One-Pot Synthesis of 4-(2,3-Dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)-Substituted 1-Aryl-1*H*-pyrazole-3-carboxylates *via* a Tandem Three-Component Reaction

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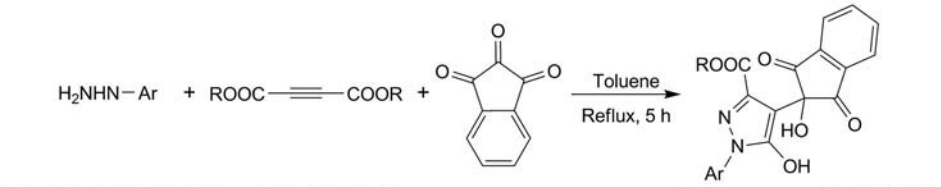
The hitherto unreported, highly functionalized 1*H*-pyrazole-3-carboxylates **3** have been synthesized in good yields *via* a one-pot three-component domino reaction of phenylhydrazines, dialkyl acetylenedicarboxylates, and ninhydrin under mild conditions for the first time. No co-catalyst or activator is required for this multicomponent reaction, and the reaction is, from an experimental point of view, simple to perform (*Scheme 1*). The structures of compounds **3** were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this type of cyclization/addition reaction is proposed (*Scheme 2*).

Introduction. – The synthesis of pyrazole derivatives has received considerable attention due to their broad spectrum of biological activities [1]. Although there are many reports related to the synthesis of pyrazoles in the literature, a search revealed that the synthesis of pyrazole derivatives with an indene moiety have not been described.

Results and Discussion. – As part of our program aimed at developing new routes for the preparation of biologically active N-containing heterocylic compounds [2], we describe an efficient synthesis of fully substituted 4-(1*H*-inden-2-yl)-1*H*-pyrazole-3-carboxylates *via* a new one-pot three-component reaction. Thus, the reaction between phenylhydrazines **1**, dialkyl acetylenedicarboxylates **2**, and ninhydrin in dry toluene at reflux temperature leads to the formation of the 1*H*-pyrazole-3-carboxylates **3** in good yields (*Scheme 1*).

The molecular structures of compounds **3** were elucidated using their elemental analysis, MS, IR, and high-field ^{1}H- and ^{13}C-NMR spectra as described for **3a** in the *Exper. Part*. The mass spectrum of **3a** exhibited the molecular-ion peak at *m*/*z* 378, which is in agreement with the proposed structure. The IR spectrum of **3a** showed absorption bands at 3342 and 3200 cm^{-1} due to stretching frequencies of two OH groups. Absorption bands at 1727 and 1600 cm^{-1} are due to the C=O and COOMe groups. The ^{1}H-NMR spectrum of **3a** showed three *singlet*s for the MeO and the two OH groups (δ(H) 2.49, 3.34, and 8.93), and the aromatic moieties gave rise to several signals in the aromatic region of the spectrum (δ(H) 7.43–8.05). The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 14 distinct resonances in agreement with the suggested structure.

Scheme 1. *Synthesis of Highly Substituted 1*H*-Pyrazole-3-carboxylates* **3**

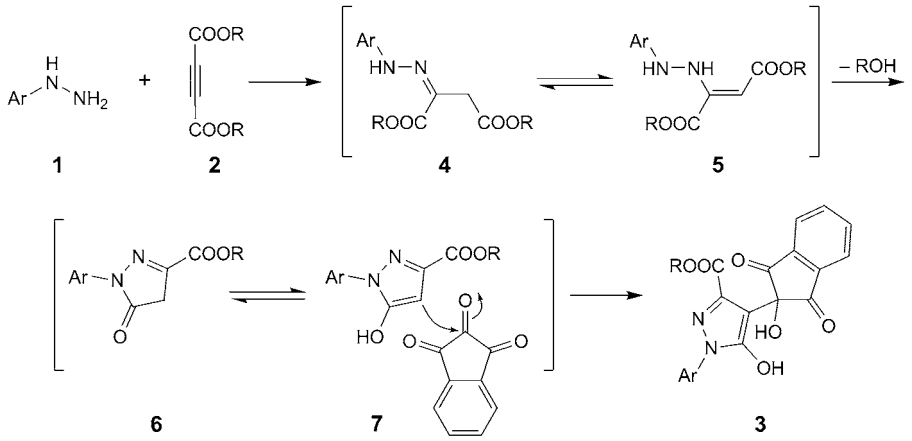


	Ar	R	Yield [%]
3a	Ph	Me	80
3b	Ph	Et	75
3c	Ph	^{i}Pr	83
3d	2,4-$(NO_2)_2$–C_6H_3	Me	78
3e	2,4-$(NO_2)_2$–C_6H_3	Et	81

