Amine-Promoted One-Pot, Multicomponent Route to Spiro-Fused-Pyran Derivatives in Aqueous Media

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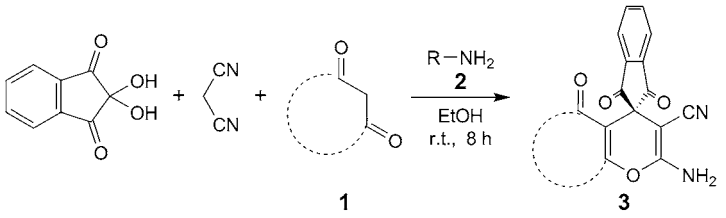
The primary amine-promoted synthesis of spiro-fused-pyran derivatives *via* the three-component reaction of ninhydrin, malononitrile, and cyclic 1,3-diketo compounds is described. This new methodology affords the title compounds in high yields and short time, and with easy workup without chromatographic purification steps or extraction. All structures were confirmed by IR, ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectroscopy. A plausible mechanism for this type of reaction is proposed (*Scheme 2*).

1. Introduction. – The routine procedure for the synthesis of pyrans is the condensation reaction of aldehydes with β-dicarbonyl compounds and alkyl malonates *via* a three-component reaction. Various catalytic systems such as (hexadecyl)(trimethyl)ammonium bromide (HMTAB) [1], (benzyl)(triethyl)ammonium chloride (TEBA) [2], rare-earth perfluorooctanoate ($RE(PFO)_3$) [3], (*S*)-proline [4], amino-functionalized ionic liquids [5], MgO, SiO_2 nanoparticles [6], and silica-bonded propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (SB-DABCO) [7] have been used for the synthesis of pyrans so far. However, most of these methods suffer from several drawbacks such as low yields, long reaction times, harsh reaction conditions, tedious workup, tiresome steps for the preparation of catalyst, application of toxic and expensive catalysts, application of hazardous solvents for the workup, and lack of general applicabilitiy. Therefore, the development of an efficient and more practical procedure for the synthesis of pyrans is of considerable interest.

With this background, and also in the context of our investigations aimed to develop syntheses of biologically important fused polycyclic heterocycles *via* multicomponent reactions [8], herein, we report an efficient method for the synthesis of polyfunctionalized spiro-fused-pyran derivatives **3** *via* the three-component condensation of ninhydrin (=2,2-dihydroxy-2*H*-indene-1,3-dione), malononitrile, and cyclic 1,3-diketo compounds **1** in the presence of aliphatic primary amines **2** as organopromoter (*Scheme 1*).

2. Results and Discussion. – Recently, our research group reported the synthesis of a novel series of polysubstituted aza[3.3.3]propellanes from the reaction of ninhydrin, malononitrile, primary amines, and dialkyl acetylenedicarboxylate or alkyl acetoacetate [9]. We also have investigated synthesis of oxa-thia-aza[3.3.3]propellanes by

Scheme 1. *Synthesis of Spiro-Fused Pyrans* via *an Amine-Promoted Three-Component Reaction*



treatment of ninhydrin, malononitrile, primary amines, and aryl isothiocyanates [10]. However, both of the mentioned syntheses were performed *via* one-pot multicomponent reactions (MCRs).

In connection with these studies, we became interested to know how a *Knoevenagel* adduct generated *in situ* from ninhydrin and malononitrile could be trapped by an enamine '*derived from the various aliphatic primary amines and cyclic 1,3-diketo compounds*' to give a heterocyclic product.

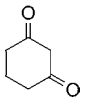
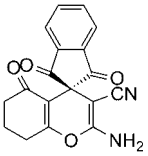
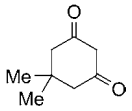
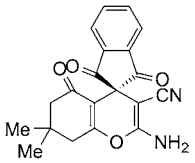
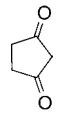
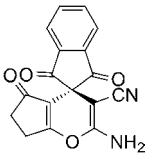
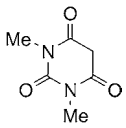
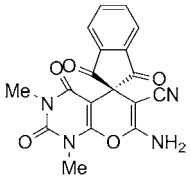
Therefore, we investigated the reaction of ninhydrin, malononitrile, cyclic 1,3-diketo compounds **1**, and an aliphatic primary amine **2** in aqueous EtOH at room temperature. It was interesting to note that neither propellanes [9] nor spiro-compounds [10] were detected at all, while spiro-fused-pyrans **3** were obtained in good yields (*Scheme 1*).

