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Studies with 1,3-Diketones: A Convenient Synthesis of Some Tetrahydro-4H-benzopyran and Tetrahydroquinoline Derivatives

Zaghloul E. Kandeel,* Ahmad M. Farag, Mohamed R. Shaaban, and Mohamed H. Elnagdi

Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt

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ABSTRACT

A facile, one-step synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran derivatives **4a–e** *via cycloaddition reactions of acrylonitrile derivatives* **1a–e** *with 1,3-cyclohexandione* **2** *is described. On the other hand, the reactions of* **2** *with the thioamides* **1f–h** *afforded 5-oxo-5,6,7,8-tetrahydroquinoline derivatives* **9a–c** *in good yields. The structures of the prepared compounds were established from their elemental analyses, spectroscopic data, and by their chemical transformations.* © *1996 John Wiley & Sons, Inc.*

In continuation of our interest in exploring the utility of α,β-unsaturated nitriles as versatile precursors for the synthesis of substituted heterocycles [1–4], we report here the results of the reactivity of acrylonitriles **1a–h** toward cyclohexan-1,3-dione (**2**). Thus, refluxing of equimolar amounts of each **1a–c** and **2** in ethanol in the presence of a catalytic amount of piperidine afforded 1:1 adducts for which several possible isomeric structures can be written (Scheme 1). The acyclic structures **3** and **5** are readily excluded based on ^{1}H NMR spectra of the isolated products, which revealed in each case a pyran H-4 as a singlet at ~δ 4.0. Structures **3** and **5** would be expected to show multiplets for several coupled protons linked to sp^3 carbon atoms. Therefore, structure **4** is assigned to each of the products isolated. The isomeric structure **6** is excluded on the basis of the ^{1}H NMR spectra of the isolated products, which revealed three CH_2 signals near δ 2.60, 2.40, and 1.90, respectively. Compounds **4a–c** are assumed to be formed via the nonisolable Michael adducts **3a–c**, which readily cyclize under the reaction conditions (Scheme 1). Compound **2** reacted also with **1d** and **1e** (generated in situ from the reaction of formaldehyde or acetaldehyde with malononitrile) to yield the cyclohexanopyrans **4d** and **4e**, respectively.

In contrast to the behavior of each of the compounds **1a–e** toward **2**, compounds **1f,g** reacted with **2** under the same experimental conditions to afford the quinoline-2-thione derivatives **9a,b**, respectively. Structure **9** is assumed to be formed via initial Michael adduct **7** followed by its cyclization to **8** and subsequent oxidation to **9** (Scheme 2). Although cyclization of **7** to the aminobenzothiopyran **11** is also possible, structure **9** was assigned to each of the isolated products on the basis of their ^{1}H NMR spectra, which revealed the absence of the thiopyran H-4. Moreover, the reaction products were proved to be stable under conditions that were expected to effect the opening of the thiopyran ring [5].

Similarly, compound **2** reacted with **1h** (generated in situ from the reaction of acetaldehyde and cyanothioacetamide) to afford the cyclohexanopyridine-2-thione **9c** in good yield (Scheme 2).

Furthermore, the reactivity of **9c** toward cinnamonitriles **1a,b** was also examined. Thus, compound **9c** reacts with an equimolar amount of **1a** or **1b** in ethanol in the presence of a catalytic amount of pi-

* To whom correspondence should be addressed.

