$AlCl_3$-DMF REAGENT IN THE FRIEDEL-CRAFTS REACTION. APPLICATION TO THE SYNTHESIS OF SYMMETRICAL BENZOPHENONE DERIVATIVES

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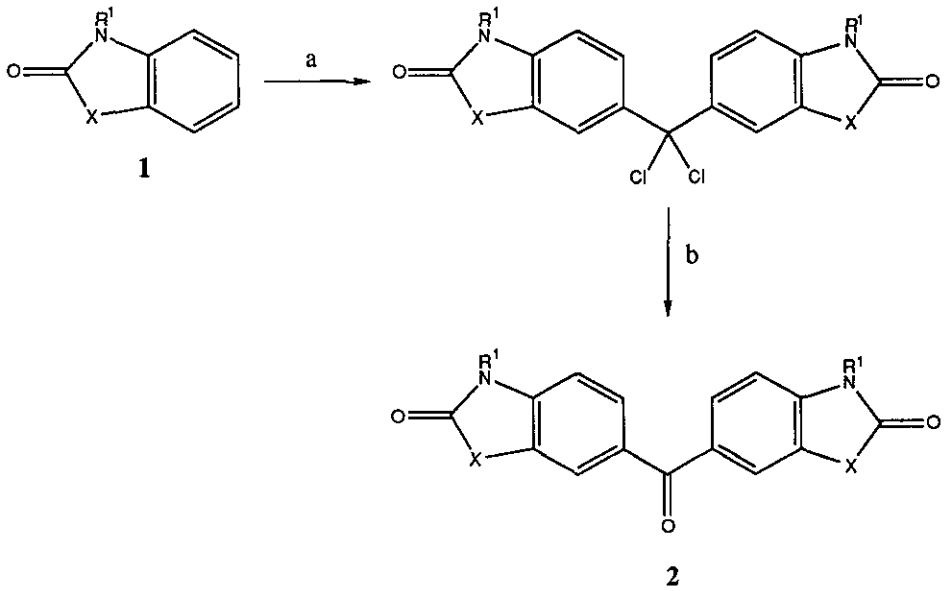
Abstract- Synthesis of series of symmetrical benzophenone derivatives by *C*-alkylation reaction of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone with carbon tetrachloride in presence of $AlCl_3$-DMF reagent is reported.

Recently, we reported on the use of the aluminium chloride-*N*,*N*-dimethylformamide ($AlCl_3$-DMF) reagent in the Friedel-Crafts (FC) *C*-acylation reaction of 2(3*H*)-benzoxazolones and 2(3*H*)-benzothiazolones.[1-3] These heterocycles are highly basic substrates toward a Lewis acid such as $AlCl_3$; they are therefore extensively complexed and become consequently extremely desactivated in this electrophilic aromatic substitution process[4] such as the FC reaction. Use of $AlCl_3$-DMF allows to circumvent this problem.[3] These acylation reactions were found to proceed with high regioselectivity. The precise position of acylation was unequivocally assigned by X-ray single-crystal diffraction in the case of 6-benzoyl-2(3*H*)-benzoxazolone and 6-benzoyl-2(3*H*)-benzothiazolone.[5,6] The assignment of the position of acylation was extended to other terms by use of high-field ^{1}H-NMR.[3] Use of $AlCl_3$-DMF was also applied successfully to the Haworth reaction of 2(3*H*)-benzothiazolones[2] and to the synthesis of various serotonine receptor ligands.[7,8]

The corresponding alkylation reaction does not proceed satisfactorily, as multiple alkylation products are obtained. In this paper, we present the first successfull reaction of FC *C*-alkylation in which a single compounds was obtained. The case reported here is that of the synthesis of symmetrical benzophenones.



1

2

Figure. 1. Synthesis of symmetrical benzophenones. R^1 = H, CH_3, CH_2-C_6H_5, or CH_2-4-fluoro-C_6H_4. X = O, S. Methods: a. CCl_4, $AlCl_3$-DMF; b. H_2O quenching.