Initially, we explored the reaction of ninhydrin with malononitrile at room temperature in the presence of Et_3N (0.1 mmol) that afforded the expected *Knoevenagel* adduct intermediate. Next, the sequential one-pot addition of cyclic 1,3-diketo compound **1** in the presence of aliphatic primary amine **2** as organocatalyst in EtOH at room temperature successfully gave the spiro-fused pyran derivatives **3** in 62–84% yields. It was found that the reaction using an equimolar amount of primary amine (such as $EtNH_2$, $PrNH_2$, or $BuNH_2$) resulted in a higher yield (*Table*) and shorter time. When this reaction was carried out without a promoter, product **3** was not formed.

The molecular structures of all products **3a**–**3d** were elucidated from their mass spectrometric analyses, and IR, and ^{1}H- and ^{13}C-NMR spectra as described for **3a**. The mass spectrum of **3a** displayed the molecular-ion peak at *m*/*z* 320, which is in agreement with the proposed structure. In the IR spectrum of **3a**, two absorption bands at 3380 and 3271, a sharp band at 2194, and two absorption bands at 1732 and 1666 cm^{-1}, corresponding to NH_2, CN, C=O, and NC=C stretching frequencies, respectively, clearly indicated the most significant functional groups of the product. The ^{1}H-NMR spectrum of **3a** exhibited three broad signals and one sharp *singlet* at δ(H) 1.94, 2.27, 2.70, and 7.64, respectively, attributed to CH_2 and NH_2 groups. Four aromatic H-atoms gave rise to characteristic signals in the aromatic region of the spectrum. Observation of 14 distinct signals in the ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** was in agreement with the proposed structure. In the aliphatic region, there were five characteristic signals at δ(C) 19.7, 26.3, 39.0, 52.0, 53.4, corresponding to CH_2, *C*CN, and C_{spiro}. Resonances due to C=*C*C and CN appeared at δ(C) 110.9 and 116.7, respectively.

We could not establish an exact mechanism for the formation of **3**, however, a plausible way to it is shown in *Scheme 2*. It is assumed that product **3** results from the

Table. *Spiro-Fused-Pyran Derivatives* **3** *Prepared by a Three-Component Reaction*

Cyclic 1,3-diketone **1**	Product **3**	Yield [%]
1a 	**3a** 	81
1b 	**3b** 	86
1c 	**3c** 	82
1b 	**3d** 	75

initial formation of **4** by standard *Knoevenagel* condensation of ninhydrin and malononitrile. Subsequent *Michael*-type addition of the enamine **5** (formed *in situ* by reaction of cyclic 1,3-diketo compounds **1** and primary amine **2**) to **4** yields intermediate **6**, which is transformed to intermediate **7**, by a formal 1,3-H shift. Finally, intermolecular nucleophilic substitution of H_2O on **7**, followed by cyclization and tautomerization, affords the corresponding product **3**. To support the proposed mechanism, first, the *Knoevenagel* adduct **4** was synthesized *via* condensation of ninhydrin and malononitrile, and then reaction of **4** with cyclic 1,3-diketo compounds **1** in the presence of primary amine **2** afforded the corresponding product **3** in 75–86% yield (*Table*).

In summary, we have developed a primary amine-driven three-component condensation reaction using ninhydrin, malononitrile, and cyclic 1,3-diketo compounds that affords corresponding spiro-fused-pyran derivatives. The facile and convenient reaction conditions, the inexpensive reagents, and avoiding expensive transition metal catalysts when compared to existing procedures render this reaction the method of choice for the preparation of substituted spiro-fused-pyran derivatives for both the economic and the environmental reasons.