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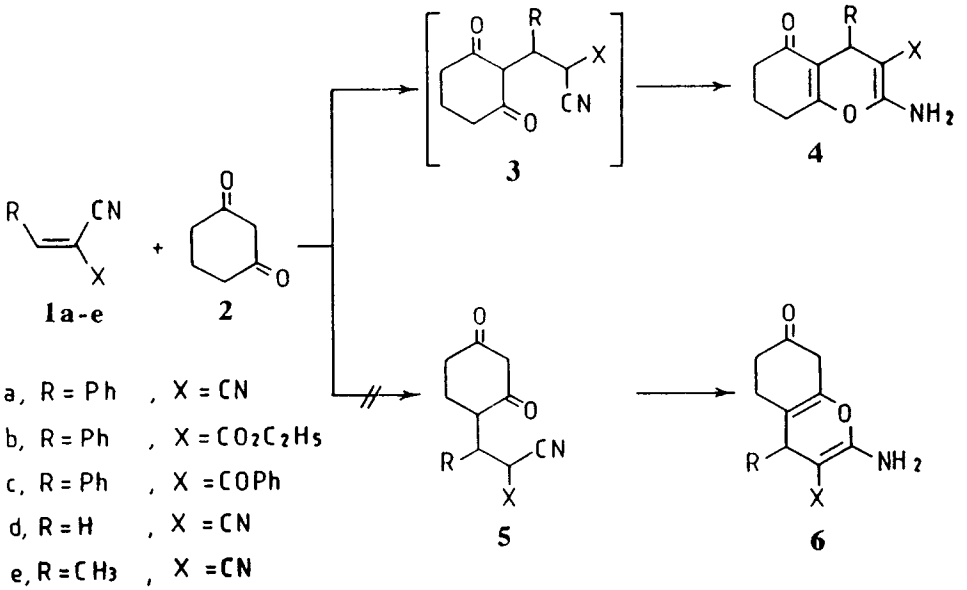
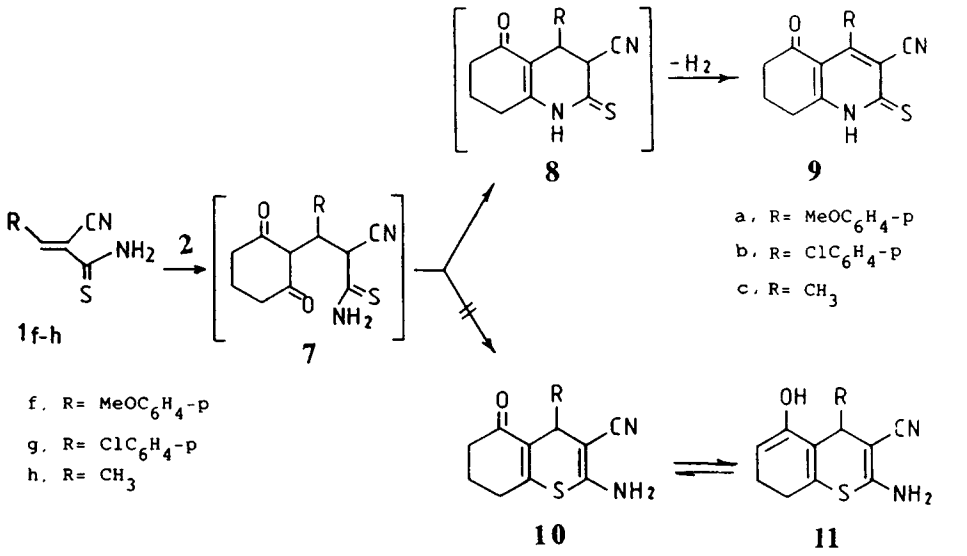
SCHEME 1



SCHEME 2



peridine to yield a 1:1 adduct that may be formulated as **13** or **15** (Scheme 3). Structure **15** was readily ruled out on the basis of the ^{1}H NMR spectra of the product isolated, which revealed the disappearance of the characteristic signal corresponding to the methyl protons of **9c**. The formation of **13** is assumed to proceed via the addition of the methyl anionic center of the conjugate base of **9c** to the activated double bond in **1a** or **1b** to afford the nonisolable intermediate **12**, which undergoes cyclization, under the reaction conditions, to give the final product.

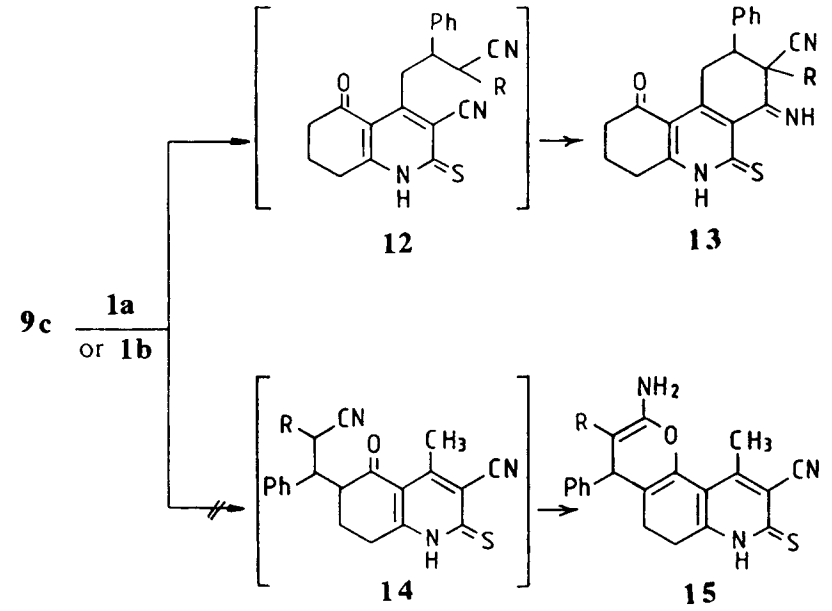
EXPERIMENTAL

Melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. IR spectra were obtained in KBr discs on a Pye Unicam Sp 1100 spectrophotometer. ^{1}H NMR spectra were measured in DMSO-d_6 using TMS as an internal standard on a Varian EM390 (90 MHz) NMR spectrometer. Microanalyses were performed by the Microanalytical Center of Cairo University.

