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[a012]

Synthesis of novel benzoannelated eight-membered heterocycles: easy access to benzo[f][1,4]oxazocin-1-ones

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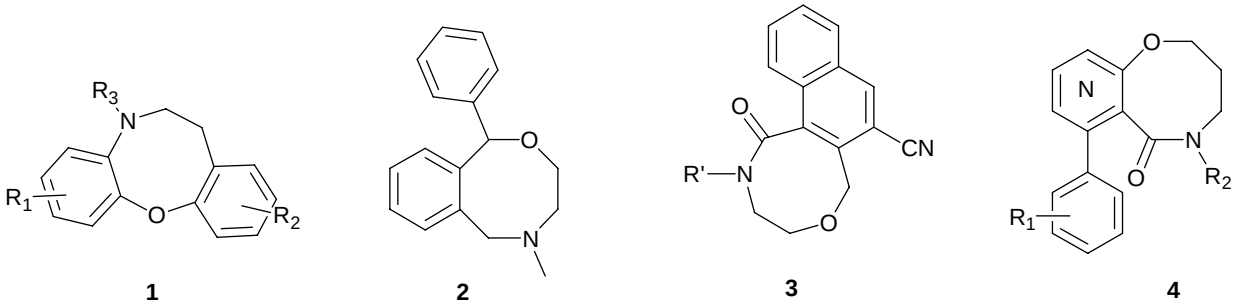
Abstract: Medium-sized N-heterocycles, in particular eight-membered azocines, are key structures occurring in many natural products and in some compounds having biological activities. We described here an easy access to benzo[f][1,4]oxazocin-1-ones starting from 2-acetylbenzoic acid.

Keywords: eight-membered N, O heterocycles, ethanolamines, $ZnCl_2$

Introduction

The abundance of medium rings incorporating oxygen or nitrogen atoms in medicinally interesting compounds[1] continues to ensure that they are important synthetic targets for organic chemists.[2]

For example, the benzoxazocine ring is often present in pharmaceutical agents as a core structural motif. Related heterocycles of the dibenzoxazocine ring **1** have significant anti-inflammatory properties;[3] the benzoxazocine Nefopam **2** is a non-narcotic analgesic.[4] Recently, Ohnmacht et al. have reported the activity of naphto-oxazocine **3** as NK1 antagonists[5] and Seto et al. have described the synthesis of pyrido- and pyrimido-oxazocinones **4** and their application as NK1 antagonists.[6] (Scheme 1)

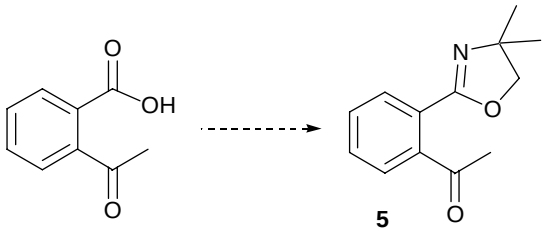


1 **2** **3** **4**

Scheme 1

Results and Discussion

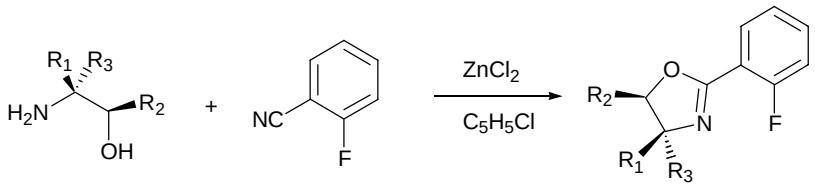
During a part of our research, we wanted to synthesize 1-[2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-ethanone **5** starting from 2-acetylbenzoic acid. (Scheme 2)



Scheme 2

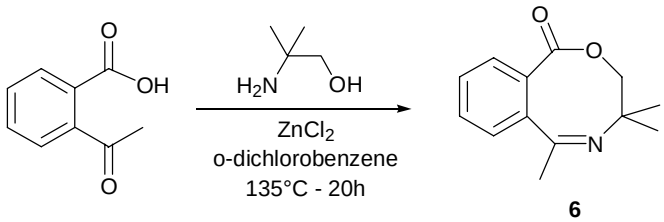
In a first attempt, we tried a very classical procedure[7] widely used for the synthesis of oxazoline rings: formation of acyl chloride, addition of 2-amino-2-methylpropanol and then cyclization with thionyl chloride. However, we never obtained the desired compound **5** but only degradation products which were not identifiable.

