Facile One Pot Microwave Assisted Solvent-Free Synthesis of Novel Spiro-Fused Pyran Derivatives via the Three-Component Condensation of Ninhydrin with Malononitrile and Active Methylene Compounds

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Three-component condensation of ninhydrin, malononitrile, and some nucleophilic reagents in the presence of piperidine under microwave irradiation without solvent afforded the corresponding spiro-fused pyran derivatives. The structures of the products were proved by elemental analyses, IR, ^{1}H NMR and MS spectroscopy.

Keywords: Ninhydrin; Malononitrile; Nucleophilic reagents; Spiropyrans.

INTRODUCTION

The reaction allowed the synthesis of new spiro-type compounds as an important target in chemical synthesis because of their expected biological activities[1,2] and the study of the peri- and regioselectivity of this reaction. Particular attentions have been focused on spiropyrans due to their potential applications to industrial fields.[3-5] Furthermore, pyrans and fused pyrans are biologically interesting compounds with antibacterial activities,[6] antifungal activities,[7] antitumor activity,[8] and hypotensive effects.[9] On the other hand, ninhydrin is a unique tricarbonyl compound which is widely used in biochemical and medical settings for the analysis of amino acids.[10] Recently, microwave irradiation has been widely used in the synthesis of heterocyclic compounds with good yields and short reaction time.[11-14] A dry media technique by microwave heating has attracted much attention[15-18] and offers several advantages: solvents are often expensive, toxic, difficult to remove in the case of aprotic dipolar solvents with high boiling points, and are agents that pollute the environment. The absence of solvent also reduces the risk of hazardous explosions when the reaction takes place in a closed vessel in the microwave oven. In view of the above-mentioned findings and as a part of our program aimed at the development of new simple and efficient procedures for the synthesis of spiro[19-21] and condensed[22-25] heterocyclic derivatives, the present work is aimed at synthesizing different spiro-fused pyrans via the three-component condensation of ninhydrin with malononitrile and active methylene compounds under microwave irradiation without solvent.

RESULTS AND DISCUSSION

The hitherto synthesized compounds were prepared according to the sequence of reactions that are illustrated in Schemes I-III. Thus, 6-amino-5-cyano-3-oxo-1-phenyl-spiro-4,2′-[indan-1′,3′-dione]-2H,4H-pyrano[2,3-c]pyrazole (**7**) was prepared by the reaction of ninhydrin (**1**) with malononitrile (**2**) and 1-phenyl-pyrazolidine-3,5-dione (**3**) in the presence of a catalytic amount of piperidine under microwave irradiation without solvent for 3 minutes (Scheme I).

The structure of compound **7** was established from its elemental analysis and spectral data (Table 1). The gross formula, $C_{21}H_{12}N_4O_4$, of compound **7** was confirmed by the mass spectrum, which exhibited the molecular ion at *m/z* 384. Its IR spectrum showed a strong absorption band of the nitrile group at 2220 cm^{-1} and intense bands at 3330-3200 cm^{-1} indicating the presence of stretching vibrations of an NH_2 and NH groups. The ^{1}H NMR spectrum of **7** in DMSO-d_6 demonstrated a characteristic singlet at δ 3.4 for the NH_2, a multiplet at δ 7.3-7.7 for the aromatic protons, and a singlet at δ 9.1 ppm for the NH proton.

The formation of **7** was rationalized in terms of the initial formation of 2-(dicyano-methylene)-indan-1,3-dione (**4**)[26] followed by the addition of the active methylene reagent **3** (Michael donors) to the activated double bond in **4** (Michael acceptors) forming acyclic intermediate Michael adducts **6**. The subsequent intramolecular cyclization of **6** by the addition of the enol OH to the cyano group formed the isolated product.[27] The different course of the reaction can probably be explained by the formation of an intermediate **5**, which re-

