Monatshefte für Chemie 130, 1393–1397 (1999)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Friedel-Crafts Acylation of 2(3*H*)-Benzoxazolone: Investigation of the Role of the Catalyst and Microwave Activation

Messaoud Liacha[1], **Saïd Yous**[1], **Jacques H. Poupaert**[2], **Patrick Depreux**[1,*], and **Hocine Aichaoui**[1]

[1] Institut de Chimie Pharmaceutique Albert Lespagnol, F-59006 Lille, France
[2] Unité de Chimie Pharmaceutique, Ecole de Pharmacie, Faculté de Médecine, Université Catholique de Louvain, B-1200 Bruxelles, Belgium

Summary. To study the scope and limitations of the use of complexed species of $AlCl_3$ in *Friedel-Crafts* reactions, we investigated the acetylation and benzoylation of 2(3*H*)-benzoxazolone and 3-methyl-2(3*H*)-benzoxazolone varying the amide complexing agent. We replaced dimethylformamide by *N*-methylformamide, dimethylacetamide, pyrrolidone, *N*-methylpyrrolidone, tetramethylurea, and dimethylsulfoxide. However, there was no particular advantage of substituting dimethylformamide by another amide ligand. This can probably be ascribed to the fact that the complex formed between $AlCl_3$ and the complexing agent becomes too stable. Alternatively, a route using polyphosphoric acid and microwave activation was explored. The major advantage of running the reaction in a microwave oven was that a good yield was reached in a rather short period of time.

Keywords. 2(3*H*)-Benzoxazolone; *Friedel-Crafts* reaction; $AlCl_3$-*DMF* complex; Microwave irradiation.

***Friedel-Crafts*-Acylierung von 2(3*H*)-Benzoxazolon: Untersuchungen zur Rolle des Katalysators und zur Aktivierung durch Mikrowellen**

Zusammenfassung. Im Zuge der Untersuchung komplexierter Spezies von $AlCl_3$ im Rahmen von *Friedel-Crafts*-Reaktionen wurde die Acetylierung und Benzoylierung von 2(3*H*)-Benzoxazolon und 1-Methyl-2(3*H*)-benzoxazolon unter Variation des komplexierenden Amidagens untersucht. Es wurde dabei Dimethylformamid durch N-Methylformamid, Dimethylacetamid, Pyrrolidon, N-Methylpyrrolidon, Tetramethylharnstoff oder Dimethylsulfoxid ersetzt; es konnten jedoch keine Vorteile gegenüber Dimethylformamid beobachtet werden. Dieses Resultat beruht vermutlich darauf, daß der Komplex zwischen $AlCl_3$ und diesen Amiden zu stabil ist. Darüber hinaus wurde auch die Möglichkeit, Polyphosphorsäure und Mikrowellenaktivierung einzusetzen, untersucht. Der besondere Vorteil liegt hiebei in den guten Ausbeuten, die bei relativ kurzen Reaktionszeiten erzielt werden können.

* Corresponding author

Introduction

In a series of recent papers, we have reported on the $AlCl_3$-*DMF* complex as a useful catalyst in the *Friedel-Crafts* (*FC*) reaction [1–4]. This catalyst displays a rather unique behaviour in the acylation of electron-rich compounds which are quite basic substrates. Using classical *Lewis* acid catalysts ($AlCl_3$, BF_3, $ZnCl_2$, $TiCl_4$, *etc.*), these substrates are strongly complexed; they become therefore heavily deactivated in electrophilic substitution reactions such as the *FC* reaction, and yields are low. When $AlCl_3$-*DMF* is used as a catalyst, acylation products are obtained in good yields. The use of the $AlCl_3$-*DMF* catalyst has been exemplified in several publications concerning the acylation of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone using activated forms of carboxylic acids (acid halides or anhydrides) [5–12].

The initial paper of the series [1] was seminal in that several other groups were prompted to investigate the same or similar *Lewis* acid-base complexes such as $AlCl_3$-*DMSO*, $AlCl_3$-dimethylsulfone, or $AlCl_3$-nitromethane [13–15]. The $FeCl_3$-graphite complex can be regarded as another example of a *Lewis* salt used as *FC* catalyst [16].