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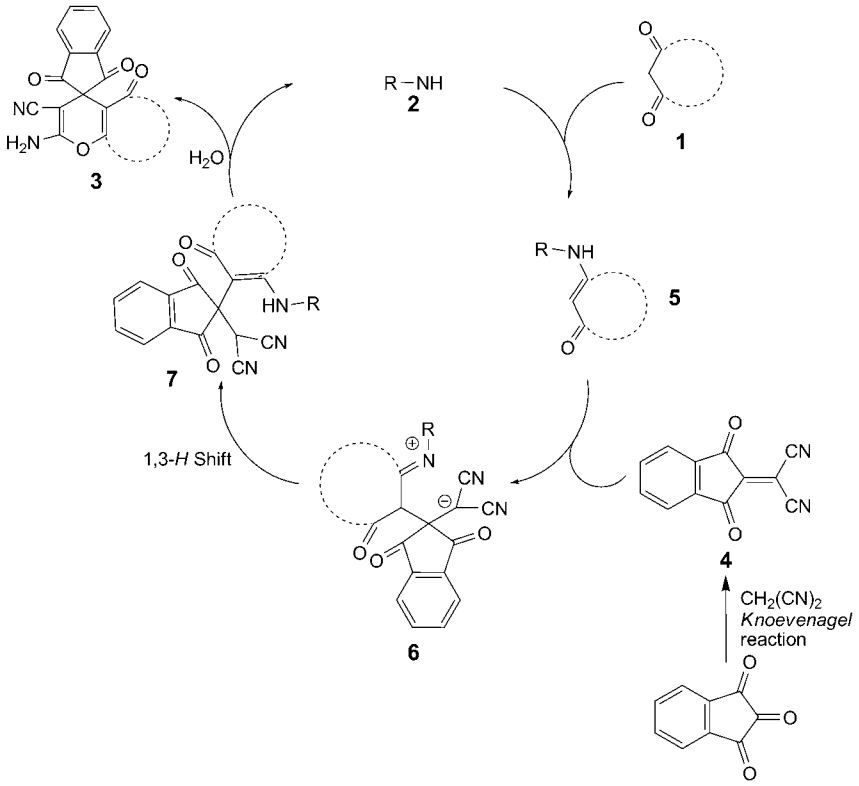
Scheme 2. *Mechanism Proposed for the Synthesis of* **3**



Experimental Part

General. The primary amines, cyclic 1,3-diketo compounds, ninhydrin, and malononitrile, were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. IR Spectra: KBr pellets, *NICOLET FT-IR 100* spectrometer; $\tilde{\nu}$ cm^{-1}. ^{1}H- (400 and 500 MHz) and ^{13}C-NMR (100 and 125 MHz): *Bruker DRX-400 AVANCE* and *Bruker DRX-500 AVANCE* spectrometers. MS: *FINNIGAN-MAT 8430* mass spectrometer; at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN–O–Rapid* analyzer.

General Procedure (exemplified for **3a**). A soln. of ninhydrin (0.16 g, 1 mmol), malononitrile (0.66 g, 1 mmol), and Et_3N (0.01 g, 0.1 mmol) in EtOH (3 ml) was stirred for 1 h, then treated with a soln. of cyclohexane-1,3-dione **1a** (0.112 g, 1 mmol) and $BuNH_2$ (0.073 g, 1 mmol) in EtOH (1 ml). The mixture was stirred at r.t. for 7 h. After completion of the reaction (TLC (AcOEt/hexane 1:2)), the mixture was filtered, and the precipitate was washed with EtOH (5 ml) to afford pure **3a**. All products gave satisfactory spectroscopic data in accordance with the assigned structures.

