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Unsymmetrical Diarylketones from Electron-rich Heterocyclic Arenes

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Summary. $AlCl_3$-mediated chlorocarbonylation of a first arene by oxalyl chloride followed by *in situ Friedel-Crafts* acylation of a second electron-rich arene expeditiously provides, in a one-pot procedure, either symmetrical or unsymmetrical benzophenones with yields ranging from 17–52%. Best results are obtained when the more activated substrate is used as the second arene. Another advantage is that the resultant benzophenone precipitates from the reaction mixture allowing facile workup.

Keywords. Heterocycles; *Lewis* acids; *Friedel-Crafts* acylation; Benzophenone; 2(*3H*)-Benzoxazolone; Oxalyl chloride.

Introduction

Diarylketones serve as useful synthons in the elaboration of pharmacological tools and the diphenylmethane pharmacophore is encountered in numerous clinically relevant drugs such as methadone, phenytoin, progabide, tolcapone, *etc*. In particular, diarylketones are very useful for the synthesis of 5,5-diarylhydantoins [1]. In this connection, this scaffold was used recently with great success in the design of CB_1-cannabinoid receptor antagonists [2, 3]. In an effort to gain access to 5,5-diarylhydantoins bearing electron-donating substituents on the aromatic moieties, we have searched for a straightforward synthesis of diarylketones possessing the above prerequisites. These compounds could then be utilized in the *Bucherer-Berg* synthesis of such 5,5-diarylhydantoins as an advantageous alternative to the *Biltz*'s synthesis of phenytoin [3]. Indeed, benzils substituted with electron-donating groups in *ortho*- or *para*-position give poor yields of hydantoin when reacted with urea in basic medium [4].

Whereas many synthetic methods are available to prepare such diarylketones, in spite of numerous limitations, the *Friedel-Crafts* (*FC*) acylation of arenes by an

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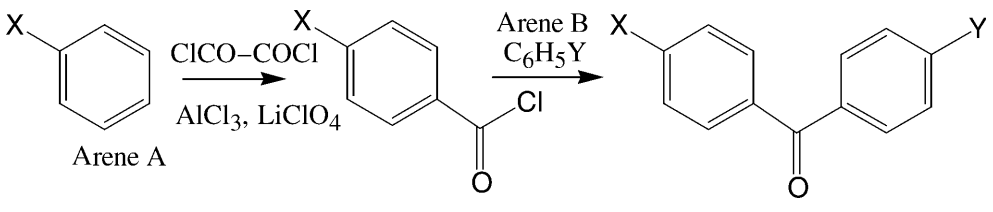
aroyl halide in the presence of a *Lewis* acid catalyst remains the method of choice. A paradoxical limitation of this method arises when the arene is electron-rich because the extensive complexation of the aromatic substrate by the *Lewis* acid drastically reduces the reactivity of the arene leading to low yields or no conversion at all [5]. The problem is partially alleviated when the *Lewis* acid is complexed by an appropriate *Lewis* base. In this context, the use of the $AlCl_3 \cdot DMF$ complex as a catalyst in the acylation of electron-rich aromatic substrates is well documented [6–8]. A major practical limitation of this approach is that a considerable excess of catalyst (up to 10-fold) is necessary to obtain good yields [9].

The $AlCl_3$-mediated chlorocarbonylation of arenes has been known for many years [10, 11]. There were a few reports of the *in situ* coupling of the intermediate complexed aroyl chloride with an additional arene to prepare symmetrical benzophenones [12, 13]. Recently, an interesting contribution to the synthesis of unsymmetrical diarylketones was brought about by *Taber* and *Sethuraman* who made use of the well-known $AlCl_3$-mediated chlorocarbonylation of arenes to generate *in situ* the aroyl halide species, which was coupled in a one-pot procedure with an arene to prepare an unsymmetrical diarylketone [14]. This technique appears to be an efficient approach for synthesizing both symmetrical and unsymmetrical diarylketones with the advantage that the method does not require a huge excess of $AlCl_3$. The yields reported by these authors ranged from 54 to 77%.

