$AlCl_3$–DMF Reagent in the Friedel–Crafts Reaction. Application to the Acylation Reaction of 2(3*H*)-Benzothiazolones

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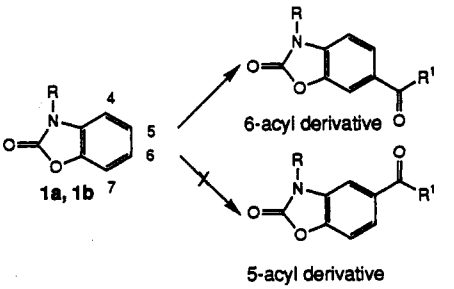
Introduction

Recently,[1,2] we reported on the use of the aluminum chloride–*N*,*N*-dimethylformamide ($AlCl_3$–DMF) reagent in the Friedel–Crafts C-acylation reaction of 2(3*H*)-benzoxazolones (Scheme 1, **1a**, **1b**). This process was found to proceed with high regioselectivity and was applied to the Haworth reaction performed on 2(3*H*)-benzoxazolones.[3] The precise position of acylation was unequivocally assessed in the case of 6-benzoyl-2(3*H*)-benzoxazolone by X-ray single-crystal diffraction[4] and by ^{1}H-NMR spectroscopy for the whole series. The 6-acyl derivative was the only product which could be isolated from the reaction medium; no evidence (HPLC, ^{1}H-NMR spectroscopy) could be found for the concomitant formation of the 5-acyl derivative.[5] The 5-acyl derivatives were synthesized by an alternative route.[6]

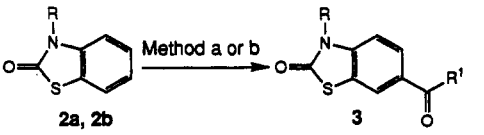
Since the pioneering discovery of the hypnotic properties of 2-benzoxazolinone, the 2(3*H*)-benzoxazolone ring has become an important building block in medicinal chemistry and has led to the discovery of a number of derivatives endowed with antiepileptic, antipyretic, analgesic, antispamodic, antitubercular, antibacterial, antimicrobial, and antifungal effects.[1] It is noteworthy that the 2(3*H*)-benzoxazolone ring can be considered as a cyclic analogue of pyrocatechol.[5]

6-Acyl-2(3*H*)-benzoxazolones have particularly interesting analgetic properties and constitute valuable starting materials for further medicinal developments. Therefore, it was deemed worthwhile to prepare the corresponding sulfur analogues. It should be stressed that the literature provides only limited information as to the existence of acyl-2(3*H*)-benzothiazolones. The patent literature mentions a few synthetic intermediates only scarcely described on the point of view of their spectroscopic and physicochemical properties and used in the preparation of other more elaborate heterocyclic systems.[7-9] These intermediates were thought to be substituted in the 5-position. In this connection, we planned, therefore, to extend our previous observations on the acylation chemistry of 2(3*H*)-benzoxazolones to the Friedel–Crafts acylation reaction of 2(3*H*)-benzothiazolones using the $AlCl_3$–DMF reagent (Scheme 2, **2a**, **2b**).

Scheme 1



Scheme 2



Results and Discussion

This reaction readily takes place at 75–85 °C for aliphatic acid chlorides and at 90–100 °C for aromatic acid chlorides. In all cases, only the 6-acyl derivative was formed as evidenced by high-field (400-MHz) ^{1}H-NMR spectroscopy. Yields of analytically pure material were in the range of 55–75% (Table 1). Evidence for the position of acylation was gained from ^{1}H-NMR spectroscopy observations (including NOE transfer experiments) and, in the case of 6-benzoyl-2(3*H*)-benzothiazolone, by X-ray single-crystal diffraction.[10] It should be noted that this conclusion is contrary to that reached by Japanese authors in three recent European patents[7-9] (*vide supra*).

It had been shown previously that 6-acylation of 2(3*H*)-benzoxazolone could be effected using carboxylic acids or anhydrides and polyphosphoric acid (PPA). The behavior of 2(3*H*)-benzothiazolones in this reaction appears to be parallel to that of 2(3*H*)-benzoxazolones and, along this line, the PPA method (Scheme 2, method B), while providing good yields for aliphatic and aromatic acids, proved not to be general and could not be employed efficiently in the case of dicarboxylic acids or carboxylic acids containing halogenoalkyl or heterocyclic moieties. In these instances, again, use of the $AlCl_3$–DMF reagent and acid chlorides or anhydrides permits ready access to the 6-acyl derivatives.