We next turned our attention to another method of formation of oxazolines. In 1996, Helmchen[8] described the one-pot reaction of an amino alcohol with 2-halobenzonitrile under catalysis with $ZnCl_2$ as an application of Witte[9] procedure. (Scheme 3)



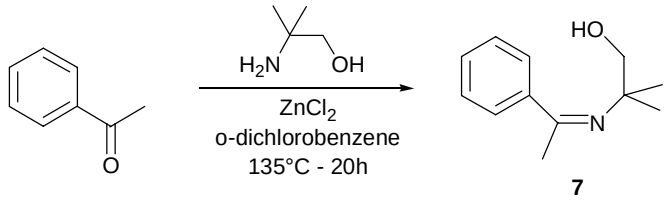
Scheme 3

So, 2-acetylbenzoic acid was treated with 2-amino-2-methylpropanol in o-dichlorobenzene at 135°C in presence of $ZnCl_2$ as catalyst and the reaction was followed by TLC. We observed the disappearance of the starting material and the formation of one compound we supposed to be **5**. However, after treatment and characterization, we supposed that product **6** has been formed during the reaction. (Scheme 4)



Scheme 4

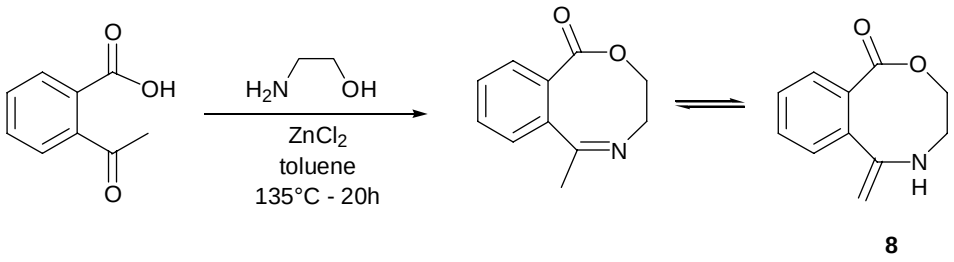
Indeed, the ^{13}C NMR spectrum did not show any carbonyl signal so that we supposed that both carboxylic acid and ketone have reacted. We have verified this reactivity by reacting acetophenone with 2-amino-2-methylpropanol under the same conditions: compound **7** was obtained quantitatively. (Scheme 5) We supposed that, in a first time, the imine's formation may happen and in second time, the lactonization may proceed. The proposed structure of compound **6** was confirmed by GCMS (IC) analysis.



Scheme 5

It should also be noted that the temperature is very important as the same reaction conducted at 120°C did not give any results and the starting materials were recovered. On another hand, toluene could be used as solvent when reaction is performed in sealed tube at 135°C (bath temperature). Toluene is a more convenient solvent as it is easier to remove than o-dichlorobenzene.

We have made the same reaction between 2-acetylbenzoic acid and 2-aminoethanol. This time, we obtained the compound **8** in the enamine form. (Scheme 6) Indeed, in the ^{1}H NMR spectrum, we did not observe any signal for CH_3 but two doublets (at 4.97 and 5.24 ppm) were present.



Scheme 6

In conclusion, when trying to synthesize oxazoline on 2-acetylbenzoic acid, we have observed an "unexpected" reactivity and we have isolated benzo[f][1,4]oxazocin-1-ones. We have reported here our first results concerning this easy access to eight-membered N,O heterocycles; extension of this work is currently under study and will be reported in due course.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on an AC Bruker 250 MHz spectrometer in $CDCl_3$.

To a mixture of dry toluene (5 mL), 2-acetylbenzoic acid (5 mmoles, 1 equiv.) was added the aminoalcohol (6.5 mmoles, 1.3 equiv.) and zinc chloride (10 mol%). The mixture was stirred at 135°C for 20h. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation. The obtained crude product was purified by column chromatography on silica gel or by recristallization.

4,4,6-trimethyl-3,4-dihydrobenzo[f][1,4]oxazocin-1-one 6

GCMS (EI): 202 (100), 187 (28) – GCMS (IC): 218 $[M+H]^+$
IR (KBr) 1699 cm-1 (C=O)
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.57 (s, 3H), 1.59 (s, 3H), 1.73 (s, 3H), 2.12 (sl, OH), 4.12 (d, 1H, J=8.75Hz), 4.28 (d, 1H, J=8.75Hz), 7.48-7.57 (m, 3H), 7.71-7.74 (m, 1H).

^{13}C NMR (250 MHz, $CDCl_3$): δ = 23.7 (CH_3), 24.4 (CH_3), 28 (CH_3), 59.6 (C), 83.4 (CH_2), 100.1 (C), 121.7 (CH), 124 (CH), 129.9 (CH), 132.7 (CH), 133.4 (C), 147.2 (C), 170.5 (C).

2-Methyl-2-(1-phenyl-ethylideneamino)-propan-1-ol 7

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.94 (s, 3H), 1.36 (s, 3H), 1.61 (s, 3H), 3.47 (d, 1H, J=8Hz), 3.67 (d, 1H, J=8Hz), 7.22-7.34 (m, 3H), 7.52 (m, 2H).

^{13}C NMR (250 MHz, $CDCl_3$): δ = 27.3, 28.7, 31.2, 60, 77.4, 97.6, 125.5, 127.1, 128.1, 146.4.

6-Methylene-3,4,5,6-tetrahydro-benzo[f][1,4]oxazocin-1-one 8

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.90-4.00 (m, 4H), 4.97 (d, 1H, J=2.5Hz), 5.24 (d, 1H, J=2.5Hz), 7.48-7.62 (m, 2H), 7.68 (d, 1H, J=7.5Hz), 7.81 (d, 1H, J=7.5Hz).

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