C-FORMYLATION OF SOME 2(3*H*)-BENZAZOLONES AND 2*H*-1,4-BENZOXAZIN-3(4*H*)-ONE

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Received July 23, 1996
Accepted November 1, 1996

The *C*-formylation of 1,3-dimethyl-2(3*H*)-benzimidazolone and 4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one was performed using 1,1-dichloromethyl methyl ether at the Friedel–Crafts reaction conditions. The formylation of 3-methyl-2(3*H*)-benzoxa- and -thiazolone at the 6-position was carried out by modified Duff's method with hexamethylenetetramine in trifluoroacetic acid.
Key words: Formylation; Benzoheterocycles.

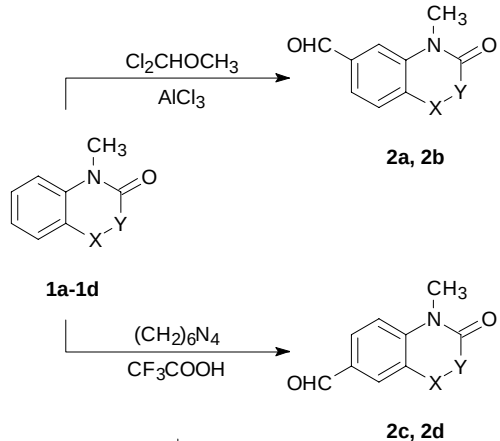
6-Acyl-2(3*H*)-benzoxa-, -thiazolones and 7-acyl-2*H*-1,4-benzoxazin-3(4*H*)-ones have particularly interesting CNS, analgesic and normolipemic activity[1,2]. While the acylation of 2(3*H*)-benzimidazolones and 2*H*-1,4-benzoxazine-3(4*H*)-ones is performed with routine Friedel–Crafts methods[3], the acylation of 2(3*H*)-benzoxa-, -thiazolones was found to be more difficult and occurs under irregular conditions[4,5]. This is the case of the *C*-formylation reaction of 3-methyl-2(3*H*)-benzoxazolone in polyphosphoric acid and hexamethylenetetramine in which certain problems arise related to the yields and purity of the resulting 6-formyl derivatives.

In the present communication we report our results from the development of improved alternative methods for the synthesis of *C*-formyl derivatives of 2(3*H*)-benzazolones and 2*H*-1,4-benzoxazin-3(4*H*)-one. The importance of the resulting compounds is related to their use as starting materials for the preparation of DOPA-analogs, and a series of compounds with expected analgesic, antipyretic and psychotropic activity[6].

The conversion of 1,3-dimethyl-2(3*H*)-benzimidazolone (**1a**) and 4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one (**1b**) to the corresponding 1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carbaldehyde (**2a**) or 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carbaldehyde (**2b**) was realized by a method using 1,1-dichloromethyl methyl ether in the presence of aluminium chloride (Scheme 1).

This method, however, was not successful for the formylation of 3-methyl-2(3*H*)-benzoxa-, -thiazolones **1c** and **1d**. The problem was successfully resolved by the application of a modification of the Duff's method, namely formylation with hexamethylene

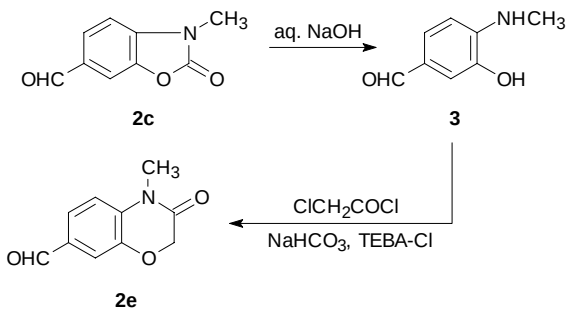
tetramine in trifluoroacetic acid (TFA) according to Scheme 1. The formylated derivatives **2c** and **2d** were obtained in good yields and sufficiently pure.



1, 2	X	Y
a	N-CH_3	bond
b	O	-CH_2-
c	O	bond
d	S	bond

SCHEME 1

The same method was applied to 4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one in order to investigate its effect on the yield of formylated material. The reaction gave both the 6- and 7-substituted isomers **2b** and **2e** in equal amounts. The latter was proved by comparison of its physical properties and spectral data with those of a pure sample synthesized *via* an independent route starting with the hydrolysis of 3-methyl-2-oxo-2,3-dihydrobenzoxazole-6-carbaldehyde (**2c**) yielding 3-hydroxy-4-methylaminobenzaldehyde (**3**). The closure to the oxazinone cycle was realized with chloroacetyl chloride in conditions of phase-transfer catalysis (Scheme 2).



SCHEME 2

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage microscope and are uncorrected. IR spectra (chloroform solutions) were recorded on a Specord 71 spectrometer. ^{1}H NMR spectra ($CDCl_3$ solutions; δ, ppm; *J*, Hz) were recorded on a Bruker AC 250 with tetramethylsilane as internal standard. TLC was performed on silica gel 60 F254 (Merck) plates with solvent system toluene–ethylacetate–chloroform (3 : 1 : 1).