In this paper, we report the results of the application of this method to electron-rich heterocyclic systems such as 2(*3H*)-benzoxazolone, 2(*3H*)-benzothiazolone, and 2-indolinone. This work was motivated also in part by the recent report that 6-benzoyl-2(*3H*)-benzothiazolone is endowed with interesting analgesic properties due to the release of opioid peptides in the periphery [15].

Results and Discussion

We first optimized the reaction by examining 2(*3H*)-benzoxazolone (**1**) as a model electron-rich aromatic substrate used both as arene A and B (Scheme 1). Initial attempts done using *Taber*'s conditions of solvent, temperature, and $AlCl_3$/arene ratio were met with poor success resulting in mediocre extent of arene consumption and complex reaction mixtures. We anticipated that *N*-acylation could interfere in the process as, during our exploration of the reaction under acidic conditions, when we substituted $AlCl_3$ with K10 montmorrillonite [16], we obtained in high yield 3-benzoyl-2(*3H*)-benzoxazolone (**2**) by treatment of **1** with benzoic anhydride. An authentic sample of **2** was obtained by treatment of **1** by benzoyl chloride and triethylamine in refluxing *THF*, as previously described [17]. While **2** readily



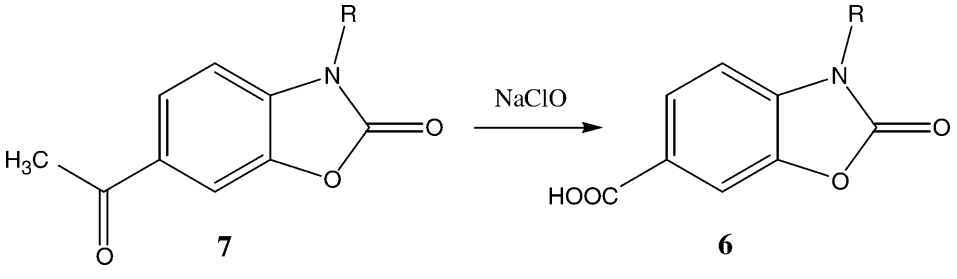
Scheme 1

undergoes N–C acyl migration at elevated temperature (165°C) in the presence of a *Lewis* acid such as $AlCl_3$ [17], it is stable at room temperature and does not rearrange to benzophenone **3** (Figure 1) under *Taber*'s conditions, or at 50°C. Compound **2** was smoothly converted to **3** by treatment with polyphosphoric acid (*PPA*) when submitted to microwave irradiation. However, we were unable to isolate **2** as an intermediate during direct acylation of **1** using either benzoyl chloride or benzoic anhydride in the presence of $AlCl_3 \cdot DMF$.

To overcome the problems mentioned above, the model arene was switched to 3-methyl-2(*3H*)benzoxazolone (**4**). Indeed, direct acylation of **1** using the $AlCl_3 \cdot DMF$ complex as catalyst always results in lower yields than **4**. Owing to previous experience, initial attempts were made at 85°C using the $AlCl_3 \cdot DMF$ complex as catalyst. Again, complex reaction mixtures were obtained. The breaktrough came when lithium ions were added to the reaction medium. At first, lithium chloride was used. The use of lithium ions as adjuvant in the *FC* reaction is well illustrated in the literature by several recent reports [18–20]. The optimal conditions for the synthesis of benzophenone **5** were obtained by running the reaction in CH_3NO_2 in the presence of $AlCl_3$ and $LiClO_4$.

