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Triphosgene in Heterocyclic Chemistry: A Novel Synthesis of the Antiinflammatory Prodrug Droxicam

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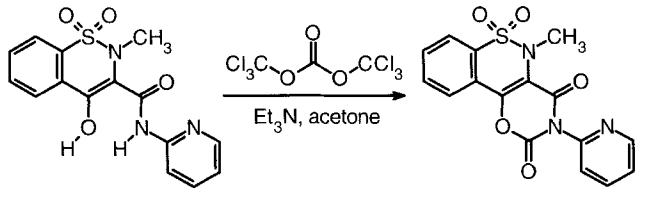
The oxicams (piroxicam (**1**), tenoxicam) are among the most widely used nonsteroidal antiinflammatory drugs. In order to overcome unwanted side effects like gastrointestinal damage, several prodrugs of oxicams have been developed by reversibly derivatizing the acidic enol groups of the drugs [1].

Droxicam (5-methyl-3-(2-pyridyl)-2H,5H-1,3-oxazino-[5,6-*c*][1,2]benzothiazine-2,4(3H)-dione-6,6-dioxide) (**2**) represents a prodrug of the well established drug piroxicam (**1**) containing an additional oxazinedione ring. After absorption, **2** is rapidly cleaved into the active metabolite **1** in the intestinal mucosa. The pharmacological profile of droxicam (**2**) is similar to that of piroxicam (**1**), but the prodrug shows greatly improved gastrointestinal tolerance [2]. Recently, however, undesired hepatotoxic effects of **2** were reported [3].

As described in patents [4], **2** can be prepared from **1** by cyclocondensation with either excess ethyl chloroformate in pyridine or with phosgene in dichloromethane. Since the reaction with phosgene gave only poor yield, we wish to report here an alternative synthesis of **2** from **1** using triphosgene (bis(trichloromethyl)carbonate) as carbonylating agent. Triphosgene has been established as an excellent substitute for phosgene in the last few years [5, 6]. It is an easy to handle, stable solid and can be used for chlorinations, carbonylations, and related reactions in almost *stoichiometric* amounts (1 equiv. of triphosgene formally releases 3 equiv. of phosgene). There are numerous examples of the construction of heterocyclic rings by carbonylation of bifunctional precursors with triphosgene [5, 6], but to the best of our knowledge this reagent has not yet been applied to the synthesis of 1,3-oxazine-2,4-diones from hydroxy-carboxamides [7].



1 **2**

Piroxicam (**1**) was dissolved in acetone/triethylamine and treated with 0.5 equiv. of triphosgene. Complete conversion to **2** was achieved within a few hours at room temperature (tlc control) and crude droxicam (**2**) was obtained in almost quantitative yield after aqueous work-up. Acetone proved to be the solvent of choice. Running the same reaction in THF gave significantly lower yield. Reaction of **1** with triphosgene in dioxane/water with potassium carbonate [8] as base gave only partial conversion to **2**. Recrystallization of the crude product from acetone gave analytically pure **2**, whose spectroscopic data (^{1}H NMR, ^{13}C NMR, MS) were in complete accordance with the values published in literature [2, 9].

In conclusion, we have demonstrated a new application of triphosgene in heterocyclic chemistry and used this method for a simple and effective synthesis of the prodrug droxicam (**2**).

Experimental

NMR (internal standard: TMS, δ in ppm): Bruker AM 400 (400 MHz). – MS: Finnigan MAT 8430 (70 eV). – IR: Pye-Unicam PU 9800 FT-IR-Spectrometer. – Elemental analyses: Carlo Erba CHNO-Elemental Analyzer 1106.

Droxicam (**2**)

A stirred mixture of piroxicam (**1**) (1.0 g, 3.0 mmol), triethylamine (0.76 g, 7.5 mmol) and acetone (10 ml) was treated dropwise with a solution of triphosgene (0.445 g, 1.5 mmol) in acetone (5 ml) and stirring was continued for 4 h at ambient temperature. The resulting suspension was treated with water (100 ml) and stirred at ambient temperature for 15 min. Then the precipitate was collected by filtration. Recrystallization from acetone gave analytically pure **2** (0.93 g, 86%) as pale yellow crystals, *m.p.* 252 °C (ref. [2]: *m.p.* 251–253 °C). – MS: *m/z* (%) = 357 (18) [M$^+$]; 237 (80); 173 (35); 168 (29); 117 (70); 104 (100); 76 (33). – IR (KBr): ν (cm^{-1}) 1785; 1708; 1426; 1407; 1352; 1272; 1182; 1161; 761. – ^{1}H NMR (DMSO-d$_6$): δ (ppm) 8.66 (dd, J = 2.0/5.0 Hz, 1 H); 8.18–

8.00 (m, 5 H); 7.67 (br. d, J = 8.0 Hz, 1 H); 7.60 (ddd, J = 7.7/ 5.0/ 1.0 Hz, 1 H); 3.10 (s, 3 H). – ^{13}C NMR (DMSO-d_6): δ (ppm) 158.0; 149.5; 148.5; 147.4; 145.9; 139.4; 134.1; 133.8; 133.7; 125.6; 125.1; 123.8; 123.7; 123.5; 117.1; 36.4.

$C_{16}H_{11}N_3O_5S$	Calcd.: C 53.78 H 3.10 N 11.76
(357.3)	Found: C 53.95 H 3.14 N 11.47.

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