2-Amino,-5,6,7,8-tetrahydro-5-oxo-4-aryl-4H-benzopyran-3-carbonitriles (**4a–g**)

General Procedure. To a solution of each **3** (1.12 g, 10 mmol) in ethanol (20 mL) was added an equimolar amount of the appropriate cinnamonitrile derivative **1a–c** (10 mmol) and 2 drops of piperidine. The reaction mixture was heated under reflux for 2 hours. The solid products obtained were collected by filtration, washed with ethanol, and then crystallized

SCHEME 3



a, R = CN
b, R = $CO_2C_2H_5$

from the proper solvent to give **4a–c**. **4a**: yield 81%, mp 241°C (DMF); lit. [6] (mp 239–241); ν_{max}/cm^{-1} (KBr) 3350, 3190 (NH_2), 2220 (CN), 1680 (CO); δ_H(DMSO) 7.52–7.13 (5H, m), 6.90(2H, br), 4.22(1H, s), 2.61–2.52(2H, m), 2.30–2.20(2H, m), 1.91–1.82(2H, m); found: C, 72.4; H, 5.3; N, 10.4%. $C_{16}H_{14}N_2O_2$ requires C, 72.16; H, 5.30; N, 10.52%. **4b**: yield 76%, mp 187°C (ethanol); ν_{max}/cm^{-1} (KBr) 3420, 3310 (NH_2), 1720(ester CO), 1685(ring CO); δ_H(DMSO) 7.60(2H, br), 7.3–7.1(5H, m), 4.50(1H, s), 4.02–3.91(2H, q), 2.65–2.60(2H, m), 2.33–2.23(2H, m), 1.95–1.85(2H, m), 1.13–1.05(3H, t); found: C, 69.0; H, 5.9; N, 4.5. $C_{18}H_{19}NO_4$ requires C, 68.99; H, 6.11; N, 4.47%. **4c**: yield 73%, mp 198°C (ethanol); ν_{max}/cm^{-1} (KBr) 3350(NH_2), 1684, 1650(CO); δ_H(DMSO) 7.63(2H, br); 7.23–6.95(10H, m), 4.52(1H, s), 2.65–2.60(2H, m), 2.32–2.22(2H, m), 1.95–1.85(2H, m); found: C, 76.5; H, 5.3; N, 4.2%. $C_{22}H_{19}NO_3$ requires C, 76.50; H, 5.54; N, 4.06%.

2-Amino-5,6,7,8-tetrahydro-5-oxo-4H-benzopyran-3-carbonitrile **4d** *and 2-Amino-5,6,7,8-tetrahydro-5-oxo-4-methyl-4H-benzopyran-3-carbonitrile* **4e**

General Procedure. To a solution of paraformaldehyde (0.3 g, 10 mmol) in DMF (15 mL) or acetaldehyde (0.44 g, 10 mmol) in absolute ethanol (20 mL) was added malononitrile (0.66 g, 10 mmol), cyclohexan-1,3-dione (**2**) (1.12 g, 10 mmol), and a few drops of piperidine. The reaction mixture was heated under reflux for 5 hours and then left to cool. The solid products thus formed were collected by filtration, washed with ethanol, dried, and then recrystallized from the proper solvent to give **4d** or **4e**. **4d**: yield 79%, mp 202°C (DMF); ν_{max}/cm^{-1} (KBr) 3400(NH_2), 2220(CN), 1690(CO); δ_H(insoluble in the common NMR solvents); found: C, 62.9; H, 5.4; N, 14.9%. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.30; N, 14.73%. **4e**: yield 80%, mp 197°C (ethanol); ν_{max}/cm^{-1} (KBr) 3410, 3220 (NH2), 2218(CN), 1690(CO); δ_H(DMSO) 6.85(2H, br), 3.19(1H, q), 2.58–2.50(2H, m), 2.35–2.30(2H, m), 1.95–1.80(2H, m), 1.12(3H, d); found: C, 65.0; H, 5.7; N, 13.5%. $C_{11}H_{12}N_2O_2$ requires C, 64.69; H, 5.92; N, 13.72%.