The structure of **5** was assigned on the basis of the following two arguments: first, ^{13}C NMR owing to the number of signals and their attribution clearly indicated that we had obtained a symmetrical benzophenone; second, when the reaction medium was quenched by water after short reaction times (typically 30–60 min), it was possible to isolate 2,3-dihydro-3-methyl-2-oxo-benzoxazol-6-carboxylic acid (**6**, 47% yield). The regioselectivity of the reaction was therefore established since treating the known 6-acetyl-3-methyl-2(*3H*)-benzoxazolone (**7**) [21] with NaClO (haloform reaction) produced the same acid **6** (Scheme 2). The same chlorocarbonylation – *FC* coupling reaction was then reproduced with 3-benzyl-2(*3H*)-benzoxazolone (**8**). The only product isolated was the corresponding symmetrical benzophenone **9**, indicating that under these reaction conditions no competing acylation took place on the *N*-benzyl moiety.

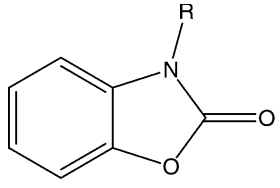
Next, we extended the investigation of the reaction sequence (Scheme 1) to unsymmetrical benzophenones with arene A being either benzene (**10**) or chlorobenzene (**11**) and arene B being either 2(*3H*)-benzoxazolone (**1**), 2(*3H*)-benzothiazolone (**12**), 3-methyl-2(*3H*)-benzoxazolone (**4**), 3-methyl-2(*3H*)-benzothiazolone (**13**), or 2-indolinone (**14**). The times and temperatures for the chlorocarbonylation and subsequent *in situ* acylation for the successful conversions are reported in Table 1.



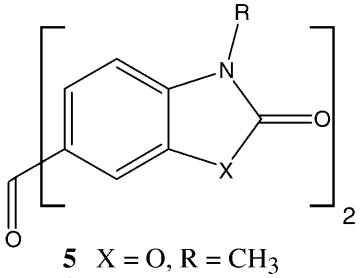
Scheme 2

Table 1. Synthesis of benzophenones (*cf.* Scheme 1) *via* chlorocarbonylation (Step 1) and subsequent *in situ FC* acylation (Step 2)

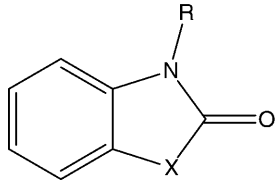
Arene A	Step 1 t/h, T/°C	Arene B	Step 2 product (yield/%)
4	2, rt	**4**	**5** (47)
8	2, rt	**8**	**9** (43)
13	2, rt	**13**	**20** (51)
10	0.5, 10	**4**	**15** (52)
11	10, rt	**4**	**16** (37)
10	0.5, 10	**13**	**17** (52)
11	10, rt	**13**	**18** (47)
10	0.5, 10	**14**	**19** (17)



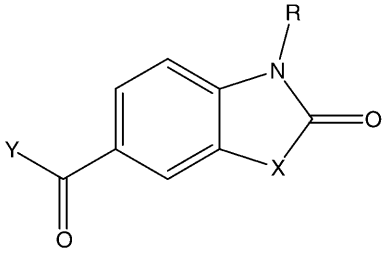
1 R = H
2 R = CO–C_6H_5
4 R = CH_3
8 R = CH_2–C_6H_5



5 X = O, R = CH_3
9 X = O, R = CH_2–C_6H_5
20 X = S, R = CH_3



12 X = S, R = H
13 X = S, R = CH_3
14 X = CH_2, R = H



3 X = O, Y = C_6H_5 R = H
15 X = O, Y = C_6H_5, R = CH_3
16 X = O, Y = 4–Cl–C_6H_5, R = CH_3
17 X = S, Y = C_6H_5, R = CH_3
18 X = S, Y = 4–Cl–C_6H_5, R = CH_3
19 X = CH_2, Y = C_6H_5, R = H

Fig. 1. Structures of compounds **1**–**9** and **12**–**20**

With a less activated substrate such as chlorobenzene (**11**), the chlorocarbonylation required longer reaction time and higher temperature. In each case, 1.3 equivalent of oxalyl chloride with respect to arene A were employed. It should be emphasized that the yields reported are for reactions using a 1:1 molar ratio of arene A and B, and this is in accordance with *Taber*'s report [14]. With the

heterocycles bearing a free NH, the reaction either failed (for **1** and **12**) or gave very low yield (for **14**, 17% yield). Attempts to run the reaction with *meta*-directing substituted substrates (as arene A) such as nitrobenzene or benzonitrile also failed. Inverting arene A and B was unsuccessful, which clearly indicates that the more activated substrate has to be used as the second arene.