In the very same way as for the Friedel–Crafts acylation of 2(3*H*)-benzoxazolones, the $AlCl_3$–DMF/2(3*H*)-benzothiazolone ratio was found to be critical: the acylation in the present case was found to proceed with a satisfactory rate and yield the product only when this ratio was in the range of 7–11. This point is reminiscent of the keen observation made by Shen *et al.*[11] who recently drew

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(1) Aichaoui, H.; Poupaert, J. H.; Lesieur, D.; Hénichart, J.-P. *Tetrahedron* **1991**, *47*, 6649–6654.
(2) Aichaoui, H.; Poupaert, J. H.; Lesieur, D.; Hénichart, J.-P. *Bull. Soc. Chim. Belg.* **1992**, *101*, 1053–1060.
(3) Aichaoui, H.; Lesieur, D.; Hénichart, J.-P. *J. Heterocycl. Chem.* **1992**, *29*, 171–175.
(4) Mairesse, G.; Boivin, J. C.; Thomas, D. J.; Bermann, M. C.; Bonte, J. P.; Lesieur, D. *Acta Crystallogr.* **1991**, *47*, 882–884.
(5) Bonte, J. P.; Lesieur, D.; Lespagnol, C.; Plat, M.; Cazin, J. C.; Cazin, M. *Europ. J. Med. Chem.* **1974**, *9*, 491. Cf. also: Vaccher, M. P.; Lesieur, D.; Lespagnol, C.; Bonte, J. P.; Lamar, J. C.; Beaughard, M.; Dureng, G. *II Farmaco* **1986**, *41*, 257–269.
(6) Aichaoui, H.; Lesieur, I.; Henichart, J.-P. *Synthesis* **1990**, 679.
(7) Takaya, T.; Takasugi, H. *Eur. Pat.* 1984, 0-120-589 A1.
(8) Terali, T.; Shiokawa, Y.; Okumura, K.; Sato, Y. *Eur. Pat.* 1984, 0-122-494 A1.
(9) Ueda, N.; Tamigushi, I.; Katamura, Y. *Eur. Pat.* 1985, 0-132-817 A1.
(10) Mairesse, G.; Boivin, J. C.; Thomas, D. J.; Bermann, M. C.; Bonte, J. P.; Lesieur, D. *Acta Crystallogr.* **1991**, *47*, 882–884.
(11) Shen, Y.; Liu, H.; Chen, Y. *J. Org. Chem.* **1990**, *55*, 3961–3962.

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Table 1. Compounds 3

R	R1	mp (°C)	yield (%)	cryst solv
H	CH_3	189–191	60[a]	C_2H_5OH
CH_3	CH_3	145–146	62[a]	C_2H_5OH
H	$CH_2C_6H_5$	240 dec	65[a]	dioxane
CH_3	$CH_2C_6H_5$	164–166	66[a]	C_2H_5OH
H	$CH_2CH_2C_6H_5$	174–177	55[a]	C_2H_5OH
CH_3	$CH_2CH_2C_6H_5$	175–177	60[a]	C_2H_5OH
H	3-C_5H_4N	237–239	73[a]	C_2H_5OH
CH_3	3-C_5H_4N	176–178	76[a]	C_2H_5OH
H	CH_2CH_2COOH	241–242	55[a]	C_2H_5OH
CH_3	CH_2CH_2COOH	226–227	60[a]	C_2H_5OH
H	C_6H_5	216–217	80[b]	C_2H_5OH
CH_3	C_6H_5	147–148	82[b]	C_2H_5OH
H	4-Cl-C_6H_5	>270	75[b]	C_2H_5OH
CH_3	4-Cl-C_6H_5	>270	75[b]	C_2H_5OH
H	2,6-Cl-C_6H_5	>270	84[b]	CH_3OH
CH_3	4-OCH_3-C_6H_5	226–228	45[b]	C_2H_5OH
H	2-C_4H_3S	223–224	20[b]	C_2H_5OH
CH_3	2-C_4H_3S	223–225	20[b]	C_2H_5OH
H	C_2H_5	204–205	50[b]	n-C_3H_7OH
CH_3	C_2H_5	177–178	60[b]	C_2H_5OH
H	n-C_3H_7	143–145	50[b]	C_2H_5OH
CH_3	n-C_3H_7	115–116	57[b]	C_2H_5OH
H	n-C_4H_9	142–143	60[b]	C_2H_5OH
CH_3	n-C_4H_9	93–94	55[b]	C_2H_5OH