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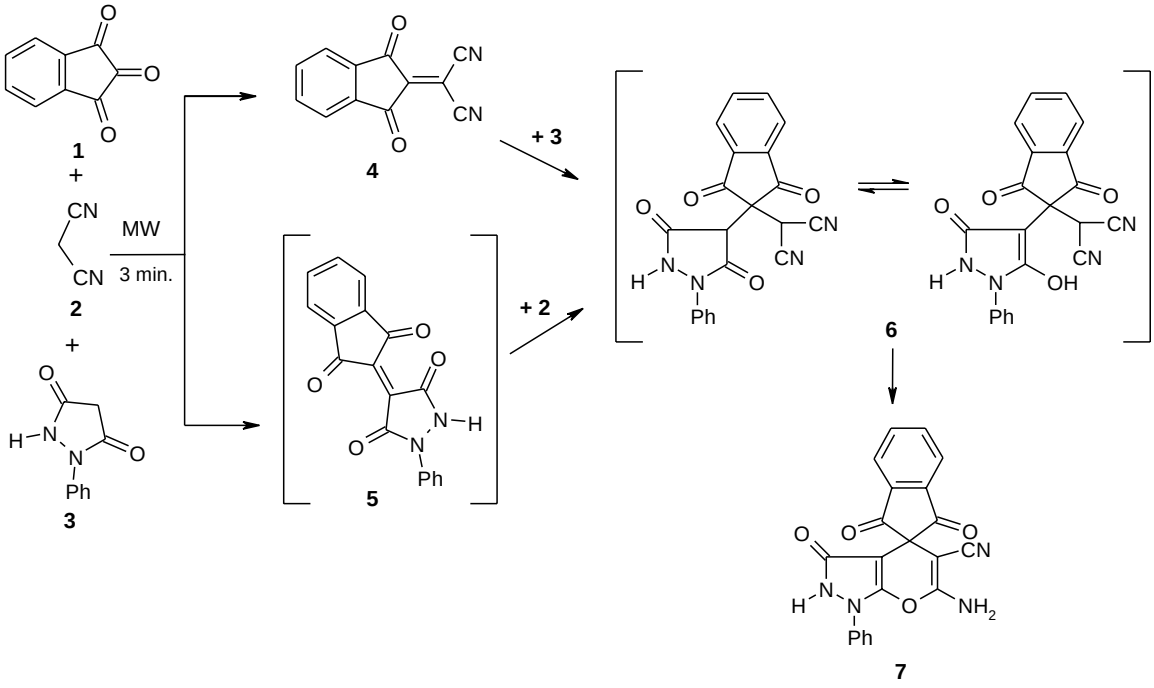
Scheme I

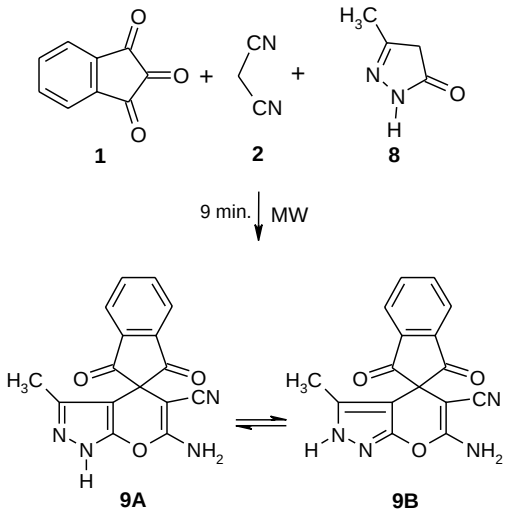


acted with malononitrile to give **7** (Scheme I).

Structural proof was obtained through a two-component condensation of **4** with **3** under the previous conditions. Further confirmation of structure **7** was made by comparison with an authentic sample, prepared from the reaction of **1** with **2** and **3** using the conventional thermal[28,29] method in refluxing ethanol containing a catalytic amount of piperidine for 4 hours, which showed agreement by MP, IR, and ^{1}H NMR data.

Similarly, 3-methyl-3-pyrazolin-5-one **8** was reacted with **1** and **2** under the previous conditions to give the corresponding spiropyrano[2,3-c]pyrazole **9A**, which can exist in the tautomeric form **9B**, and its structure was deduced on the basis of analytical and spectral data (Scheme II and Table 1). Its IR spectrum showed the NH_2 and NH absorption bands at 3500-3200 cm^{-1}, a strong absorption band of the nitrile group at 2200 cm^{-1}, and bands at 1740 cm^{-1} and 1700 cm^{-1} for the two carbonyl groups. The ^{1}H NMR spectrum of **9** in DMSO-d_6 demonstrated a characteristic singlet at δ 1.6 for the methyl protons, a singlet at δ 6.2 for the amino group, a multiplet at δ 7.6-8.2 due to the phenyl protons, and a singlet at δ 10.9 ppm for the NH proton. However, the question about whether the hydrogen atom is positioned at the *N*(1) or *N*(2) atom of the pyranopyrazoles remains unclear. In the literature, there is no consensus of opinion regarding the structures of pyranopyrazoles derived from pyrazol-5-ones.[30-36]