5-Oxo-5,6,7,8-tetrahydroquinolin-2-thione-3-carbonitriles **9a,b**

General Procedure. To a solution of **2** (1.12 g, 10 mmol) in dioxane (20 mL) was added an equimolar amount (10 mmol) of either **1f** or **1g** and a few drops of piperidine. The reaction mixture was heated under reflux for 4 hours and then allowed to cool. The yellow crystalline products thus formed were collected by filtration, washed with ethanol, and then recrystallized from DMF to afford **9a** and **9b**, respectively. **9a**: yield 82%, mp 266°C; ν_{max}/cm^{-1} (KBr) 3310(NH), 2225(CN), 1686(CO); δ_H(DMSO) 14.0(1H, s), 7.25–7.0(4H, m), 3.61(3H, s), 2.61–2.51(2H, m), 2.3–2.2(2H, m), 1.96–1.87(2H, m); found: C, 66.0; H, 4.7; N, 9.0; S, 10.1%. $C_{17}H_{14}N_2O_2S$ requires C, 65.79; H, 4.55; N, 9.03; S, 10.33%. **9b**: yield 85%, mp 282°C; ν_{max}/cm^{-1} (KBr) 3300(NH), 2215(CN), 1685(CO);

δ_H(DMSO) 14.1(1H, s), 7.30–6.95(4H, m), 2.65–2.51(2H, m), 2.32–2.20(2H, m), 1.96–1.82(2H, m); found: C, 61.2; H, 3.6; N, 8.7; S, 10.1%. $C_{16}H_{11}ClN_2OS$ requires C, 61.05; H, 3.52; N, 8.90; S, 10.18%.

5-Oxo-5,6,7,8-tetrahydroquinolin-2-thione-4-methyl-3-carbonitrile **9c**

To a solution of **2** (2.24 g, 20 mmol) in absolute ethanol (30 mL) was added cyanothioacetamide (2 g, 20 mmol), acetaldehyde (0.88 g, 20 mmol), and a few drops of piperidine. The reaction mixture was stirred at room temperature for 24 hours and then heated under reflux for 3 hours. The yellowish solid product thus formed was collected by filtration, washed with ethanol, and crystallized from DMF to afford **9c**: yield 78%, mp 270°C; ν_{max}/cm^{-1} (KBr) 3200(NH), 2218(CN), 1680(CO); δ_H(DMSO) 14.20(1H, s), 3.03–2.97(2H, t), 2.69(3H, s), 2.56–2.50(2H, t), 2.02–1.91(2H, m); found: C, 60.4; H, 4.9; N, 13.0; S, 14.5%. $C_{11}H_{10}N_2OS$ requires C, 60.53; H, 4.62; N, 12.83; S, 14.69%.

Reaction of **9c** *with Cinnamonitriles* **1a,b**

General Procedure. To a solution of **9c** (1.09 g, 5 mmol) in ethanol (10 mL) was added an equimolar amount (5 mmol) of either **1a** or **1b** followed by 2 drops of piperidine. The reaction mixture was heated under reflux for 4 hours. The solid products formed were collected by filtration, washed with ethanol, and crystallized from DMF to afford **13a** and **13b**, respectively. **13a**: yield 72%, mp 180°C; ν_{max}/cm^{-1} (KBr) 3310(NH), 2221(CN), 1685(CO); δ_H(DMSO) 12.0(1H, s), 7.72–6.95(5H, m), 4.15(1H, s), 3.2(1H, t), 3.0–2.9(2H, s), 2.61–2.51(2H, m), 2.3–2.2(2H, m), 1.96–1.85(2H, m); found: C, 67.5; H, 4.4; N, 15.3; S, 8.7%. $C_{21}H_{16}N_4OS$ requires C, 67.72; H, 4.33; N, 15.04; S, 8.61%. **13b**: yield 70%, mp 177°C; ν_{max}/cm^{-} (KBr) 3320(NH), 1710(ester CO), 1680(CO); δ_H(DMSO) 13.2(1H, s), 7.3–6.8(5H, m), 4.2(1H, s), 4.0–3.9(2H, q), 3.20(1H, t), 3.0–2.9(2H, s), 2.65–2.60(2H, m), 2.33–2.23(2H, m), 1.96–1.86(2H, m), 1.15–1.05(3H, t); found: C, 65.7; H, 4.9; N, 10.2; S, 7.5%. $C_{23}H_{21}N_3O_3S$ requires C, 65.85; H, 5.05; N, 10.02; S, 7.64%.

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