Benzophenone can be synthesized by *C*-alkylation reaction of benzene by carbon tetrachloride in presence of $AlCl_3$[10,11] to generate the intermediate dichlorodiphenylmethane, which is not isolated but hydrolyzed directly to benzophenone upon quenching with water. This reaction gives 80-89 % yield. For the reasons exposed above, this technique can not be directly applied to 2(3*H*)-benzoxazolones and 2(3*H*)-benzothiazolones (Figure 1). In the case of a highly activated substrate such as anisole, its conversion to 4,4'-dimethoxybenzophenone proceeded in our hands in 25 % yield using the $AlCl_3$-DMF reagent, while under the conditions described in the Organic Syntheses,[12] only trace amount of the same material could be detected by TLC. The major part of the isolated material consisted of phenolic material due to extensive *O*-demethylation. Use of the $AlCl_3$-DMF reagents allows therefore the preparation of the symmetrical benzophenones (*cfr* Figure 1). This is, to our knowledge, the first example of regioselective *C*-alkylation of 2(3*H*)-benzoxazolones and 2(3*H*)-benzothiazolones derivatives. Results are reported in Table 1. We obtained symmetrical benzophenones derivatives with good yields and high purities after one crystallization. Conversely, treatment of either 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone with *t*-butanol for example in presence of an acid under various reaction conditions, in PPA for example, invariably yields a mixture of several *C*-alkylated species.

Table 1. Compounds 2

	X	R^1	mp (°C)	yield (%)	cryst. solv
a	O	H	390	75	DMF
b	O	CH_3	304-305	80	DMF
c	O	$CH_2C_6H_5$	209	82	C_2H_5OH
d	O	CH_2-4-fluoro-C_6H_4	218	78	C_2H_5OH
e	S	H	320*	79	C_2H_5OH
f	S	CH_3	263*	83	DMF
g	S	$CH_2C_6H_5$	230*	84	C_2H_5OH
h	S	CH_2-4-fluoro-C_6H_4	235*	82	C_2H_5OH

* Decomposition

EXPERIMENTAL

Melting points were determined using an Electrothermal melting point apparatus; they are uncorrected. The IR spectra were recorded on a Perkin-Elmer 457 spectrophotometer using KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Brucker AC 300 spectrometer with TMS as internal standard and the chemical shifts are reported in the delta scale in parts per million (δ, ppm). All compounds were found homogeneous in TLC (Merck silicagel 60F254, dicloromethane / acetone, 90/10, v/v). Carbon tetrachloride and $AlCl_3$ were purchased from Merck.

3-Methyl-2(*3H*)-benzoxazolinone and 3-methyl-2(*3H*)-benzothiazolinone were reported previously.[1]

The following examples are representative of the series published here.

General procedure for the synthesis of 3-alkylbenzoxazolin-2-one and 3-alkylbenzothiazolin-2-one

Under mechanical stirring, to a solution of 2(*3H*)-benzoxazolone (2.7 g, 20 mmol) or 2(*3H*)-benzothiazolone (3.02 g, 20 mmol) in dropwise anhydrous DMF (17.2 mL, 230 mmol) was added

anhydrous K_2CO_3 (11 g, 80 mmol) and alkyl halide (24 mmol). The reaction mixture was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto ice-water (200 mL), and the resulting precipate was filtered, washed with water, dried, and recristallized from ethanol.

3-Benzylbenzoxazolin-2-one (1, X = O, R^1 = CH_2-C_6H_5).

yield 88 %. mp 123-124°C; IR (KBr): 2940-2800 cm^{-1} (C-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O); ^{13}C-NMR ($CDCl_3$, δ ppm): 154.77 (C=O lactam), 142.74, 134.75, 130.90, 127.66, 110.03, 108.92 (arom. benzoxazolone), 128.97, 128.28, 123.81, 122.54 (arom. benzyl), 46.11 (CH_2). Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.87 ; H, 5.18 ; N, 6.49.

3-(4-Fluorobenzyl)benzoxazolin-2-one (1, X = O, R^1 = CH_2-4-fluoro-C_6H_4).

yield 92 %. mp 130°C; IR (KBr): 2940-2800 cm^{-1} (C-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O); ^{13}C-NMR ($CDCl_3$, δ ppm): 154.69 (C=O lactam), 142.74, 130.71, 129.57, 129.48, 110.16, 108.76 (arom. benzoxazolone), 164.27, 160.98, 123.88, 122.68, 116.12, 115.82 (arom. benzyl), 45.41 (CH_2). Anal. Calcd for $C_{14}H_{11}NO_2F$: C, 69.13; H, 4.14; N, 5.76. Found: C, 69.21 ; H, 4.35 ; N, 5.97.