Scheme II



The efficiency of the above reactions prompted us to extend this procedure to the synthesis of different fused spiropyran derivatives. Thus, ninhyrin (**1**) reacted with **2** and 1-methylhydantoin (**10**), tetrahydrofuran-2,4-dione (**11**), 2-indolinone (**12**), and barbituric acid derivatives **13a-c** to give the corresponding spiropyrans **14-17**, respectively (Scheme III). The structures of compounds **14-17** were deduced from their elemental analyses and their IR, MS and ^{1}H NMR spectra (Table 1). For example, the elemental analysis of com-

Table 1. Characterization data of the prepared compounds

Compd.	M. P. (°C) Cryst. Solvent. (Yield)	Mol. For. (Mol. Wt)	Analytical Data Calcd./Found (%)				Spectral Data
			C	H	N	S	
7	189-190 (EtOH) (92%)	$C_{21}H_{12}N_4O_4$ (384.35)	65.63 65.56	3.15 3.18	14.58 14.66		IR (υ_{max}/cm^{-1}): 3330, 3250 (NH_2), 3200 (NH), 2220 (CN), 1690, 1660 (CO), 1600, 1580 (C=C, C=N); ^{1}H-NMR: δ 3.4 (s, 2H, NH_2), 7.3-7.7 (m, 9H, Ar-H), 9.1 (s, 1H, NH); MS: 384 (M^+, 23%).
9	250-252 (EtOH) (83%)	$C_{16}H_{10}N_4O_3$ (306.28)	62.75 62.72	3.29 3.33	18.29 18.35		IR (υ_{max}/cm^{-1}): 3500, 3400 (NH_2), 3200 (NH), 2200 (CN), 1740, 1700 (CO), 1640, 1590 (C=C, C=N); ^{1}H-NMR: δ 1.6 (s, 3H, CH_3), 6.2 (s, 2H, NH_2), 7.6-8.2 (m, 4H, Ar-H), 10.9 (s, 1H, NH).
14	265-267 (EtOH) (91%)	$C_{16}H_{10}N_4O_4$ (322.28)	59.63 59.60	3.13 3.15	17.38 17.35		IR (υ_{max}/cm^{-1}): 3450, 3400 (NH_2), 3250 (NH), 2200 (CN), 1745, 1700, 1675 (CO), 1620, 1580 (C=C, C=N); ^{1}H-NMR: δ 2.5 (s, 3H, CH_3), 7.9-8.4 (m, 6H, Ar-H and NH_2), 10.7 (s, 1H, NH).
15	258-260 (EtOH) (87%)	$C_{16}H_8N_2O_5$ (308.25)	62.34 62.39	2.62 2.57	9.09 9.05		IR (υ_{max}/cm^{-1}): 3400, 3330 (NH_2), 2210 (CN), 1760, 1740, 1720 (CO), 1640, 1590 (C=C, C=N); ^{1}H-NMR: δ 5.2 (s, 2H, CH_2), 8.0 (s, 2H, NH_2), 8.3-8.5 (m, 4H, Ar-H); MS: 308 (M^+, 19%).
16	246-248 (EtOH) (95%)	$C_{20}H_{11}N_3O_3$ (341.33)	70.38 70.50	3.25 3.22	12.31 12.26		IR (υ_{max}/cm^{-1}): 3400, 3300 (NH_2), 3240 (NH), 2200 (CN), 1740, 1700 (CO), 1625, 1590 (C=C, C=N); ^{1}H-NMR: δ 7.2 (s, 2H, NH_2), 7.7-8.1 (m, 8H, Ar-H), 10.2 (s, 2H, 2NH); MS: 341 (M^+, 65%).
17a	183-185 (EtOH) (95%)	$C_{16}H_8N_4O_5$ (336.27)	57.15 57.23	2.40 2.50	16.66 16.55		IR (υ_{max}/cm^{-1}): 3400, 3330 (NH_2), 3200 (NH), 2200 (CN), 1745, 1720, 1700 (CO), 1600 (C=C, C=N); ^{1}H-NMR: δ 4.50 (s, 2H, NH_2), 7.8-8.2 (m, 4H, Ar-H), 9.8 (s, 2H, 2NH); MS: 336 (M^+, 35%).
17b	210-212 (EtOH) (94%)	$C_{16}H_8N_4O_4S$ (352.33)	54.54 54.50	2.29 2.40	15.90 16.05	9.10 8.97	IR (υ_{max}/cm^{-1}): 3450, 3300 (NH_2), 3200 (NH), 2200 (CN), 1740, 1715, 1690 (CO), 1640, 1600 (C=C, C=N); ^{1}H-NMR: δ 4.55 (s, 2H, NH_2), 7.6-8.1 (m, 4H, Ar-H), 9.85 (s, 2H, 2NH); MS: 352 (M^+, 15%).
17c	242-244 (EtOH) (90%)	$C_{20}H_{16}N_4O_4S$ (408.44)	58.81 58.73	3.95 3.90	13.72 13.78	7.85 8.01	IR (υ_{max}/cm^{-1}): 3400, 3300 (NH_2), 2200 (CN), 1740, 1715, 1690 (CO), 1660, 1590 (C=C, C=N); ^{1}H-NMR: δ 1.01-1.14 (t, 3H, *J* = 6.9 Hz, CH_3), 1.26-1.39 (t, 3H, *J* = 6.9 Hz, CH_3), 3.96-4.38 (q, 2H, *J* = 6.9 Hz, CH_2), 4.51-4.62 (q, 2H, *J* = 6.9 Hz, CH_2), 7.8 (s, 2H, NH_2), 7.9-8.2 (m, 4H, Ar-H); MS: 408 (M^+, 33%).
19	280-282 (CH_3CN) (96%)	$C_{18}H_{12}N_2O_4$ (320.31)	67.50 67.55	3.78 3.80	8.75 8.66		IR (υ_{max}/cm^{-1}): 3400, 3350 (NH_2), 2200 (CN), 1740, 1700, 1675 (CO), 1640, 1590 (C=C, C=N). ^{1}H-NMR: δ 2.1-2.35 (m, 6H, 3CH_2), 7.5 (s, 2H, NH_2), 7.8-8.2 (m, 4H, Ar-H); MS: 320 (M^+, 35%).

