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SYNTHESIS OF DIALKYLAMINOCARBONYL *N*-CHLOROCARBONYL-*N*-PHENYL-4-AMINOBENZO-α-PYRONE DERIVATIVES

Radana M. Đuđić and Branka B. Rodić-Grabovac

The title compounds were prepared by condensation of N-chlorocarbonyl-N-phenyl-4-aminobenzo-α-pyrone with diethylamine, dibutylamine and isopropylamine. The starting compound used for condensation with amines was obtained by a reaction of N-phenyl-4-aminobenzo-α-pyrone with oxalyl chloride.

KEYWORDS: 4-aminobenzo-α-pyrone; dialkylaminocarbonyl derivatives

INTRODUCTION

It is well-known that many dialkylaminoalkylarylamides exhibit physiological activity towards central nervous system and many of them are used for therapeutic purposes. The known local anesthetics like butanilcaine, lidocaine and many others (1) belong to this type of compounds. The aim of this work was the synthesis of dialkylaminocarbonyl derivatives of *N*-phenyl-4-aminobenzo-α-pyrone. Since physiological activity of 4-hydroxybenzo-α-pyrone (2-4) and its derivatives (5-10) is well-known, we introduced dialkylaminocarbonyl group into the heteroaryl segment of benzo-α-pyrone system in order to obtain new potentially physiologically active compounds. Starting compound was *N*-chlorocarbonyl-*N*-phenyl-4-aminobenzo-α-pyrone which was obtained from *N*-phenyl-4-aminobenzo-α-pyrone with oxalyl chloride.

This paper describes the reaction of *N*-phenyl-4-aminobenzo-α-pyrone /**1**/ with oxalyl chloride and the condensation of thus obtained chlorocarbonyl derivative with three different amines (Scheme 1).

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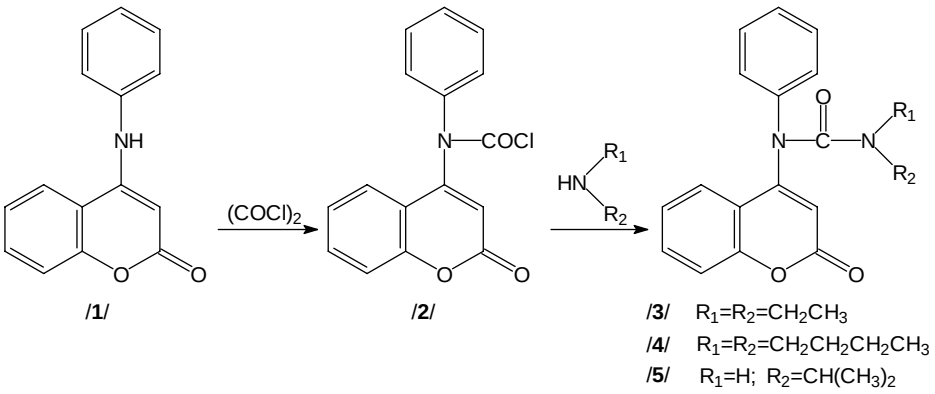


Scheme 1.

EXPERIMENTAL

Melting points were determined using Kofler apparatus and were not corrected. The IR spectra were recorded on the Perkin-Elmer 782 spectrophotometer and the band positions were given in cm^{-1}. The NMR spectra were recorded on Gemini-200 spectrometer (H^1-NMR at 200 MHz), in DMSO-d_6 at room temperature.

*N-chlorocarbonyl-N-phenyl-4-aminobenzo-α-pyrone /**2**/*

To a stirred solution of *N*-phenyl-4-aminobenzo-α-pyrone (**1** ;1g, 0.004 mol) in 20 ml of boiling nitrobenzene oxalyl chloride (0.5 ml, 0.0048 mol) was added dropwise. The resulting solution was stirred under reflux for 30 minutes, whereby the yellow crystals precipitated. The crude product **2** was collected, washed with hot benzene to give 0.82 g (68.9 %) yellow crystals, m.p. 292-294°C.