An alternative route employs polyphosphoric acid (*PPA*) as catalyst [17]. In all cases, regioselectivity for position 6 of the heterocycle was observed. However, in the case of ω-halogenoacids or dicarboxylic acids, *PPA* was not found as satisfactory as the $AlCl_3$-*DMF* complex, since either the expected acylation product was not formed or low yields were obtained. The problem of ω-halogenoacids has been addressed in a previous paper [3]. In an effort to further study the scope and limitations of the use of complexed species of $AlCl_3$ in the *Friedel-Crafts* reaction, we investigated the acetylation and benzoylation of 2(3*H*)-benzoxazolone (**1**) and 3-methyl-2(3*H*)-benzoxazolone (**2**) as pilot reactions varying the amide complexing agent (Fig. 1). In a second part, we also briefly report on the use of *PPA* taking advantage of the well-known potentialities offered nowadays by the use of microwave ovens. Microwave irradiation has been shown to be a very useful alternative to conventional heating for chemical reactions [18].

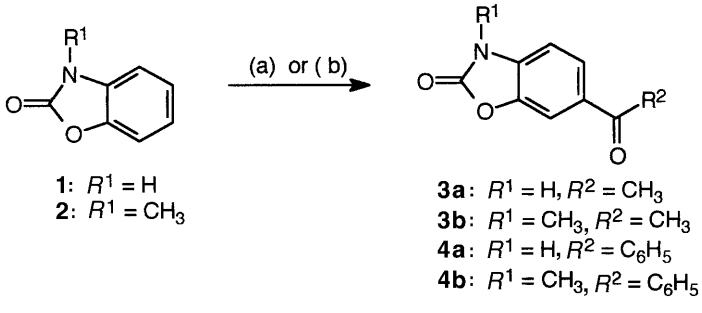

Fig. 1. Regioselectivity in the *FC* acylation of 2(3*H*)-benzoxazolone (**1**, $R^1 = H$) and 3-methyl-2(3*H*)-benzoxazolone (**2**, $R^1 = CH_3$); $R^2 = CH_3$ or C_6H_5; methods: (a) R^2COCl, $AlCl_3$-*X* (*X* = complexing agent), 85°C; (b) R^2COOH, *PPA*, 80–125°C

Results and Discussion

As already mentioned above, the major problem in the *FC* acylation of electron-rich aromatic compounds and in the particular case of **1** is the complexation of the substrates by *Lewis* acids. The substrates become therefore highly deactivated. This problem can be alleviated to some extent using $AlCl_3$-*DMF* as a catalyst [9]. In an effort to further substantiate the effect of the complexing agent on $AlCl_3$ we replaced dimethylformamide (*DMF*) by *N*-methylformamide (*NMF*), dimethylacetamide (*DMA*), pyrrolidone (*PYR*), and *N*-methylpyrrolidone (*MPY*). The ratios *DMF*/substrate and $AlCl_3$/substrate were kept constant at 3.5 and 10, which are the optimal values found empirically and documented in previous publications [1, 2, 5].

As can be judged from Table 1, no particular advantage arises from substituting *DMF* by another amide ligand, and in the case of compounds endowed with higher basicity, *e.g.*, tetramethylurea (*TMU*), *DMSO*, or sulfolan the yield of benzoylation of **1** (4 h at 85°C) was found to be rather low (10–15%). This can probably be ascribed to the fact that the complex formed between $AlCl_3$ and the complexing agent becomes too stable.

To evaluate if there was indeed a correlation between this trend in the yields and the basicity of the various complexing partners of $AlCl_3$, we performed quantum chemical calculations using the AM1 method (Table 2) [19].