Overall yields (Table 1) were found within the range of 17–52%. While these yields can be considered as relatively low, it has to be taken into account that the compounds were isolated by precipitation and recrystallization (not chromatography) and that this one-pot procedure competes rather well with the classical approach involving the construction of the carboxylic acid, activation to aroyl halide, and subsequent *FC* coupling. This approach, however, is not competitive for the synthesis of symmetrical benzophenones as *FC* reaction of **4** with carbon tetrachloride in the presence of $AlCl_3 \cdot DMF$ and *in situ* hydrolysis of the *gem*-dichloromethane intermediate gives **5** with a higher yield (80%) [9].

Conclusion

We have shown that *Taber*'s synthesis of benzophenones can be applied to heterocyclic arenes. This process involves the $AlCl_3$-mediated chlorocarbonylation of a first arene (termed here arene A) by oxalyl chloride followed by the *in situ Friedel-Crafts* acylation of a second electron-rich arene (termed arene B) and expeditiously provides, in a one-pot procedure, either symmetrical or unsymmetrical benzophenones with yields ranging from 17–52%. Best results are obtained when the more activated substrate is used as second arene. The desired benzophenones precipitate from the reaction mixture allowing for easy isolation by filtration and recrystallization. This reaction sequence is quite simple from the experimental point of view and might prove useful for the elaboration of a sortiment of heterocyclic benzophenones using a fast parallel synthesis technique.

Experimental Section

General Procedures

Melting points (uncorrected) were determined in open capillary tubes using a Büchi SMP 20 melting point apparatus. IR spectra were recorded using a dispersion of the product in KBr disks by means of a Perkin-Elmer Model 297 spectrometer. ^1H and ^{13}C NMR spectra were recorded using an AC 300 P Bruker spectrometer. The NMR spectra were recorded at ambient temperature using tetramethylsilane (TMS) as internal reference. Elemental analyses were obtained by courtesy of Prof. *B. Masereel* (FUNDP, Namur, Belgium). All compounds reported had IR, ^1H and ^{13}C NMR, MS, and elemental analysis data consistent with their structure. The experimental elemental analysis figures were found within 0.4% of the calculated values. Thin layer chromatography analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). All compounds reported here were found chromatographically homogenous in two standard solvents, *i.e.* acetone/toluene/cyclohexane (5:2:3, *v*/*v*/*v*) and methanol/chloroform equilibrated with ammonia (1:9, *v*/*v*). High-performance liquid chromatography conditions were: C-18, methanol:water (75:25, *v*/*v*), 1.5 ml/min. All compounds reported were found homogenous under these HPLC conditions. All reagents were purchased from Aldrich. Montmorrillonite K10 was a generous gift from Dr *A. Mathy* from the University of Liège (Ulg) [16]. The times and temperatures for the chlorocarbonylation step (Step 1) and yields of

the subsequent acylation (Step 2) are summarized in Table 1. Improved procedures for synthesis of some reference compounds (**2**, **3**, **7**, and **19**) or starting materials (**8**) are given hereunder. Other reference compounds were available from previous studies [9, 17].