A tentative mechanistic rationale illustrating a probable route of the reaction is shown in *Scheme 2*. We assume that the initial step is a nucleophilic addition of **1** to **2**, resulting in the formation of intermediate **4**. Then, **4** cyclizes to the 4,5-dihydro-5-oxo-1*H*-pyrazole-3-carboxylate **6** that undergoes successive keto-enol tautomerization, followed by nucleophilic addition of the enol group to ninhydrin, resulting in the formation of product **3** (*Scheme 2*).

In conclusion, we have designed a versatile, convenient, and efficient approach to construct several 1*H*-pyrazole-3-carboxylates *via* a three-component one-pot reaction of phenylhydrazines, dialkyl acetylenedicarboxylates, and ninhydrin for the first time. The advantages of operational simplicity, economic viability, generality, atom-economy, together with ecologically benign nature make this protocol a very efficient alternative to literature methods, so that a wide range of compounds of type **3** could be easily prepared for biological assays.

Scheme 2. *A Plausible Mechanism for the Formation of* **3**



Experimental Part

General. Phenylhydrazine, 2,4-dinitrophenylhydrazine, dialkyl acetylenedicarboxylate, and ninhydrin were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer, absorbances reported in cm^{-1}. ^1H- and ^{13}C-NMR spectra: in $CDCl_3$ soln., *Bruker DRX-500 AVANCE* spectrometer at 500.13 and 125.8 MHz, resp. EI-MS: *FINNIGAN MATT-8430* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer.

General Procedure. Formation of **3a.** A soln. of phenylhydrazine (0.11 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) in toluene (5 ml) was magnetically stirred for 4 h under reflux. Then, a soln. of ninhydrin (0.16 g, 1 mmol) in toluene (3 ml) was added dropwise, and the mixture was refluxed for 1 h. After completion, the mixture was filtered and the precipitate washed with cold toluene to afford the pure product **3a**.

*Methyl 4-(2,3-Dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate* (**3a**). Yield 0.30 g (80%). Yellow crystals. M.p. 200°. IR: 3342 (OH), 3200 (OH), 1727 (C=O), 1600 (COOMe). ^1H-NMR: 2.49 (*s*, OH); 3.34 (*s*, MeO); 7.43 (*t*, *J* = 8.6, 1 arom. H); 7.53 – 7.57 (*m*, 2 arom. H); 7.69 – 7.74 (*m*, 2 arom. H); 8.04 (*d*, *J* = 8, 2 arom. H), 8.05 (*d*, *J* = 8, 2 arom. H); 8.93 (*s*, OH). ^{13}C-NMR: 51.3; 74.6; 98.6; 123.0; 123.8; 127.6; 129.1; 136.3; 137.5; 138.2; 140.1; 153.0; 162.2; 197.1. EI-MS: 378 (8, M^+), 104 (67), 76 (100), 65 (25). Anal. calc. for $C_{20}H_{14}N_2O_6$ (378.34): C 63.49, H 3.73, N 7.40; found: C 63.33, H 3.61, N 7.52.

*Ethyl 4-(2,3-Dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate* (**3b**). Yield 0.29 g (75%). Yellow crystals. M.p. 270°. IR: 3221 (OH), 3210 (OH), 1712 (C=O), 1600 (COOEt). ^1H-NMR: 0.95 (br. *t*, *Me*CH_2); 2.28 (*s*, OH); 3.81 (br. *q*, MeCH_2); 7.15 (*s*, OH); 7.55 (*t*, *J* = 8.6, 1 arom. H); 7.69 – 7.71 (*m*, 2 arom. H); 7.70 – 7.73 (*m*, 2 arom. H); 8.04 (br. *m*, 4 arom. H). ^{13}C-NMR: 13.7; 60.4; 74.6; 98.5; 123.1; 123.8; 127.6; 128.8; 129.1; 136.3; 137.5; 140.2; 153.0; 161.8; 197.1. EI-MS: 232 (50), 132 (33), 104 (100), 76 (83), 50 (33). Anal. calc. for $C_{21}H_{16}N_2O_6$ (392.36): C 64.28, H 4.11, N 7.14; found: C 64.19, H 4.11, N 7.19.