2-Amino-1′,3′,5,6,7,8-hexahydro-1′,3′,5-trioxospiro[chromene-4,2′-indene]-3-carbonitrile (**3a**). Yield: 0.27 g (81%). Yellow powder. M.p. 180–182° (dec.). IR: 3380 and 3271 (NH_2), 2194 (CN), 1732 (C=O), 1666 (NC=C). ^{1}H-NMR: 1.94 (br. *s*, 2 H); 2.27 (br. *s*, 2 H); 2.70 (br. *s*, 2 H); 7.64 (*s*, 2 H); 7.99 (br. *s*, 2 H); 8.02 (br. *s*, 2 H). ^{13}C-NMR: 19.7; 26.3; 35.2; 50.0; 53.1; 110.9; 116.7; 123.0; 136.53; 140.5; 159.7; 168.2; 196.0; 199.6. EI-MS (70 eV): 338 (1, M^+), 280 (100), 232 (4), 159 (3), 133 (1), 85 (2), 57 (4). Anal. calc. for $C_{18}H_{12}N_2O_4$ (320.30): C 67.50, H 3.78, N 8.75; found C 67.54, H 3.76, N 8.73.

2-Amino-1′,3′,5,6,7,8-hexahydro-7,7-dimethyl-1′,3′,5-trioxospiro[chromene-4,2′-indene]-3-carbonitrile (**3b**). Yield: 0.30 g (86%). Yellow powder. M.p. 300–302° (dec.). IR: 3378 and 3313 (NH_2), 2192 (CN), 1716 (C=O), 1661 (NC=C). ^{1}H-NMR: 1.04 (*s*, 6 H); 2.20 (*s*, 2 H); 2.63 (*s*, 2 H); 7.68 (*s*, 2 H); 7.68–8.06 (*m*, 4 H). ^{13}C-NMR: 27.1; 32.4; 48.9; 54.1; 53.1; 110.0; 116.9; 123.1; 136.6; 140.5; 159.8; 166.5; 196.0; 199.6. EI-MS (70 eV): 348 (77, M^+), 264 (87), 236 (41), 104 (39), 83 (100), 69 (46), 55 (81). Anal. calc. for $C_{20}H_{16}N_2O_4$ (348.35): C 68.96, H 4.63, N 8.04; found C 68.89, H 4.60, N 8.15.

*2-Amino-1′,3′,6,7-tetrahydro-1′,3′,5-trioxo-5*H*-spiro[cyclopenta[*b*]pyran-4,2′-indene]-3-carbonitrile* (**3c**). Yield: 0.25 g (82%). Yellow powder. M.p. 294–296° (dec.). IR: 3362 and 3300 (NH_2), 2198 (CN), 1715 (C=O), 1675 (NC=C). ^{1}H-NMR: 2.51 (br. *s*, 2 H); 2.92 (br. *s*, 2 H); 7.92 (*s*, 2 H); 8.10–8.11 (*m*, 4 H). ^{13}C-NMR: 25.4; 32.8; 50.8; 52.3; 113.4; 117.0; 123.5; 137.4; 140.8; 161.5; 179.5; 198.7; 200.3. EI-MS (70 eV): 306 (71, M^+), 194 (43), 139 (40), 104 (39), 76 (100), 50 (49). Anal. calc. for $C_{17}H_{10}N_2O_4$ (306.27): C 66.67, H 3.29, N 9.15; found C 66.65, H 3.31, N 9.16.

*7′-Amino-1,1′,2′,3,3′,4′-hexahydro-1′,3′-dimethyl-1,2′,3,4′-tetraoxospiro[indene-2,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* (**3d**). Yield: 0.27 g (75%). Yellow powder. M.p. 247–249° (dec.). IR: 3385 and 3301 (NH_2), 2197 (CN), 1706 (C=O). ^{1}H-NMR: 3.01 (*s*, 3 H); 3.38 (*s*, 3 H); 8.01 (*s*, 2 H); 8.07–8.06 (*m*, 4 H). ^{13}C-NMR: 27.7; 29.4; 54.1; 53.1; 116.3; 123.2; 130.1; 136.9; 140.4; 149.5; 153.0; 159.4; 167.4; 199.7. EI-MS (70 eV): 364 (2, M^+), 264 (3), 208 (22), 152 (34), 104 (42), 83 (68), 57 (100). Anal. calc. for $C_{18}H_{12}N_4O_5$ (364.31): C 59.34, H 3.32, N 15.38; found C 60.10, H 3.25, N 16.11.

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