3-Benzoyl-2(3H)-benzoxazolone (**2**)

A solution of 1.35 g of 2(*3H*)-benzoxazolone (**1**, 10 mmol) and 2.49 g of benzoic anhydride (11 mmol) in 100 cm^3 of anhydrous CH_2Cl_2 was treated with 1 g of K10 montmorrillonite and refluxed for 4 h. After cooling, the mixture was diluted with 150 cm^3 of CH_2Cl_2, filtered over a bed of celite, washed with 5% Na_2CO_3 solution, H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to give a residue which was recrystallized from ethanol to give 1.98 g (83%) of analytically pure **2** (TLC, HPLC, mp 170–172°C, Ref. [17] 172–173°C). This material had IR, ^1H, and ^{13}C NMR spectroscopic data identical to those previously reported by *Ucar* [17] and *Cotelle* [22].

6-Benzoyl-2(3H)-benzoxazolone (**3**)

A dispersion of 2.39 g of **2** (10 mmol) in 25 g of *PPA* was irradiated at 300 W power in a regular kitchen microwave oven at times 0, 1.5, 3, 6, 9, 12, and 15 min for 30 sec. The dark mixture was allowed to stand aside for 1 h and was quenched with 500 cm^3 of ice/H_2O. The resulting precipitate was stirred for 1 h, filtered off, washed with distilled water, dried, and recrystallized from ethanol to give 2.06 g (86%) of analytically pure **3** (TLC, HPLC, mp 168–170°C, Ref. [17] 169–170°C). This material had IR, ^1H, and ^{13}C NMR spectroscopic data identical to those previously reported by *Ucar* [17].

3-Benzyl-2(3H)-benzoxazolone (**8**)

A solution of 13.50 g of **1** (100 mmol) in 250 cm^3 of *n*-butanol containing 10 g of *PEG 600* and 100 cm^3 of 10% NaOH solution was stirred mechanically at room temperature while 25.3 g of benzyl chloride (200 mmol) were added dropwise over 30 min. The emulsion was stirred vigorously for 24 h. The organic phase was then separated and the solvent was evaporated *in vacuo*. The resulting waxy residue was diluted in 250 cm^3 of ethyl acetate and washed copiously with H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to afford a solid which was recrystallized from anhydrous ethanol. After standing overnight in a refrigerator, 16.2 g of **8** (72%) were collected (mp 123–125°C, Ref. [23] 123–124°C). This material had IR, ^1H, and ^{13}C NMR spectroscopic data identical to those previously reported by *Ucar* [9].

General Method for the Preparation of Diarylketones

In a 100 cm^3 side-arm round-bottom flask, into 1.15 cm^3 of oxalyl chloride (13 mmol) were added in one portion to a solution of 10 mmol of the arene A and 6.60 g of $LiClO_4$ (62 mmol) in 50 cm^3 of CH_3NO_2 kept at 3–5°C using an ice bath. $AlCl_3$ (2.67 g, 20 mmol) was then added portionwise over 5 min. The reaction mixture was allowed to warm up to room temperature during which time progressive dissolution of the solid, darkening of the solution, and gas evolution was observed. The mixture was stirred at room temperature during the time reported for the chlorocarbonylation in Table 1. An equivalent of the arene B (10 mmol) along with an additional amount of $AlCl_3$ (2.67 g, 20 mmol) were then added portionwise. After 1 h at room temperature, the reaction mixture was heated for 12 h at 50–55°C, poured onto 500 cm^3 of ice/H_2O containing 25 cm^3 of concentrated HCl, and stirred for 1 h. The resulting precipitate was collected on a *Büchner* funnel, washed with H_2O, dried, and recrystallized from ethanol.