*1-Methylethyl-2-yl 4-(2,3-Dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)-5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate* (**3c**). Yield 0.33 g (83%). Yellow crystals. M.p. 292°. IR: 3429 (OH), 3277 (OH), 1721 (C=O), 1600 (COOPr). ^1H-NMR: 1.23 (br. *d*, 2 Me); 2.9 (*s*, OH); 4.7 – 4.11 (*m*, Me_2CH); 7.27 (br. *q*, 1 arom. H); 7.28 – 7.32 (*m*, 2 arom. H); 7.40 – 7.44 (*m*, 2 arom. H); 7.87 (*s*, OH); 7.99 – 8.03 (*m*, 4 arom. H). ^{13}C-NMR: 21.6; 68.2; 69.6; 77.2; 122.1; 122.9; 125.3; 129.2; 130.3; 136.3; 137.4; 140.8; 143.1; 162.8; 196.6. EI-MS: 132 (25), 104 (83), 76 (100), 61 (8). Anal. calc. for $C_{22}H_{18}N_2O_6$ (406.39): C 65.02, H 4.46, N 6.89; found: C 65.09, H 4.39, N 6.71.

*Methyl 4-(2,3-Dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)-1-(2,4-dinitrophenyl)-5-hydroxy-1*H*-pyrazole-3-carboxylate* (**3d**). Yield 0.36 g (78%). Yellow crystals. M.p. 240°. IR: 3399 (OH), 3236 (OH), 1724 (C=O), 1600 (COOMe), 1506, 1330 (NO_2). ^1H-NMR: 2.27 (*s*, OH); 3.36 (*s*, MeO); 6.48 (*s*, 1 arom. H); 7.26 (br. *d*, 1 arom. H); 7.37 (br. *d*, 2 arom. H); 7.53 (*d*, *J* = 5, 2 arom. H); 8.43 (br. *d*, 1 arom. H); 8.75 (*s*, OH). ^{13}C-NMR: 57.2; 84.2; 87.59; 122.8; 125.6; 128.1; 131.2; 137.0; 137.1; 137.2; 137.3; 139.8; 144.1; 149.4; 154.78; 196.9. EI-MS: 468 (4, M^+), 368 (50), 83 (67), 57 (100). Anal. calc. for $C_{20}H_{12}N_4O_{10}$ (468.33): C 51.28, H 2.59, N 11.96; found: C 51.34, H 2.55, N 11.88.

*Ethyl 4-(2,3-Dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)-1-(2,4-dinitrophenyl)-5-hydroxy-1*H*-pyrazole-3-carboxylate* (**3e**). Yield 0.39 g (81%). Yellow crystals. M.p. 250°. IR: 3460 (OH), 3254 (OH), 1713 (C=O), 1603 (COOMe), 1509, 1333 (NO_2). ^1H-NMR: 1.29 (*s*, *Me*CH_2); 2.49 (*s*, OH); 3.31 (br. *q*, MeCH_2); 6.81 (*s*, 1 arom. H); 7.24 (br. *d*, 1 arom. H); 7.40 (br. *d*, 2 arom. H); 7.53 (br. *d*, 2 arom. H); 8.17 (br. *d*, 1 arom. H); 8.83 (*s*, OH). ^{13}C-NMR: 13.9; 60.9; 81.0; 87.6; 123.1; 125.2; 128.1; 128.7; 128.8; 129.5; 129.9; 135.9; 137.4; 138.4; 138.6; 149.9; 196.9. EI-MS: 482 (9, M^+), 368 (55), 83 (61), 57 (100). Anal. calc. for $C_{21}H_{14}N_4O_{10}$ (482.36): C 52.29, H 2.93, N 11.62; found: C 52.33, H 11.5, N 11.52.

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