is perhaps less surprising because the reaction of potassium phenolates with CF_2Br_2 and CF_2BrCl to form (bromodifluoromethoxy)-benzenes, has been described to give low yields and low halogen selectivity, see [21].

[2] Halogen-exchange fluorinations with HF in the presence of electron acceptors (especially pyridine) have been reviewed (see [22]). Olah et al. [23] have described formation of mixtures of $C_6H_5OCCl_2F$ and $C_6H_5OCClF_2$ upon treatment of (trifluoromethoxy)benzene with $AlCl_3$. Similar results were reported by Desbois ([11] and references therein).

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PII: S0022-1139(99)00259-6

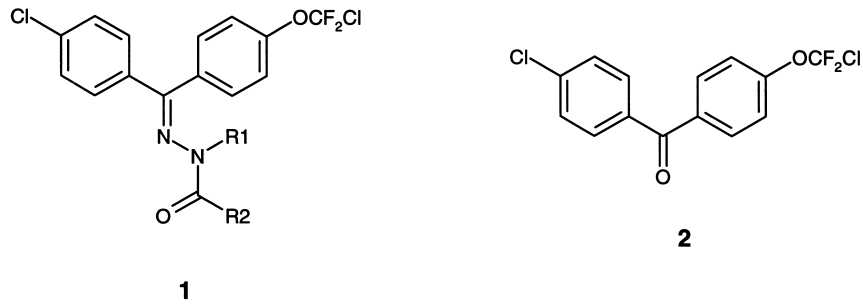

Fig. 1. Insecticidal benzophenone hydrazone derivatives **1** and intermediate **2**.

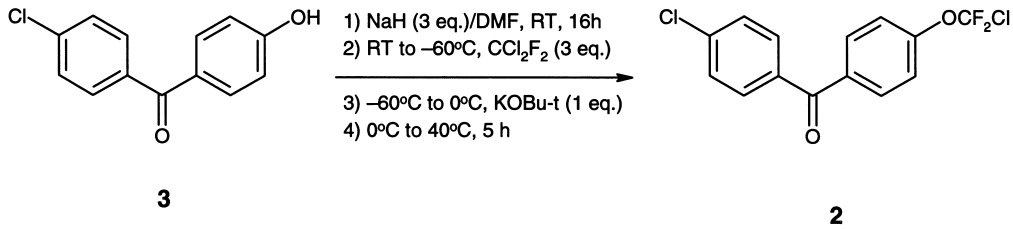

Fig. 2. Small-scale synthesis of the benzophenone **2**.

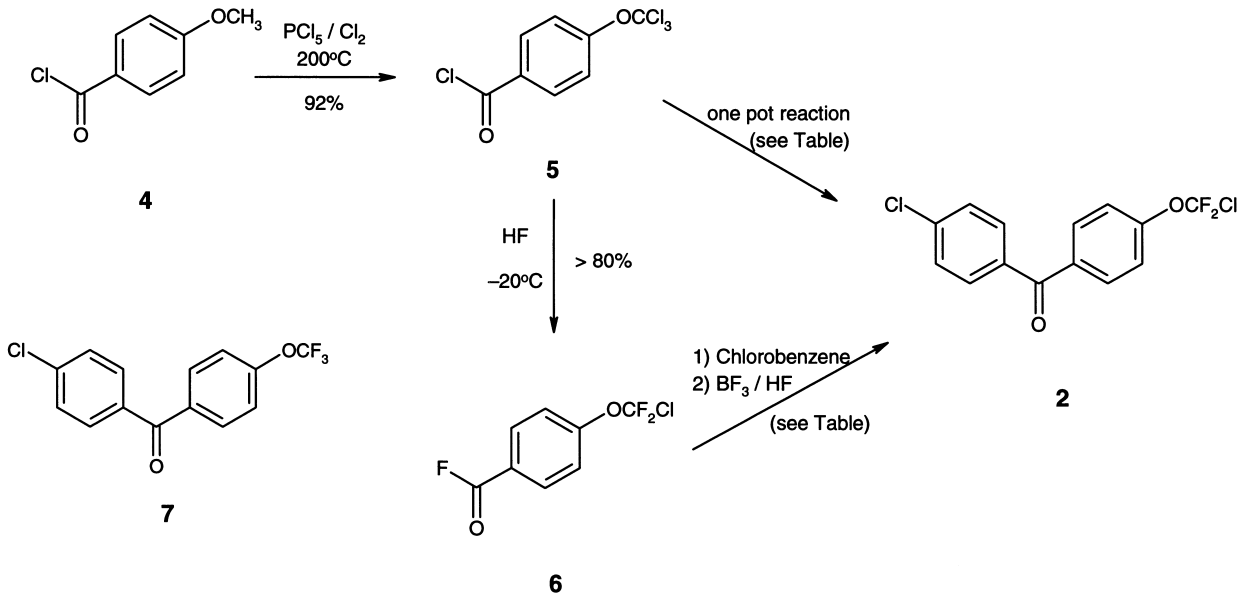

Fig. 3. Successful synthesis of **2**.