Table 1. Variation of solvent in the *Friedel-Crafts* reaction of **1** and **2** resulting in **3a**, **3b**, **4a**, and **4b**

	3a		**3b**		**4a**		**4b**	
Solvent	Yield (%)	Reaction time (h)	Yield (%)	Reaction time (h)	Yield (%)	Reaction time (h)	Yield (%)	Reaction time (h)
DMF	68	3.5	70	2.5	66	4	75	4.5
NMF	60	5	65	3.5	61	4.5	63	5
DMA	65	4.5	68	3	60	5	62	5
PYR	65	4.5	68	3	58	5.5	60	5.5
MPY	52	4.5	61	2.5	51	5.5	62	5

Table 2. Electron densities of the solvents used acording to AM1 calculations

	Electron Density at	
Solvent	Oxygen	Nitrogen
Dimethylformamide	−0.373	−0.358
N-Methylformamide	−0.376	−0.402
Dimethylacetamide	−0.371	−0.352
Pyrrolidinone	−0.359	−0.396
N-Methylpyrrolidinone	−0.356	−0.354
Dimethylsulfoxide	−0.875	–
Tetramethylurea	−0.417	−0.364

The electron density at the oxygen atom was found to be rather constant for all amide complexing agents (*ca.* −0.36). However, as expected, the electron density at the oxygen atom is significantly higher for *TMU* (−0.417) and *DMSO* (−0.875), thus reflecting higher basicity and, consequently, higher complex stability. As the sign of the electron density at the nitrogen atom was found to be negative it can be inferred that this atom is also involved in complexation, which is in agreement with the empirical finding that the ratio $AlCl_3$/*DMF* had to be higher than one to induce catalytic activity.

When using a *Brönsted* acid, the protic acid chosen must be sufficiently acidic to promote the formation of the acylium ion; it should not be too acidic, however, so as to only slightly protonate the substrate. An optimal choice in accordance with this balance appears to be *PPA* which offers the additional bonus of scavenging water either by clustering or hydrolysis of *PPA* itself.

The *FC* reaction of **1** with benzoic acid using *PPA* and thermal activation has been thoroughly studied. This reaction (120°C, 120 min) is generally performed employing a considerable excess of *PPA* (∼1200 g *PPA*/mol of carboxylic acid) which may represent a drawback when the reaction has to be run on a large scale. We therefore investigated the preparation of **4b** using 350 g of *PPA* (84% of P_20_5)/mol of the carboxylic acid. After several unsuccessful attempts, good conditions were found involving short microwave irradiation times at partial power values. The reaction performed in a microwave oven proceeds in good yield (65%) in 2.5 min (Table 1) and, as previously observed under classical thermal conditions, yields exclusively the 6-acyl derivative **4b**.

Experimental

A Normatron 112 microwave oven from Normalab was used for the microwave activation experiments. 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. ^{1}H NMR spectra were recorded using a AC 300 P Bruker spectrometer at ambient temperature with *TMS* as internal reference (δ scale). Elemental analyses were obtained from the *Service Central d' Analyses du C.N.R.S.* at Solaise Vernaison, France. All compounds reported here had IR, ^{1}H and ^{13}C NMR, and MS, data consistent with their structure. The experimental elemental analysis values 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 standard solvents, *i.e.* acetone/toluene/cyclohexane (5:2:3, v/v/v). HPLC conditions were as follows: C-18, methanol:water (75:25, v/v), 1.5 cm^3/min. All compounds were found to be homogenous under these conditions.

General procedure for the FC acylation of 2(3H)-benzoxazolone (**1**) *and 3-methyl-2(3H)-benzoxazolone* (**2**)

53.3 g (0.4 mol) of $AlCl_3$ were placed in a three neck round bottom flask (250 cm^3). The flask was then equipped with a reflux condenser with a $CaCl_2$ tube, a mechanical stirrer, and a pressure equilibrating dropping funnel. *DMF* or the complexing agent (0.115 mol) was added dropwise over 10 min. The flask was then placed in an oil bath thermostatized at 45°C, and the substrate (**1** or **2**; 0.04 mol) was added in portions over 5 min. Care was taken during this addition to ensure the

formation of an homogeneous paste. The acylating agent (acetyl chloride or benzoyl chloride, 0.06 mol) was then added dropwise over 10 min, and the temperature was subsequently raised to 85°C in the case of acetyl chloride and to 95°C in the case of benzoyl chloride. The reaction time is reported in Table 1. The products were isolated by addition of ice water (1 dm^3). The precipitate was stirred for 1 h, collected on a Büchner funnel, dried, and recrystallized from ethanol. The yields are reported in Table 1. The physical properties (m.p., IR, ^{1}H NMR) are in accordance with published data [9, 17].

