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ORIGINAL PAPER

Only acridine derivative from Hantzsch-type one-pot three-component reactions

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Abstract A three-component Hantzsch-type condensation of different anilines with dimedone and benzaldehyde leads to the formation of a unique acridine derivative with an unusual breaking of a C–N bond. The reaction was also carried out employing rapid microwave or conventional heating and sonication as alternative energy sources, and only this 1,8-dioxodecahydroacridine was obtained.

Keywords Multicomponent reactions · Hantzsch-type condensation · Acridine derivatives · *N*-unsubstituted acridinone

Introduction

Acridine derivatives have a wide spectrum of biological activities as antibacterial, antimalarial, anticancer, and mutagenic properties, principally connected with their ability to inhibit the enzymes acting on nucleic acids [1].

In previous work, we reported a series of quinoline derivatives as potential antiparasitic agents prepared via microwave-assisted Friedländer synthesis [2]. Among them, the acridine derivative **1** was obtained employing cyclohexanone as starting material. More recently, compound **2** was synthesized according to Ref. [2] using 5,5-dimethyl-1,3-cyclohexanedione (dimedone, Fig. 1). This compound (TDR70446) showed no activity against the causative agents of Chagas disease, sleeping sickness, and leishmaniasis, and resulted moderately cytotoxic [3]. Furthermore, the National Cancer Institute (NCI, USA) selected **2** (NSC747293) for in vitro one-dose testing against 60 cell lines and it exhibited no growth inhibition.

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Results and discussion

In the context of our ongoing research, we wished to prepare other acridine derivatives from benzaldehyde, aniline, and dimedone under solvent-free conditions. When the reactants were exposed to microwave irradiation (MW) at 400 W for 8 min in equimolar amounts, no defined product was observed. Surprisingly, when dimedone was in slight excess (5–10%), a white solid product was obtained in 30% yield. A ratio of 2:1 improved the yield of 3,4,6,7,9,10-hexahydro-3,3,6,6-tetramethyl-9-phenylacridine-1,8(2*H*,5*H*)-dione **3** up to 85% (Scheme 1). The structure of this compound was established from its spectral data (^{1}H NMR, ^{13}C NMR, IR, and MS) and analytical data, which agreed with the literature [4].

The reported methods to obtain **3** and its analogues employed ammonium hydroxide solution in 70% yield [4], ammonium acetate and benzaldehydes with electron-attracting groups [5], ammonium acetate with tris(pentafluorophenyl)borane catalysis [6], or the previously prepared enaminone instead of aniline [7], as well as by catalytic hydrogenation of the 3,3,6,6,-tetramethyloctahydroacridine-1,8-dione derivative [8].

1,4-Dihydropyridines (DHPs) are well-known compounds because of their pharmacological profile as calcium channel modulators. Some methods are available in literature for the synthesis of acridine compounds containing an 1,4-DHP nucleus from dimedone, aldehyde, and different

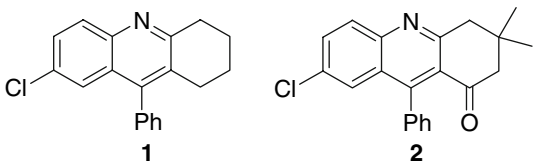


Fig. 1 Structures of acridine derivatives **1** and **2**

anilines or ammonium acetate via traditional heating in organic solvent, under MW, and using ionic liquids (ILs) [9].

On the other hand, when anilines (or 1-naphthylamine) and dimedone were used in 1:1 ratio, 9-aryl-3,4,9,10-tetrahydro-3,3-dimethylacridine-1(2*H*)-one **4** was obtained [5, 9], meanwhile the ratio 1:2 provided 9,10-disubstituted-decahydroacridine-1,8-diones **5** (Scheme 2).

The above-mentioned compounds are generally prepared through a Hantzsch synthesis under a wide variety of reaction conditions. Chebanov et al. [10] proposed that the use of the high-boiling polar DMF as solvent appears optimal to obtain the target compounds, without oxygen-containing heterocycles contamination.

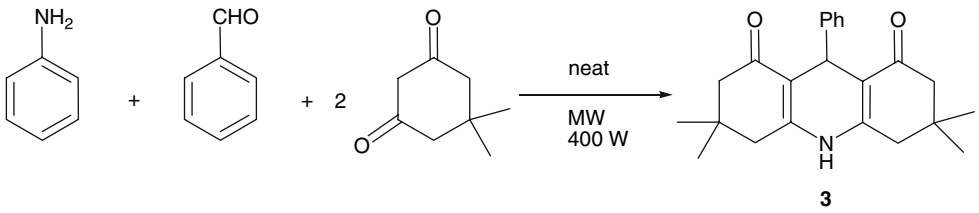
More recently, compound **5** and several analogues were prepared in good yields in CH_3CN under reflux in the presence of Amberlyst-15, an efficient heterogeneous catalyst [11]. Moreover, they were also synthesized employing an acidic IL [12].