[a] Refers to method a (Scheme 2). [b] Refers to method b (Scheme 2).

attention to the fact that, when using $AlCl_3$, there are circumstances where the substrate is more extensively complexed than the electrophile-generating species. The case reported was that of nitrobenzene.[11] As the nitro group is a strongly electron-withdrawing substituent which decreases the basicity of the benzene ring, we believe the analysis of Shen *et al.* applies even more to electron-donating substituents possessing lone pairs available for complexation. The well-known difficulty to acylate acetanilide, under Friedel–Crafts reaction conditions using $AlCl_3$, addresses this point particularly well. To alleviate this problem, we have therefore proposed the use of the $AlCl_3$–DMF reagent where $AlCl_3$ is partially complexed by DMF and, consequently, complexes to a lesser extent the aromatic substrate. Under these conditions, there exists indeed a dynamic equilibrium between the complexed entities of the aromatic substrate and products formed, the electrophile-generating species, and DMF.

It should be noted that the observed regioselectivity in favor of the 6-position is consistent with energy estimates obtained by molecular mechanics (energy minimization and molecular dynamics) calculations performed in the particular case of the 5- and 6-benzoylarenium ions species which are supposed to be intermediates along the reaction coordinate of the 5- and 6-benzoyl-2(3*H*)-benzothiazolones. These calculations were based on Allinger's MMP2 force field.[13,14] The 6-benzoylarenium ion was indeed found to have a lower potential energy than its corresponding 5-congener ($\Delta\Delta E = 10.6 \pm 1.5$ kcal/mol) while both 5- and 6-benzothiazolones had very similar energy ($\Delta\Delta E < 0.2$ kcal/mol). These data are consistent with previous calculations performed by the same methods on 2(3*H*)-benzoxazolones;[3] they support the concept of a kinetic control of the reaction involving an acylium ion as reactive electrophilic species and are in accordance with the much higher activation of the 6- over the 5-position in the electrophilic acylation of the 2(3*H*)-benzothiazolone ring.

Conclusion

The reactivity of 2(3*H*)-benzothiazolones parallels that of 2(3*H*)-benzoxazolones in the Friedel–Crafts acylation. 2(3*H*)-Benzothiazolones react with acyl chlorides or anhydrides in the presence of a large excess (7–11 equiv) of the $AlCl_3$–DMF reagent to give 6-acyl-2(3*H*)-benzothiazolones with yields in the range of 55–75%. This method appears so far general. 2(3*H*)-Benzothiazolones also react with carboxylic acids or anhydrides in the presence of polyphosphoric acid to yield 6-acyl-2(3*H*)-benzothiazolones. This method, however, cannot be applied to dicarboxylic acids or carboxylic acids containing a halogenoalkyl or heterocyclic moiety.

Experimental Section

Melting points are uncorrected. The IR spectra were recorded using potassium bromide pellets. ^{1}H-NMR spectra were recorded in the δ scale with TMS as internal reference. All compounds gave satisfactory elemental analysis figures (C, H, N, S, figures within 0.4% of the calculated data, measured by the Central Analytical Services of the CNRS at Vernaison, France), IR and ^{1}H-NMR spectra (either 80 or 400 MHz); they were pure in TLC (Merck Silica gel 6OF254, cyclohexane/ethyl acetate (50/50, v/v)). The following examples are representative of the series.