IR (ν_{max}): 1770(CO),1710,(C=C arom.).^{1}H-NMR δ: 8.25-7.0 (m, 9H arom.), 6.65 (d, 1H, 3-H). *Anal. found*: C 64.88, H 3.21, N 4.93. *Calcd. for* $C_{16}H_{10}ClNO_3$: C 64.10,H 3.34, N 4.67.

*N-(N,N´-diethylaminocarbonyl)-N-phenyl-4-aminobenzo-α-pyrone /**3**/*

A suspension of *N*-chlorocarbonyl-*N*-phenyl-4-aminobenzo-α-pyrone (**2**; 1 g, 0.0033 mol) and diethylamine (0.28 ml, 0.0033 mol) in 30 ml of benzene was heated under reflux for 3 h while the starting solid material was gradually dissolved. A small amount of unreacted starting material was filtered off. The filtrate was evaporated to a small volume and cooled, whereupon the crystalline product **3** precipitated. Crude product **3** (0.66g 57.58%) was collected and washed with ether to give yellow crystals m.p. 124-126°C.

IR(ν_{max}): 2950 and 2920 (CH_2, CH_3), 1715 and 1645 (CO), 1610 (C=C, arom). ^{1}H-NMR δ: 7.70-6.80 (m, 10H, arom and 3-H), 3.30 (m, 4H, CH_2), 1.25 (m, 6H, CH_3). *Anal. found*: C 68.10, H 5.46, N 7.84. *Calcd. for* $C_{20}H_{20}O_3 \times H_2O$: C 67.80, H 6.21, N 7.90.

*N-(N,N′-dibutylaminocarbonyl)-N-phenyl-4-aminobenzo-α-pyrone /**4**/*

A suspension of *N*-chlorocarbonyl-*N*-phenyl-4-aminobenzo-α-pyrone (**2** ;1.5 g, 0.0049 mol) in 30 ml of boiling benzene was treated with dibutylamine (0.83 ml, 0.0049 mol) under reflux for 1.5 h. After the work-up as described above, pure product **4** (0.90g, 46.94 %) was obtained as yellow crystals m.p. 108-110°C.

IR(ν_{max}): 3070, 2955 and 2895 (CH_2, CH_3), 1710 and 1645 (CO), 1610 (C=C, arom). ^{1}H-NMR δ: 7.60-7.10 (m, 9H, arom), 6.90 (t, 1H, 3-H), 3.20 (t, 4H, 2×CH_2), 1.80-1.20 (m, 8H, 4×CH_2), 1.00-0.80 (m, 6H, CH_3).

Anal. found: C 70.41, H 6.95, N 7.00. *Calcd. for* $C_{24}H_{28}O_3N_2$: C 70.24, H 7.30, N 6.83.

*N-(N′-isopropylaminocarbonyl)-N-phenyl-4-aminobenzo-α-pyrone /**5**/*

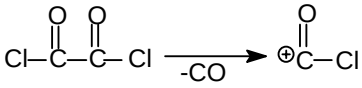
N-chlorocarbonyl-*N*-phenyl-4-aminobenzo-α-pyrone (**2**; 1.5 g, 0.0049 mol) was allowed to react with isopropylamine (0.42 ml, 0.0049 mol) in 40 ml of boiling benzene for 2 h. The work-up as desribed above gave crude product **5** (0.92 g, 59.18%) in the form of yellow crystals m.p.140-142°C.

IR(ν_{max}): 3300 (NH), 3075 and 2975 (CH, CH_3), 1720 and 1670 (CO), 1610 (C=C, arom). ^{1}H-NMR δ: 8.75 (d,1H, NH), 8.20-7.10 (m, 9H arom), 6.80 (t, 1H, 3-H), 1.50-1.20 (m, 7H, CH, and 2×CH_3). *Anal. found*: C 71.00, H 5.41, N 8.35. *Calcd. for* $C_{19}H_{18}O_3N_2$: C 70.81, H 5.59, N 8.69.