temperature, thus minimising the formation of the unwanted OCF_3 compound **7**. The synthesis of compound **6** from intermediate **5** would additionally benefit from the fact, that readily available ([12], chlorination of chlorothioformates in [13], chlorination of anisoles in [14], with Cl_2/PCl_3 and irradiation in [15] and with CCl_4 and irradiation in [16]) (trichloromethoxy)benzenes can be transformed selectively into (chlorodifluoromethoxy)benzenes using either HF or SbF_3 ([12], with HF in [17,18] and with SbF_3 in [19,20]). The preparation of acid fluoride **6** and its Friedel–Crafts reaction with chlorobenzene in HF with BF_3 as Lewis acid was consequently studied.

Chlorination of the acid chloride **4** with Cl_2 in the presence of PCl_5 at 200°C (chlorination of anisoles in [14]) gave 4-(trichloromethoxy)benzoylchloride **5** in excellent yield. Subsequent fluorination of **5** with HF at low temperature gave **6** in yields higher than 80%.[3] Friedel–Crafts reaction of **6** in the presence of chlorobenzene using HF/BF_3 as Lewis acid yielded **2** in reasonable yields, but a

[3] The preparation of this acid fluoride has been described from **5** using excess HF at a temperature of 90–100°C [24]. This high reaction temperature would in our opinion cause a considerable amount of overfluorination.

Table 1
Selected experiments[a]

Entry	Scale (mol)	Isolation of **6**	Eq. of BF_3	Temperature of addition of BF_3 (°C)	Yield of crude	Percentage of **2** pure[b]	Ratio[c] **2**:**7**
1	0.0089	Yes	18	0	68	45	60:40
2	0.0365	Yes	12	0	76	NP[d]	85:15
3	0.0830	No	6	–5	95	69	98:2

[a] Compare the experimental procedures.
[b] With respect to **5**; a high excess of BF_3 does not increase the reaction rate but the building of side products and resinification.
[c] Measured on the crude product by means of ^{19}F NMR.
[d] Not purified.

considerable amount of the trifluoromethoxy compound **7** was obtained as by-product (Table 1, entry 1). The reaction conditions were systematically modified and the most pertinent experiments are reported in Table 1. Lowering the amount of BF_3 improved the ratio OCF_2Cl:OCF_3 (Table 1, entry 2). Making use of the fact that HF is used as solvent and/or reagent in both steps (**5** to **6** and **6** to **2**), a one-pot reaction **5** to **2** avoiding the isolation of the acid fluoride **6** was performed. Entry 3 in Table 1 shows then on decreasing the amount of BF_3 to 6 eq. (still ensuring a complete conversion), using HF as solvent, and lowering the temperature to below 0°C, an excellent yield of **2** containing only traces of **7** was obtained. Under these conditions, the pernicious halogen exchange reaction C–Cl to C–F was essentially suppressed.

3. Experimental procedures

General. NMR spectra were recorded on a Bruker-AC-F250 spectrometer using $(CH_3)_4Si$ or CF_3Cl as internal standards. Mass spectra (EI-MS, 70 eV) were recorded on a Finnigan MAT212. The melting points are uncorrected and were determined on a Kofler apparatus. Solvents and reagents were obtained from commercial sources and used without further purification. Stirring Monel 400 autoclaves from Autoclave Europe were used. 4-(Trichloromethoxy)-benzoylchloride (**5**) was prepared in 92% yield from commercially available **4** according to the procedure of Yagupolsky and Troitskaya (chlorination of anisoles in [14]).

*3.1. Preparation of 4-(chlorodifluoromethoxy)-benzoylfluoride (**6**)*

4-(Trichloromethoxy)benzoyl chloride (**5**) (10.0 g, 36.5 mmol) was introduced into a 0.3 l autoclave and cooled to –25 to –20°C by means of an acetone/CO_2 bath. HF (50 g) was condensed into the apparatus; then allowed to warm to RT (18 h). The autoclave was evacuated and the excess HF distilled off. The crude oily product **6** (7.4 g, 90%) was used directly in the Friedel–Crafts experiments. ^{19}F NMR ($CDCl_3$, 235 MHz) δ/ppm: –8.0 (COF), –28.7 (CF_2Cl). ^1H NMR ($CDCl_3$, 250 MHz) δ/ppm: 8.12 (d, 2H, $J = 8$ Hz), 7.40 (d, 2H).