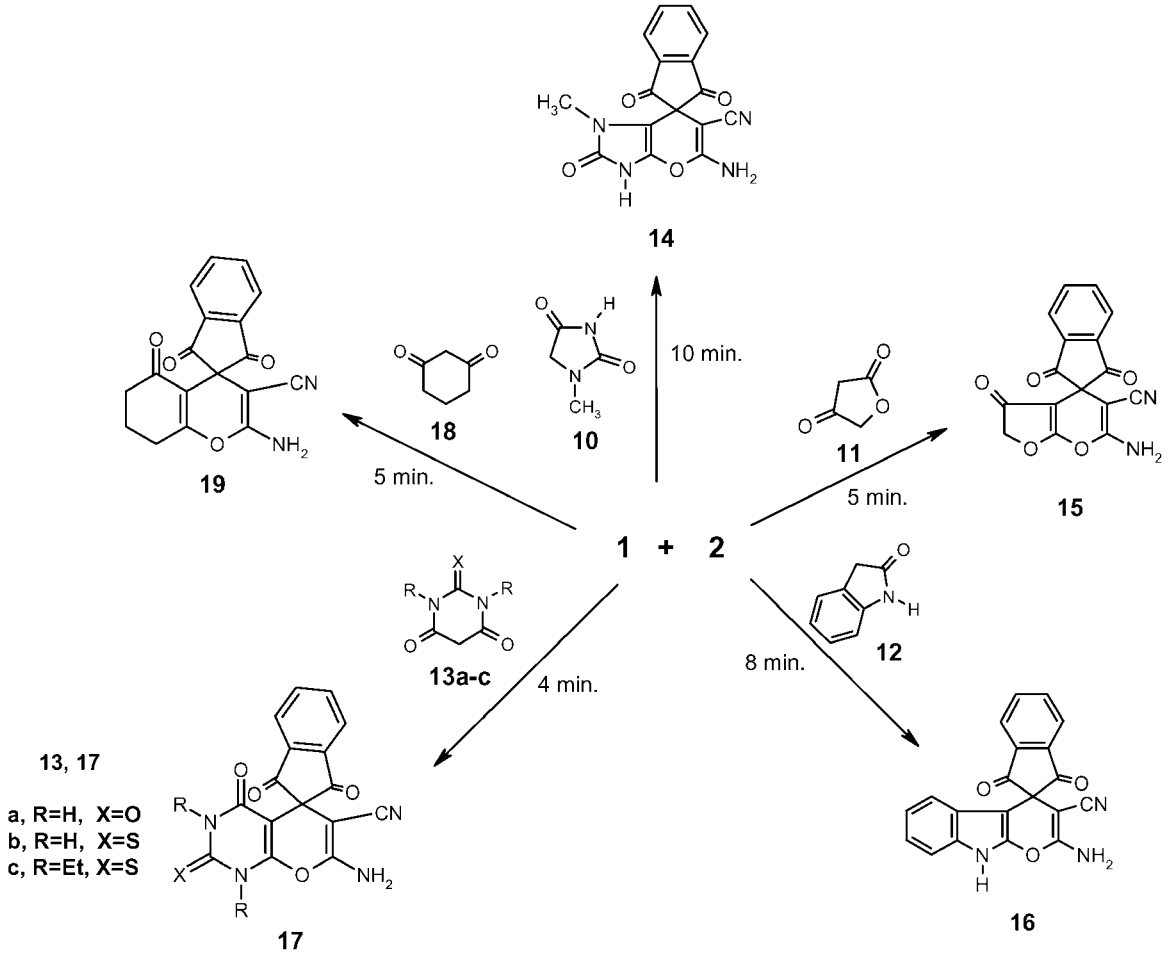
pound **16** supported the proposed structure molecular formula as $C_{20}H_{11}N_3O_3$. The ^{1}H NMR spectrum of **16** revealed two broad singlets at δ 7.2 and 10.2 ppm, assigned to the NH_2 and NH protons, respectively, and at δ 7.7-8.1 ppm assigned to the aromatic protons. Furthermore, its mass spectrum gave the molecular ion peak at *m/z* 341 (M^+, 65%) which was found to be in good agreement with the assigned structure.