RESULTS AND DISCUSION

N-chloro carbonyl-*N*-phenyl-4-aminobenzo-α-pyrone (**2**), which was obtained by treatment of *N*-phenyl-4-aminobenzo-α-pyrone (**1**) with oxalyl chloride, was used as a convenient starting compound for the preparation of target dialkylaminocarbonyl derivatives. Introduction of the chlorocarbonyl as well as the chlorooxalyl group by an action of oxalyl chloride onto different aromatic compounds has already been described in the literature (11,13). Chlorocarbonyl derivative (**2**) was obtained by treatment of *N*-phenyl-4-aminobenzo-α-pyrone (**1**) with oxalyl chloride in refluxing nitrobenzene. Formation of *N*-chlorocarbonyl derivative (**2**) was unexpected since it is well known that the benzo-α-pyrone system (15) preferentially reacts with electrophiles at the position 3. The structure of (**2**) was confirmed by an absence of the absorption band for NH group in its IR spectrum, as well as by absence of the NH proton signal in the NMR spectrum. Furthermore, there was a signal at 6.65 ppm in the NMR spectrum, which confirmed the presence of H-3 in the benzo-α-pyrone system. Since it was found that acyl halides tend to eliminate carbon monoxide under certain conditions, if the remaining portion of the alkyl group is stable as reported (14) (Scheme 2), it can be assumed that the elimination of carbon monoxide from oxalyl chloride, in our case, took place at solvent's boiling point, by forming the electro-

philic agent $^{\oplus}$COCl, which then reacted with the NH group at C-4 of the benzo-α-pyrone system.



Scheme 2.

The condensation reactions of *N*-chlorocarbonyl-*N*-phenyl-4-aminobenzo-α-pyrone (**2**) with diethylamine, dibutylamine and isopropyl-amine gave the corresponding dialkyl-aminocarbonyl derivatives (**3**), (**4**), (**5**) as shown in Scheme 1. Reactions were carried out in the refluxing benzene, to afford the reaction products in yields ranging from 46.94 to 59.18%.

CONCLUSION

N-chlorocarbonyl-*N*-phenyl-4-aminobenzo-α-pyrone was prepared by treatment of *N*-phenyl-4-aminobenzo-α-pyrone with oxalyl chloride in boiling benzene. Under these reaction conditions the elimination of carbon monoxide from oxalyl chloride took place, yielding the reactive electrophilic agent ($^{\oplus}$COCl). Quite unexpectedly, the electrophilic agent attacked the NH group, instead of C-3, of *N*-phenyl-4-aminobenzo-α-pyrone to furnish the *N*-chlorocarbonyl-*N*-phenyl-4-amino-benzo-α-pyrone. Condensation reactions of this chlorocarbonyl derivative with diethylamine, dibutylamine and isopropyl-amine gave the corresponding amides **3** - **5** , as potential biologically active compound.

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СИНТЕЗА ДИАЛКИЛАМИНОКАРБОНИЛ ДЕРИВАТА *N*-ХЛОРКАРБОНИЛ-*N*-ФЕНИЛ-4-АМИНОБЕНЗО-α-ПИРОНА

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Диалкиламинокарбонил деривати *N*-хлоркарбонил-*N*-фенил-4-аминобензо-α-пирона добијени су кондензацијом са диетиламином, дибутиламином и изопропиламином. Полазно једињење за кондензацију са аминима добијено је реакцијом *N*-фенил-4-аминобензо-α-пирона са оксалил хлоридом. Реакције кондензације вршене су уз рефлукс у бензену у трајању од 1,5-3 сата. Изопропиламинокарбонил дериват изолован је директним хлађењем реакционе смесе, док су диетиламинокарбонил и дубитиламинокарбонил деривати изоловани након упаравања и хлађења реакционе смесе. Одговарајући амиди *N*-хлоркарбонил-*N*-фенил-4-аминобензо-α-пирона добијени су у приносу од 46,94-59,18%.

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