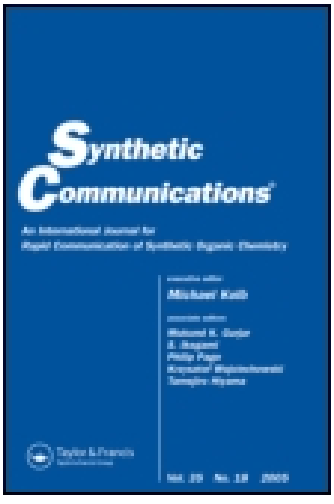

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Two-Step Novel Synthesis of 2-Amino-6-(1,3-dioxo-2,3-dihydro-1H-inden-2-yl) and 5-(1,3-Dioxo-2,3-dihydro-1H-inden-2-yl)-2-imino-

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Two-Step Novel Synthesis of 2-Amino-6-(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-4,7-diphenyloxepine-3-carbonitrile and 5-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-imino-6-phenyl-2*H*-pyran-3-carbonitrile

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Abstract: Starting from indan-1,3-dione, a novel two-step synthesis of the oxepine derivatives **5a,b** and the pyran derivatives **7** and **8** under very simple reaction conditions is described.

Keywords: oxepin derivatives, pyran derivatives, indan-1,3-dione chemistry

INTRODUCTION

Oxepine derivatives (Klaivanolide from the plant *Uvaria klaineava*) are known as potent antileishmanial agents[1] and as antiallergic drugs.[2] Because activity in this particular area has not been especially high, we report herein the synthesis of new derivatives of the oxepine molecule as well as a new pyran heterocycle, both linked to an indandione moiety that is expected to increase their biological activity.[3–5] This motivation is in addition to our interest in the synthesis of functionally substituted heterocycles utilizing enaminones[3–7] as precursors for the targeted compounds. The synthesis of these classes of compounds allows for good yield and is simple and facile. Also, it represents a novel one-step synthesis of the seven-membered oxepine ring from 1,3-diketone.

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RESULTS AND DISCUSSION

Treatment of 2-phenacylindan-1,3-dione (**1**)[8] with dimethyl formamide dimethylacetal in dry xylene under reflux afforded the unkown enaminone derivative **2** in (80%) yield. Structure of compound **2** was confirmed by its spectral and elemental analysis.

Compound **2** was treated with arylidenemalononitriles (**3a,b**) in ethanol containing a catalytic amount of piperidine (0.5 mL) to give the oxepine derivatives **5a,b**. Compound **5** is believed to be formed via the Michael-type addition of the enaminone **2** to the activated double bond in **3**, followed by dimethylamine elimination and cyclization to give the oxepine **5**.

On the other hand, when **2** was treated with malononitrile under the same reaction conditions, the iminopyran derivative **7** was obtained. Compound **7** underwent hydrolysis in aqueous hydrochloric acid to give the pyranone derivative **8** in good yield.

Elemental analyses of the synthesized compounds were found to be in accordance with the proposed structures.