Preparation of 3-methyl-6-benzoyl-2(3H)-benzoxazolone (**4b**) *using PPA and microwave activation*

In a 250 cm^3 round bottomed flask, 100 g of *PPA* were preheated at 65°C. Under mechanical stirring, an intimate mixture (mortar ground) of 12.2 g of benzoic acid (0.1 mol) and 14.9 g of **2** was added in portions over 5 min. When a homogenous paste was obtained, a magnetic stirring bar was placed in the flask that was transferred to the micro wave oven. Under magnetic stirring, the reaction medium was heated for 2.5 min at 25% of the maximum power (corresponding to 275 W) and allowed to stand for additional 20 min after which time it was diluted by 1 dm^3 of ice water. The resulting precipitate was filtered over a Büchner funnel, dried, and recrystallized from ethanol to yield 65% of the tittle compound.

References

[1] Aichaoui H, Poupaert JH, Lesieur D, Hénichart JP (1991) Tetrahedron **47**: 6649
[2] Aichaoui H, Poupaert JH, Lesieur D, Hénichart JP (1992) Bull Soc Chim Belg **101**: 1053
[3] Poupaert JH, Kanyonyo M, Ucar H, Mouithys AM, Diouf O, Lesieur D (1996) Bull Soc Chim Belg **105**: 397
[4] Ucar H, Van Derpoorten K, Kanyonyo M, Isa M, Lambert D, Lesieur D, Poupaert JH (1996) Bull Soc Chim Belg **105**: 773
[5] Yous S, Poupaert JH, Lesieur I, Depreux, P, Lesieur D (1994) J Org Chem **59**: 1574
[6] Taverne T, Depreux P, Lesieur D, Hénichart JP, Poupaert JH (1997) Bull Soc Chim Belg **106**: 791
[7] Mairesse G, Boivin JC, Thomas DG, Bermann MC, Bonte JP, Lesieur D (1984) Acta Crystallogr C **40**: 1019
[8] Mairesse G, Boivin JC, Thomas DG, Bermann MC, Bonte JP, Lesieur D (1991) Acta Crystallogr C **47**: 882
[9] Aichaoui H., Lesieur D, Hénichart JP (1992) J Heterocyclic Chem **29**: 171
[10] Diouf O, Depreux P, Lesieur D, Poupaert JH, Caignard DH (1995) Heterocycles **41**: 1219
[11] Diouf O, Depreux P, Lesieur D, Poupaert JH, Caignard DH (1995) Eur J Med Chem **30**: 715
[12] Kanyonyo RM, Ucar H, Isa M, Carato P, Lesieur D, Renard P (1996) Bull Soc Chim Belg **105**: 17
[13] Albar HA, Khalaf AA, Bahaffi SO (1997) J Chem Res (S) 20
[14] Mata EG, Suarez AG (1997) Synthetic Commun **27**: 1291
[15] Mercer FW, Fone MM, McKenzie MT (1997) J Polymer Sci **35**: 521
[16] Gondos G, Kapocsi I (1996) J Phys Chem Solid **57**: 855
[17] Bonte JP, Lesieur D, Lespagnol C, Plat M, Cazin JC, Cazin M (1974) Eur J Med Chem **9**: 491
[18] Fernandez-Paniagua UM, Illeseas B, Martin N, Seoane C (1997) J Org Chem **62**: 3705 and references cited therein
[19] Li Z, Schegara HA (1987) Proc Natl Acad Sci **84**: 6611

Received March 12, 1999. Accepted (revised) April 7, 1999