1,3-Cyclohexanedione (**18**) when subjected to the previous reaction conditions gave the spiro-4,2′-[indan-1′,3′-dione]pyran **19** (Scheme III). The structure of compound **19** was established on the basis of analytical and spectroscopic data. Its IR spectrum showed absorption bands at 3400-3350 (NH_2), 2200 (CN) and 1740, 1700, 1675 (C=O) cm^{-1}. The ^{1}H NMR as well as the mass spectra agreed with the proposed structure of **19** (Table 1).

EXPERIMENTAL

All melting points were recorded on a Gallen Kamp ap-

Scheme III



paratus and are uncorrected. IR spectra (cm^{-1}) were recorded (as KBr pellets) on a Shimadzu 480 spectrophotometer. The ^1H NMR spectra were measured in DMSO-d_6 on 90 and 200 MHz (Varian EM-390 and Bruker WM-400) spectrometers using TMS as an internal standard; the chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Finnigan MAT 8430 mass spectrometer operating at 70 eV. Micro analytical data were performed by the Micro Analytical Unit at Cairo University.

Synthesis of spiro-4,2′-[indan-1′,3′-dione]pyrans 7,9,14-17a-c and 19 (General Procedure)

An equimolar mixture (10 mmol) of each of ninhydrin (**1**), malononitrile (**2**), and active methylene reagents with a catalytic amount of piperidine were thoroughly mixed in a 100 mL beaker and irradiated at 700 w in a Samsung M 9245 microwave oven for 3-10 minutes (monitored by TLC). The reaction mixtures were cooled and after addition of methanol (10 mL), the resulting solid product was collected by filtration and crystallized from the appropriate solvent (Table 1).

Alternative Synthesis of 7

Method (A)

A mixture of **4** (10 mmol) and 1-phenylpyrazolidine-3,5-dione (**3**) (10 mmol) with a catalytic amount of piperidine was treated as above to afford **7**, mp 189-190 °C, mixed mp 188-189 °C.

Method (B)

Equimolar amounts (10 mmol) of ninhydrin (**1**) and malononitrile (**2**) and 1-phenylpyrazolidine-3,5-dione (**3**) in ethanol (50 mL) containing a few drops of piperidine was heated under reflux for 4 h. The solid product formed was collected by filtration and recrystallized from EtOH.

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