3-Benzylbenzothiazolin-2-one (1, X = S, R^1 = CH_2-C_6H_5).

yield 90 %. mp 88-89°C; IR (KBr): 2940-2800 cm^{-1} (C-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O); ^{13}C-NMR (DMSO-d_6, δ ppm): 170.03 (C=O lactam), 136.73, 134.92, 128.69, 126.15, 111.08, 110.72 (arom. benzothiazolone), 127.70, 126.93, 123.06, 122.40 (arom. benzyl), 45.89 (CH_2). Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 69.65 ; H, 4.74 ; N, 6.05 ; S, 13.12.

3-(4-Fluorobenzyl)benzothiazolin-2-one (1, X = S, R^1 = CH_2-4-fluoro-C_6H_4).

yield 91 %. mp 90-91°C; IR (KBr): 2940-2800 cm^{-1} (C-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O); ^{13}C-NMR ($CDCl_3$, δ ppm): 170.08 (C=O lactam), 136.56, 130.86, 128.87, 126.23, 123.17, 110.96 (arom. benzothiazolone), 163.79, 160.52, 123.21, 122.53, 115.77, 115.48 (arom. benzyl), 45.79 (CH_2). Anal. Calcd for $C_{14}H_{10}NOFS$: C, 64.85; H, 3.89; N, 5.40; S, 12.36. Found: C, 64.98 ; H, 3.92 ; N, 5.63; S, 12.08.

General procedure for the synthesis of symmetrical benzophenones derivatives

Under mechanical stirring, to a mixture of anhydrous aluminium chloride (53.3 g, 400 mmol) and 100 mL of dry carbon tetrachloride in an ice bath, was added dropwise a solution of 2(*3H*)-benzoxazolone [or 3-alkyl-2(*3H*)-benzoxazolone] (40 mmol) or 2(*3H*)-benzothiazolone [or 3-alkyl-2(*3H*)-benzothiazolone] (40 mmol) in anhydrous DMF (5 mL, 67 mmol). The reaction mixture was stirred at the room temperature

during 15 h, ice water (300 mL) was then added. The resulting precipate was stirred for 1 h, filtered, washed with water, dried and recrystallized from appropriate solvent.

Di-2(3*H*)-benzoxazoloneketone (2a, R^1 = H).

yield 75 %. mp 390°C ; IR (KBr) : 3160 cm^{-1} (N-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O) ; ^{13}C-NMR (DMSO-d_6, δ ppm): 193.21 (C=O ketone), 154.59 (C=O lactam), 143.31, 134.66, 131.38, 127.12, 110.69, 109.51 (arom.). Anal. Calcd for $C_{15}H_8N_2O_5$: C, 60.82; H, 2.72; N, 9.46. Found: C, 60.52; H, 2.77 ; N, 9.67 .

Di-3-methyl-2(3*H*)-benzoxazoloneketone (2b, R^1 = CH_3).

yield 80 %. mp 304-305°C; IR (KBr) : 2940-2800 cm^{-1} (C-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O); ^{13}C-NMR (DMSO-d_6, δ ppm) : 193.17 (C=O ketone), 154.46 (C=O lactam), 143.26, 134.61, 131.22, 126.98, 110.56, 109.41 (arom.), 28.24 (CH_3). Anal. Calcd for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 62.96 ; H, 3.78 ; N, 8.76 .

Di-2(3*H*)-benzothiazoloneketone (2e, R^1 = H).

yield 79 %. mp 320°C; IR (KBr) : 3160 cm^{-1} (N-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O) ; ^{13}C-NMR (DMSO-d_6, δ ppm) : 193.03 (C=O ketone), 170.67 (C=O lactam), 140.24, 131.84, 128.95, 124.91, 123.88, 111.31 (arom.). Anal. Calcd for $C_{15}H_8N_2O_3S_2$: C, 54.87; H, 2.46; N, 8.53 ; S, 19.53. Found: C, 54.68 ; H, 2.41 ; N, 8.29 ; S, 18.44.

Di-3-methyl-2(3*H*)-benzothiazoloneketone (2f, R^1 = CH_3).

yield 83 %. mp 263°C; IR (KBr) : 2940-2800 cm^{-1} (C-H), 1670 cm^{-1} (C=O lactam), 1640 cm^{-1} (C=O); ^{13}C-NMR (DMSO-d_6, δ ppm) : 193.18 (C=O ketone), 170.72 (C=O lactam), 140.33, 131.90, 129.02, 124.98, 123.91, 111.40 (arom.), 29.07 (CH_3). Anal. Calcd for $C_{17}H_{12}N_2O_3S_2$: C, 57.29; H, 3.39; N, 7.86 ; S, 17.99. Found: C, 57.30 ; H, 3.42 ; N, 8.12 ; S, 17.75.

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