CONCLUSION

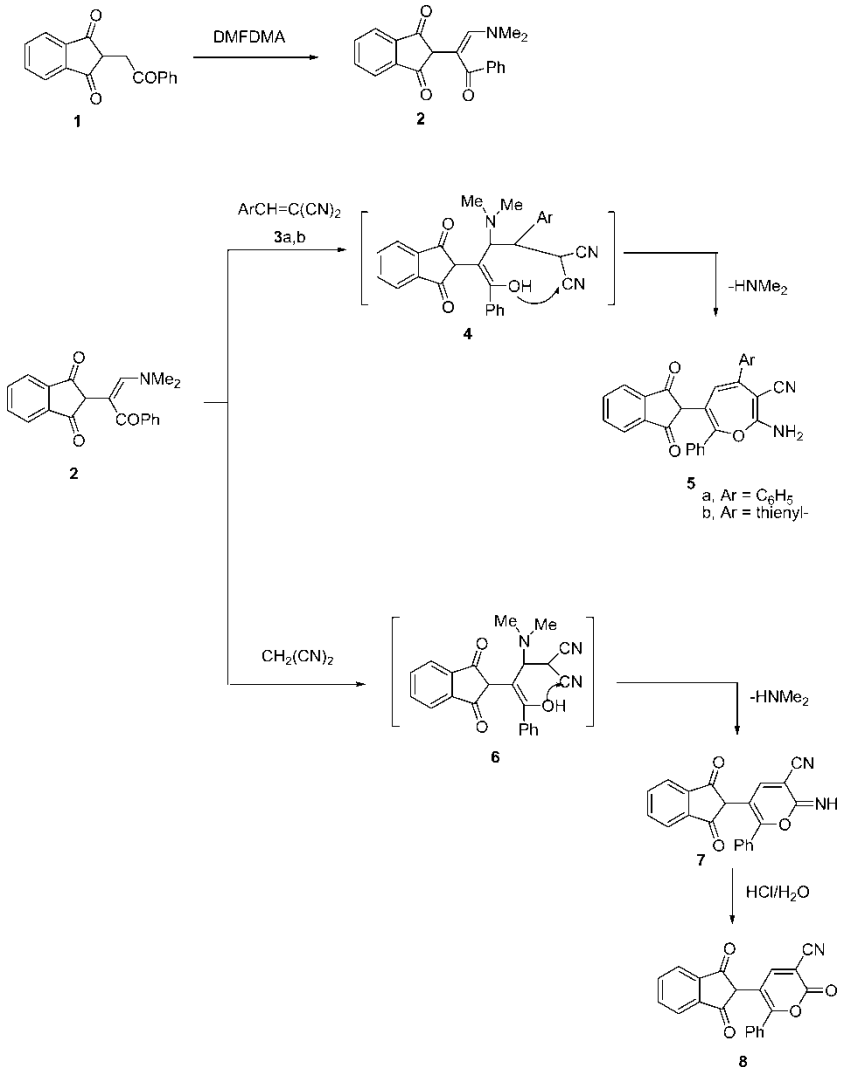
In conclusion, this article reports a novel, simple method for the synthesis of six- and seven-membered heterocycles, which may contribute to the chemistry of heterocyclic compounds as well as their expected biological activity.

EXPERIMENTAL

All melting points were obtained in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr discs using a Perkin Elmer FT spectrophotometer model Spectrum RX1. The ^{1}H and ^{13}C NMR spectra were determined on a Varian Mercury 300-MHz FT-NMR 300 with DMSO-d_6 as solvent, with chemical shifts reported in parts per million (ppm) (d) relative to TMS as internal standard. Mass spectra were measured on a GC/MS INCOS XL Finnigan MAT. Microanalysis was performed in house using a Perkin Elmer Series II CHNS/O Analyzer 2400. Reagents were purchased from Aldrich.

2-(3-Dimethylamino)-1-oxo-1-phenylprop-2-en-2-yl)-2H-inden-1, 3-dione (2)

A mixture of compound **1** (10 mmol) and DMFDMA (10 mmol) in xylene (30 mL) was heated under reflux for 4 h (Scheme 1). The reaction mixture was then evaporated under vacuum. The remaining residue was triturated



Scheme 1.

with ethanol to give a solid product that was collected by filtration and crystallized from ethanol to give compound **2** as red crystals.

Yield 70%, mp 240°C. IR: 1729, 1705 (3 CO). ^{1}H NMR (DMSO-d_6): 2.65 (s, 6H, 2N-CH_3), 5.18 (s, 1H, CH), 6.53 (s, 1H, CH), 7.45–7.97 (m, 9H, arom-H). ^{13}C NMR (DMSO-d_6): 200.5, 193.5 (3 CO), 149.1 (vinyl carbons), 63.1, 43.5 (aliphatic carbons). MS: m/z 319.00 (M^+) (100 %). Anal. calcd. for $C_{20}H_{17}NO_3$ (319.35): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.43; H, 5.12; N, 4.51%.

General Method for the Preparation of Compounds 5a,b and 7

The appropriate arylidene malononitrile or malononitrile (10 mmol) was added to a solution of compound **2** (10 mmol) in ethanol (30 mL) containing piperidine (0.5 mL). The reaction mixture was then heated under reflux for 6 h. The reaction mixture was left to cool, and the deposited solid was collected by filtration to give compounds **5a,b** and **7**.