*3.2. Friedel–Crafts experiments with **6**, typical example (see Table 1, entries 1 and 2)*

Acid fluoride **6** (2.0 g, 8.9 mmol), chlorobenzene (1.12 g, 10.0 mmol) and CH_2Cl_2 (10 ml) were introduced into a 0.3 l autoclave and cooled to –20°C by means of an acetone/CO_2 bath. HF (40 g) was introduced and the reaction brought to 0°C. BF_3 (11 g, 0.162 mol) was then added, whereupon the internal end pressure reached 12 bar. The reaction was then left at RT for 4 days (control by TLC and GC). Work up analogous to the optimised procedure (see below) left 1.92 g (68%) of crude material showing two peaks in the ^{19}F NMR spectrum (–28.3 ppm, ca. 60% and –60.0 ppm, ca. 40%). Flash-chromatography using ethyl acetate:hexane 1:20 yielded 1.25 g (45%) of a mixture of **2** and **7** as colourless crystals melting at 55–58°C (ratio **2**–**7** ca. 60–40).

*3.3. Synthesis of **2**, experimental optimised procedure (see Table 1, entry 3)*

4-(Trichloromethoxy)benzoyl chloride (**5**) (22.8 g, 0.083 mol) was introduced into a 0.3 l autoclave and cooled to –25°C by means of an acetone/CO_2 bath. Between –25 and –20°C HF (100 g) was introduced into the autoclave and after 10 min the reaction was allowed to warm to RT overnight (total reaction time 21 h). The autoclave was evacuated, the temperature brought down to –5°C (Kryomat), and chlorobenzene (10.4 g, 0.092 mol) introduced. Shortly afterwards BF_3 (12.5 g, 0.184 mol) was compressed into the autoclave (internal end pressure 10 bar) at –5°C. The reaction temperature was kept between –5 and –1°C for 40 h. BF_3 was then evacuated at this temperature and the HF distilled off. The crude material was poured onto ice and 50 ml CH_2Cl_2 added. After separation of the organic phase, the aqueous phase was extracted three times with 50 ml CH_2Cl_2. The methylene chloride extracts were washed with ice-water and dried over Na_2SO_4. After removing the solvent on a rotary evaporator a dark brown wax (25.0 g; NMR analysis: less than 2% of **7**) was obtained, which was stirred at 30°C with 50 ml of a mixture

ethylacetate:hexane 1:10. A brown tar remained insoluble and was discarded. The filtrate was cooled to 0°C overnight, and the formed colourless crystals were filtered off and washed with a little cool hexane. From the concentrated mother liquors upon addition of further hexane and cooling, two further crops of crystals (identical to the first by NMR) were obtained. Yield of **2**: 18.10 g (0.0572 mol, 69%). m.p. 56–59°C.[4] ^{19}F NMR ($CDCl_3$, 235 MHz) δ/ppm: –28.3 (OCF_2Cl, ≥98%); –60.0 (OCF_3, ≤2%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ/ppm: 7.88 (d, 2H, $J = 8$ Hz), 7.76 (d, 2H), 7.49 (d, 2H), 7.36 (d, 2H). MS: 318 ($M + 2^+$, 38), 316 (M +, 59), 281 (15), 215 (16), 207 (31), 205 (100), 180 (10), 141 (27), 139 (86), 111 (27). Elemental analysis. Calculated for $C_{14}H_8Cl_2F_2O_2$ (317.12): C, 53.03%; H, 2.54%; Cl, 22.36%; F, 11.98%. Found: C, 53.28%; H, 2.20%; Cl, 22.25%; F, 11.87%.

4. Conclusions

We have described the first Friedel–Crafts reaction leading to 4-(chlorodifluoromethoxy)benzophenone systems. Furthermore, we have developed a one-pot process for the synthesis of 4-chloro-4′-(chlorodifluormethoxy)benzophenone (**2**) suitable for a scale-up. The yields are in the range of 70% and purity is 98%. Starting from the commercially available **4**, the overall yield over two steps is ca. 65%.

Acknowledgements

We are grateful to Messrs D. Beuchat, R. Dinkel, H. Gugger, H. Kienast and A. Vitale for their skilful experimental support, and to Dr. A. O'Sullivan for his review of the manuscript.

[4] A purer sample of **2** obtained by reaction of hydroxybenzophenone **3** with CCl_2F_2 (compare Fig. 2) melted at 61–62°C and showed only one peak at –28.3 ppm in the ^{19}F NMR spectrum.

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