2,3-Dihydro-3-methyl-2-oxo-benzoxazole-6-carboxylic acid (**6**)

(a) *Chlorocarbonylation method.* To a mixture of 80 g of $AlCl_3$ (0.6 mol) and 13 cm^3 of *DMF*, heated and stirred mechanically at 85°C (oil bath), 9.0 g of 3-methyl-2(*3H*)-benzoxazolone (**4**, 60 mmol) were added in one portion. After a homogenous paste was obtained, 6.6 g of $LiClO_4$ (62 mmol) were added in one portion and 8.0 cm^3 of oxalyl chloride (90 mmol) were added dropwise over 30 min. The dark red mixture was stirred for another 6 h at 85°C and poured, while hot, onto 1 kg of ice containing 50 cm^3 of concentrated HCl. The resulting mixture was extracted three times with 250 cm^3 of ethyl acetate and the organic phase was then re-extracted with 3×50 cm^3 of 5% NaOH solution. Acidification of the aqueous phase gave a precipitate, which was filtered, dried, and recrystallized from ethanol:water (80:20, *v/v*) to give 3.96 g (35%) of **7** (mp 270°C dec). This material was identical in all respects to that obtained by the haloform reaction (*cf.* (b)).

(b) *Haloform reaction.* To a solution of 20 g of NaOH (500 mmol) in 100 cm^3 of H_2O at room temperature 9.65 g of 6-acetyl-3-methyl-2(*3H*)-benzoxazolone (**7**, 50 mmol) were added. The resulting solution was treated with 400 cm^3 of 12% NaClO solution and heated at 95°C for 1 h. The reaction mixture was acidified to $pH = 1$ with concentrated HCl and the resulting precipitate was collected on a filter, washed with distilled H_2O, dried, and recrystallized from ethanol:water (80:20, *v/v*). Yield: 67%; mp 270°C dec; IR (KBr): $\bar{\nu} = 3100$–2400 (OH), 2950 (aliph. C–H), 1780 (het. C=O), 1680 (carboxylic acid C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 13.00$ (s, COOH), 7.88 (d, $J_o = 7.89$ Hz, $J_m = 1.50$ Hz, 1H, H_5), 7.78 (d, $J_o = 7.89$ Hz, H_7), 7.35 (d, $J_m = 1.50$ Hz, H_4), 3.37 (s, N–CH_3) ppm.

5-Benzoyl-1,3-dihydro-2H-indol-2-one (**19**)

To a mixture of 53.3 g of $AlCl_3$ (0.4 mol) and 8.6 cm^3 of *DMF* (115 mmol), heated and stirred mechanically at 50°C (oil bath), 5.34 g of 2-indolinone (**14**, 40 mmol) were added in one portion. After a homogenous paste was obtained, 7.0 cm^3 of benzoyl chloride (60 mmol) were added dropwise over 30 min. When the addition was completed, the dark red mixture was stirred for another 3.5 h at 85°C and poured, while hot, onto 1 kg of ice containing 50 cm^3 of concentrated HCl. The resulting precipitate was stirred for 2 h, filtered, washed copiously with distilled H_2O, dried, and recrystallized from methanol to give 4.48 g (47%) of **19** (mp 205–206°C, Ref. [25] 204–205°C). IR (KBr): $\bar{\nu} = 3308$ (NH), 3062 (arom. CH), 2916 (aliph. CH), 1705 (ketone C=O), 1641 (het. C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 9.10$ (s, NH), 7.70 (m, H_4, H_7, $H_{1'}$, $H_{5'}$), 7.50 (m, $H_{3'}$), 6.90 (dd, $J_{6-7} = 8.0$ Hz, $J_{6-4} = 0.9$ Hz, H_6), 3.55 (s, CH_2) ppm.

6,6′-Carbonyl bis[3-benzyl-2(3H)-benzoxazolone] (**9**)

IR (KBr) $\bar{\nu} = 3010$ (arom. CH), 2940 (aliph. CH), 1670 (het. C=O), 1640 (ketone C=O) cm^{-1}; ^{13}C NMR (*DMSO*-d_6): $\delta = 193.20$ (ketone C=O), 154.52 (het. C=O), 143.28, 134.60, 131.25, 126.96, 110.62, 109.39 (het. arom. C), 142.71 (ipso), 134.75, 130.90, 127.65, 110.05 (benz. arom. C), 46.10 (CH_2) ppm.

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