2-Amino-6-(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-4, 7-diphenyloxepine-3-carbonitrile (5a)

Compound **5a** was obtained as brown crystals from ethanol, yield 75%, mp 254°C. IR: 3345, 3330 (NH_2), 2220 (CN), 1729 (CO). ^{1}H NMR (DMSO-d_6): 4.0 (br, 2H, NH_2), 5.19 (s, 1H, CH), 6.8 (s, 1H, 4H-oxepine), 7.43–8.1 (m, 14H, arom-H). ^{13}C NMR (DMSO-d_6): 193.0 (CO), 177.0, 147.0, 142.0, 130.9, 105.5, 60.5 (vinyl carbons), 141.2, 133.0, 132.5, 129.5, 129.1, 128.5, 128.1, 126.2 (aromatic protons), 115.2 (CN), 60.9 (CH). MS: m/z 430.00 (M^+) (100%). Anal. calcd. for $C_{28}H_{18}N_2O_3$ (430.45): C, 78.13; H, 4.21; N, 6.51. Found: C, 77.99; H, 4.33; N, 6.34%.

2-Amino-2-benzyl-6-(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-4-(thiophene-2-yl)oxepine-3-carbonitrile (5b)

Compound **5b** was obtained as red crystals from ethanol, yield 73%, mp 200°C. IR: 3450, 3330 (NH_2), 2220 (CN), 1729 (CO). ^{1}H NMR (DMSO-d_6): 4.0 (br, 2H, NH_2), 5.19 (s, 1H, CH), 6.8 (s, 1H, 4H-oxepine), 7.0–8.1 (m, 12H, arom-H and thiophene-H). ^{13}C NMR (DMSO-d_6): 196.00 (CO), 141.00, 137.3, 133.3, 128.5 (aromatic carbons), 136.3, 130.3, 128.00, 127.00 (thiophene carbons), 175.00, 143.00, 142.00, 137.00, 108.00, 61.00 (vinyl carbons), 115.5 (CN), 37.00 (CH). Anal. calcd. for $C_{26}H_{16}N_2O_3$ S (436.48): C, 71.54; H, 3.69; N, 6.42. Found: C, 71.59; H, 3.50; N, 6.40%.

5-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2yl)-2-imino-6-phenyl-2*H*-pyran-3-carbonitrile (7)

Compound **7** was obtained as yellow crystals from ethanl/DMF, yield 75%, mp 273°C. IR: 3400 (NH), 2220 (CN), 1729 (CO). ^{1}H NMR (DMSO-d_6): 5.6 (s, 1H, 4H-pyran), 5.9 (s, 1H, CH), 7.45–8.5 (m, 9H, arom-H), 8.83 (s, 1H, NH). MS: m/z 340 (M^+) (100%). Anal. calcd. for $C_{21}H_{12}N_2O_3$ (340.33): C, 74.11; H, 3.55; N, 8.23. Found: C, 74.40; H, 3.33; N, 8.20%.

5-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2yl)-2-oxo-6-phenyl-2*H*-pyran-3-carbonitrile (8)

A solution of compound **7** (10 mmol) in hydrochloric acid (10 mL) was refluxed for 5 min. The solution was made alkaline with aqueous 20% sodium hydroxide solution. Compound **8**, which precipitated, was collected by filtration and crystallized from methanol, yield 70%, mp 220°C. IR: 3450, 3330 (NH_2), 2220 (CN), 1729, 1700 (2 CO). ^{1}H NMR (DMSO-d_6): 5.19 (s, 1H, CH), 5.9 (s, 1H, 4H-pyran), 7.45–8.5 (m, 9H, arom-H). ^{13}C NMR (DMSO-d_6): 194.5 (2 CO), 150 (CO-O), 165.0, 135.1, 107.3, 104.2 (vinyl carbons), 141.4, 133.2, 130.5, 128.00, 126.5 (arom carbons), 115.3 (CN), 59.5 (CH). MS: m/z 341(M^+) (100%). Anal. calcd. for $C_{21}H_{11}NO_4$ (341.32): C, 73.90; H, 3.25; N, 4.10. Found: C, 73.89; H, 3.20; N, 4.31%.

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