1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carbaldehyde (**2a**)

To a suspension of $AlCl_3$ (3.33 g, 25 mmol) in dichloromethane (40 ml) was added nitromethane (2 ml) and a clear solution was obtained. 1,3-Dimethyl-2(3*H*)-benzimidazolone (**1a**; 1.63 g, 10 mmol) was added and the resulting solution is stirred and cooled with an ice bath. Dichloromethyl methyl ether (1.16 ml, 13 mmol) dissolved in dichloromethane (10 ml) was added dropwise during a 30 min period, and mixture was stirred at room temperature for an additional 1.5 h and then poured into an ice–water mixture (100 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with 3 M HCl and water, and extracted with 18% aqueous $NaHSO_3$ (15 ml). The aqueous layer was treated with 30% sodium hydroxide to destroy the bisulfite adduct and the formylated material precipitated from the solution. The solid material was separated with filtration, washed with water and dried. Yield 1.15 g (60%); m.p. 153–155 °C (50% ethanol), lit.[7] gives 151–151.5 °C. IR spectrum: 1 690, 1 715 cm^{-1} (CO). ^{1}H NMR spectrum: 3.48 s, 6 H; 7.09 d, 1 H, *J* = 8; 7.54 d, 1 H, *J* = 1.4; 7.66 dd, 1 H, *J* = 1.4 and *J* = 8; 9.96 s, 1 H.

4-Methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-6-carbaldehyde (**2b**)

This compound was synthesized by analogy of compound **2a** from the compound **1b**. Yield 40%; m.p. 144–146 °C (ethanol). IR spectrum: 1 690 cm^{-1} (CO). ^{1}H NMR spectrum: 3.43 s, 3 H; 4.73 s, 2 H; 7.12 d, 1 H, *J* = 8.3; 7.52–7.57 m, 2 H; 9.92 s, 1 H. For $C_{10}H_9NO_3$ (191.2) calculated: 62.82% C, 4.74% H, 7.33% N; found: 62.97% C, 4.68% H, 7.30% N.

3-Methyl-2-oxo-2,3-dihydrobenzoxazole-6-carbaldehyde (**2c**)

A mixture of 3-methyl-2(3*H*)-benzoxazolone (**1c**, 1.49 g, 10 mmol), hexamethylenetetramine (2.80 g, 20 mmol), and trifluoroacetic acid (15 ml) was heated at reflux for 20 h. The products were concentrated and combined with ice–water (60 ml). The resultant mixture was stirred for 30 min, made basic with sodium carbonate, and the solid separated was filtered, washed with water and dried. The formylated derivative was purified by the formation of the corresponding bisulfite adduct in full analogy with the synthesis of compound **2a**. Yield 1.2 g (68%); m.p. 145–146 °C (ethanol), lit.[4] 145–146 °C. IR spectrum: 1 700, 1 780 cm^{-1} (CO). ^{1}H NMR spectrum: 3.48 s, 3 H; 7.12 d, 1 H, *J* = 8.0; 7.72 d, 1 H, *J* = 1.3; 7.78 dd, 1 H, *J* = 1.3 and 8.0; 9.95 s, 1 H.

3-Methyl-2-oxo-2,3-dihydrobenzothiazole-6-carbaldehyde (**2d**)

This compound was synthesized by analogy of compound **2c** from the compound **1d**. Yield 76%; m.p. 130–131 °C (ethanol). IR spectrum: 1 690 cm^{-1} (CO). ^{1}H NMR spectrum: 3.52 s, 3 H; 7.19 d, 1 H, *J* = 8.0; 7.87 dd, 1 H, *J* = 1.5, *J* = 8.3; 7.98 d, 1 H, *J* = 1.5; 9.96 s, 1 H. For $C_9H_7NO_2S$ (193.3) calculated: 55.93% C, 3.65% H, 7.25% N; found: 56.21% C, 3.78% H, 7.03% N.

3-Hydroxy-4-methylaminobenzaldehyde (**3**)

A mixture of compound **2c** (1.77 g, 10 mmol) and a 10% aqueous NaOH (20 ml) was refluxed for 4 h. After cooling, the solution was acidified with concentrated hydrochloric acid. Aminophenol was liberated from its hydrochloride by slow addition of saturated sodium carbonate solution until a white precipitate formed. The precipitated product was isolated by suction and washed with water. M.p. 156–158 °C (water), lit.[8] 167–168 °C (water).

4-Methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-7-carbaldehyde (**2e**)

To a stirred solution of the 3-hydroxy-4-methylaminobenzaldehyde (**3**; 1.51 g, 10 mmol) and benzyltriethylammonium chloride (TEBA-Cl; 2.28 g, 10 mmol) in chloroform (25 ml) was added finely powdered sodium hydrogen carbonate (3.36 g, 40 mmol). The resultant mixture is cooled in an ice bath, then a solution of chloroacetyl chloride (1.36 g, 12 mmol) in chloroform (5 ml) was added dropwise. After the addition was completed, the mixture was stirred at 0–5 °C for 1 h, then heated at 55 °C for 8 h. The solvent was removed and water (40 ml) was added. The crude product was isolated by suction, washed with water, and recrystallized from ethanol. Yield 1.1 g (58%); m.p. 153–155 °C (ethanol). IR spectrum: 1 690 cm^{-1} (CO); ^1H NMR spectrum: 3.42 s, 3 H; 4.69 s, 2 H; 7.11 d, 1 H, J = 8.2; 7.50 d, 1 H, J = 1.8; 7.60 dd, 1 H, J = 1.8 and 8.2; 9.96 s, 1 H. For $C_{10}H_9NO_3$ (191.2) calculated: 62.82% C, 4.74% H, 7.33% N; found: 62.91% C, 4.77% H, 7.15% N.

We wish to thank our colleagues Dr V. Benin from Cornell University (Ithaca, New York) and Dr L. Nechev from Vanderbild University (Nashville, Tennessee) for NMR spectra.

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