Formation of **5** takes place through a Hantzsch-like mechanism via conjugate addition of the enamine intermediate **6** (obtained from dimedone and aniline) to the Knoevenagel product **7** (obtained from dimedone and benzaldehyde) followed by imino-enamino tautomerism and subsequent "6-exo-trig" cyclization [10] (Scheme 3).

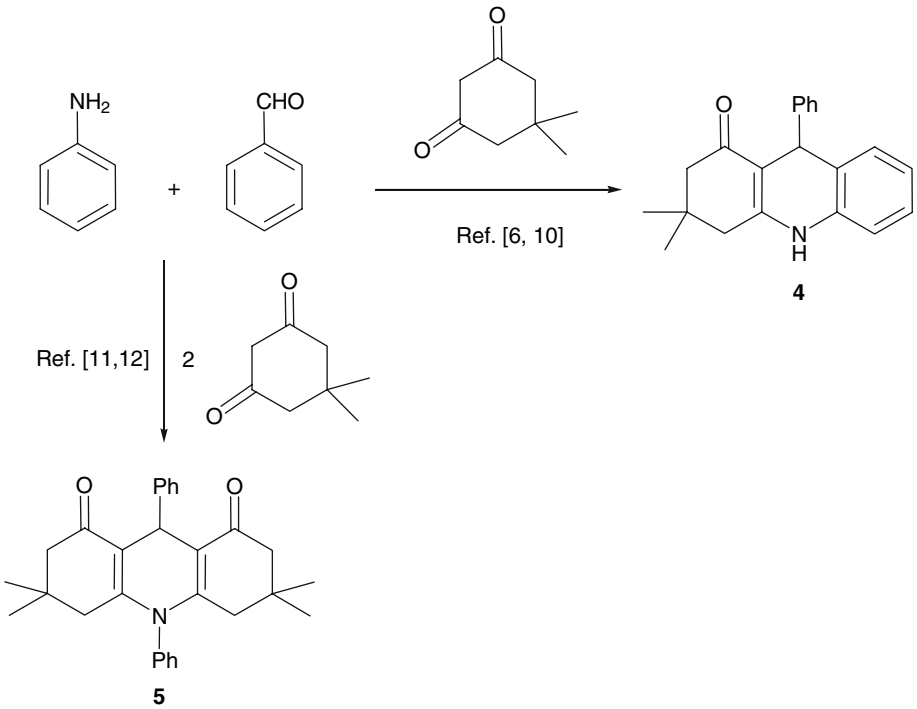
Herein, we assume a similar reaction mechanism which somehow involves the breaking of the bond between carbon and nitrogen atoms concomitant with loss of water to furnish the *N*-unsubstituted product. In order to support this, we performed the same reaction employing 4-chloroaniline, 4-methoxyaniline, and ammonium hydroxide, respectively, under conventional heating. In all cases, **3** was the only product obtained in moderate to good yields.

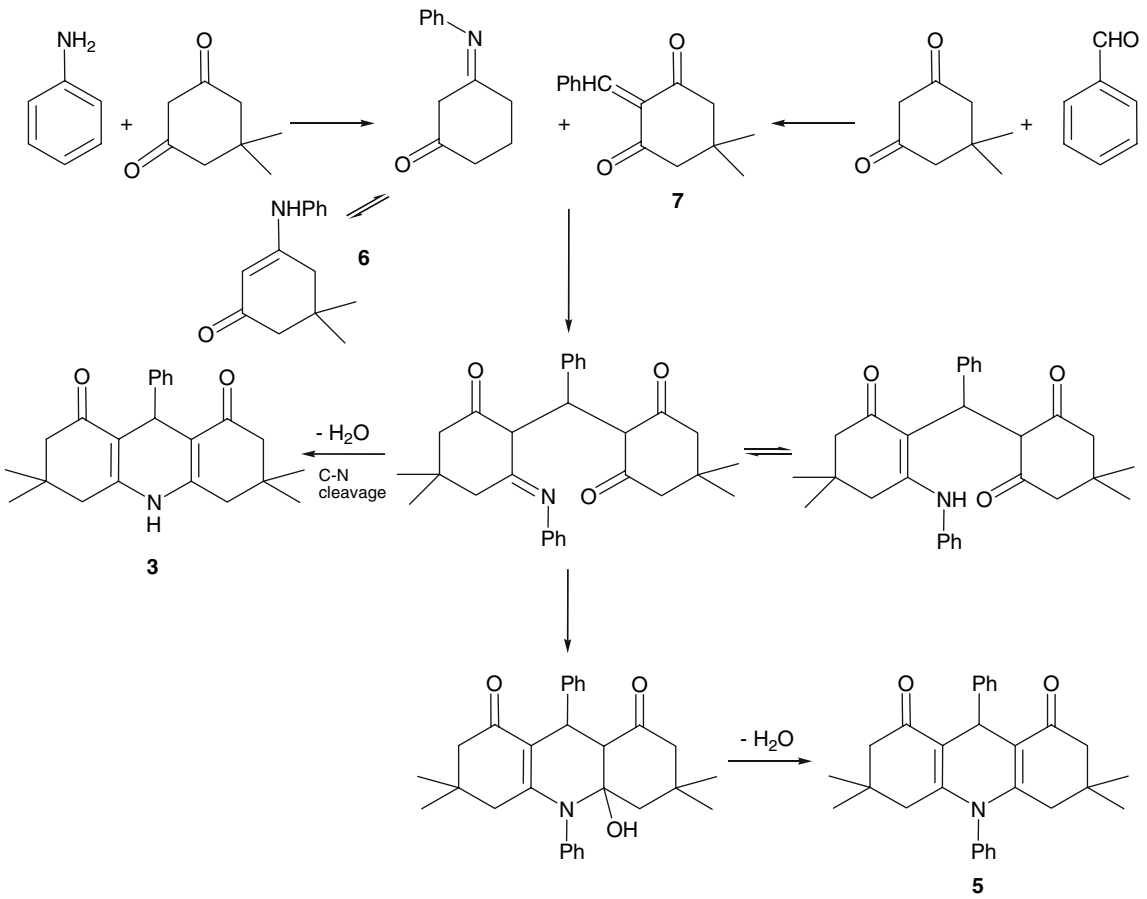
Furthermore, we carried out the reaction from aniline, benzaldehyde, and dimedone under conventional heating