4-Oxo-4-(3-methyl-2(3*H*)-benzothiazolon-6-yl)butyric Acid (3b, R^1 = C_2H_4COOH, Method A). To finely ground $AlCl_3$ (53.3 g, 0.4 mol) was added dropwise anhydrous DMF (8.6 mL, 0.115 mol) with stirring. To the mixture heated at 45 °C (oil bath) were added portionwise 3-methyl-2(3*H*)-benzothiazolone (**2b**, 40 mmol) and succinic anhydride (6.0 g, 60 mmol). The mixture was then heated at 95 °C for 5.5 h, poured into ice (1 kg), and stirred for 1 h. The resulting precipitate was filtered, washed with water, dried, and recrystallized from ethanol to give the title compound (yield: 60%): mp 226–227 °C; IR (KBr) 3300–3100, 1755, 1735, 1670, 1650 cm^{-1}; ^{1}H-NMR (acetone-d_6) 2.55 (tr, 2H), 3.25 (tr, 2H), 3.47 (s, 3H), 7.33 (d, 1H, J_{H4-H5} = 9 Hz), 8.00 (d, 1H, J_{H5-H7} = 2Hz), 8.32 (d of d, 1H, H-5), 12.0 (broad).

3-Methyl-6-nicotinoyl-2(3*H*)-benzothiazolone (3b, R^1 = C_5H_4N, Method A). To finely ground $AlCl_3$ (0.10 mol) was added dropwise anhydrous DMF (0.35 mol) with stirring. To the mixture heated at 45 °C (oil bath) were added portionwise **2b** (0.10 mol) and nicotinoyl chloride hydrochloride (0.11 mol). The reaction mixture was then heated at 90 °C for 30 h, poured onto ice, and stirred for 1 h. The resulting precipitate was filtered, washed with water, dried, and recrystallized from ethanol to give the title compound (yield 76%): mp 176–178 °C; IR (KBr) 1670, 1640 cm^{-1}; ^{1}H-NMR (DMSO-d_6, δ, ppm) 3.50 (s, 3H), 7.41 (d, 1H, J(ortho) 8.5 Hz), 7.60 (m, 1H), 7.80 (dd, 1H), 8.10 (complex m, 2H), 8.80 (m, 1H), 8.87 (d, 1H, J(a–d) = 1.8 Hz). Anal. ($C_{13}H_8N_2O_2S$) C, H, N.

6-Benzoyl-2(3*H*)-benzothiazolone (3a, R^1 = C_6H_5, Method B). Under mechanical stirring, to a solution of 2(3*H*)-benzothiazolone (**2a**, 40 mmol) in 150 mL of polyphosphoric acid was added portionwise benzoic acid (50 mmol), and the resulting solution was heated at 130 °C for 4 h. After cooling, the reaction mixture was poured onto ice–water (1.5 L), and the resulting precipitate was filtered, washed with water, dried, and recrystallized from ethanol to give **3a** (yield 80%): mp 216–217 °C; IR (KBr) 3220 1680, 1630 cm^{-1}; ^{1}H-NMR (DMSO-d_6, δ, ppm) 7.23 (d, 1H, J(ortho) 8.5 Hz), 7.60 (complex m, 6H), 8.00 (d, 1H, J(meta) 1.5 Hz), 12.17 (broad, 1H). Anal. ($C_{14}H_9NO_2S$) C, H, N.

Molecular Mechanics Calculations. Energy minimizations were initially carried out on studied compounds (5- and 6-benzoyl-2(3*H*)-benzothiazolones and the corresponding arenium ions) using Chem 3D Plus 3.0.1 (released in December 1990 by Cambridge Scientific Computing, Inc., Cambridge, MA). Chem 3D contains a new implementation of Allinger's MM2 force field.[13,14] To test the validity of the parameters used, the energy-

(12) Berliner, E. *Org. React.* **1949**, *V*, 229–289.
(13) Sprague, J. T.; Tai, J. C.; Yuh, Y.; Allinger, N. L. *J. Comput. Chem.* **1987**, *8*, 581.
(14) Buckert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, D.C., 1982.

minimized structure of 6-benzoyl-2(3*H*)-benzothiazolone was compared to that observed in the crystal[4] and was found to be nearly identical. To measure the global potential energy of the conformers population existing at the reaction temperature, molecular dynamics studies were conducted using a target temperature of 350 K along with an evolution time of 15 ps by dynamic steps of 2 fs. The heating/cooling rates was 3 kcal/atom/ps. After 5 ps allowed for thermal equilibration, potential energy figures were collected every 2 fsec, and about 5000 iterations were averaged to give the final value.

Supplementary Material Available: Data for compounds in Table 1 (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.