Scheme 1



Scheme 2





Scheme 3

(refluxing EtOH), MW (neat and EtOH solvent), and sonication (room-temperature EtOH), taking into account that many different process parameters can be utilized to modulate the selectivity, especially in multicomponent reactions (MCRs) [13]. Again, **3** was the sole product obtained in high yield, suggesting that the formation of this compound is favored in all cases, independently of the energy source.

In summary, this work shows the formation of a unique acridine derivative with an unusual breaking of a C–N bond as a fundamental novelty, whatever the temperature, reaction conditions, and anilines employed, leading to a more stable product.

Experimental

Melting points were determined in a capillary Electrothermal 9100 SERIES-Digital apparatus. ^{1}H and ^{13}C NMR spectra were recorded at rt using a Bruker 200 MHz spectrometer with TMS as the internal standard. The chemical shifts (δ) are given in ppm. Infrared spectra were recorded on a FT Perkin Elmer Spectrum One from KBr discs. UV spectra were measured with a Jasco V-570 UV/Vis/NIR spectrophotometer. Analytical TLC was performed on DC-Alufolien Kieselgel 60 F_{254} Merck. Microwave-assisted reactions were carried out in a Multiwave 3000 (Anton Paar GmbH). For reactions under sonication, Testlab tb02 equipment was used.

*7-Chloro-3,4-dihydro-3,3-dimethyl-9-phenylacridine-1(2H)-one (**2**)*

Compound **2** was prepared according to Ref. [2]. Reaction time: 3 min (MW), white solid, m.p. 207–208 °C; yield 78%; ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (d, 1H, arom), 7.72 (dd, 1H, $J = 9.20$ Hz, $J = 2.21$ Hz), 7.54–7.69 (m, 3H, Ph), 7.49 (d, 1H, arom), 7.14–7.17 (m, 2H, Ph), 3.28 (s, 2H, CH_2), 2.57 (s, 2H, CH_2), 1.24 (s, 6H, $2CH_3$) ppm; IR (KBr): $\bar{\nu} = 3,074$, 1,757, 1,645, 1,277, 837, 754 cm^{-1}.

*3,4,6,7,9,10-Hexahydro-3,3,6,6-tetramethyl-9-phenylacridine-1,8(2H,5H)-dione (**3**), typical procedure*

A mixture of 0.98 g dimedone (7 mmol), benzaldehyde (3.5 mmol), and aniline (3.5 mmol) was subjected to microwave irradiation for 8 min at 400 W, 105 °C, and 18.3 bar. The reaction mixture was cooled and a white solid precipitated. It was crystallized from EtOH to give a

white solid powder, m.p. 195–197 °C, yield 63% (Ref. [5], 190–192 °C). The same reaction was performed employing EtOH as solvent under MW (8 min, yield 85%) and also with sonication at rt (30 min, yield 73%). It was also carried out with conventional heating for 2 h in EtOH as solvent and the yield was 49%. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 11.80$ (s, 1H, NH, exchanged D_2O), 7.30–7.09 (m, 5H, arom.), 5.54 (s, 1H, CH), 2.50–2.29 (m, 8H, CH_2), 1.24 (s, 6H, $2CH_3$), 1.11 (s, 6H, $2CH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 190.42$, 189.36, 138.06, 128.19, 126.77, 125.83, 115.58, 47.06, 32.74, 31.42, 29.61, 27.40 ppm; IR (KBr): $\bar{\nu} = 3,430$, 3,022, 2,963, 2,872, 1,600, 1,374, 1,248, 776, 694 cm^{-1}. MS (EI): $m/z = 350$ ($[M + 1]^+$), 241, 199, 83, 43.

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