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One-pot synthesis of pyrazole-5-carboxylates by cyclization of hydrazone 1,4-dianions with diethyl oxalate

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Abstract—The cyclization of hydrazone dianions with diethyl oxalate afforded pyrazole-5-carboxylates.

Pyrazole-5-carboxylic acid derivatives are of considerable pharmacological relevance and also represent useful synthetic building blocks in organic and medicinal chemistry. For example, it has been recently demonstrated that pyrazole-5-carboxylic acids represent partial agonists for the nicotinic acid receptor.[1] Pyrazolo[1,5-*c*]-quinazoline-2-carboxylates, which can be regarded as tricyclic pyrazole-5-carboxylate derivatives, act as excitatory amino acid antagonists (Fig. 1).[2] Bis(benzo[*g*]indazole-3-carboxamides) exhibit antiproliferative activity against various cancer cell lines.[3] General and classical syntheses of pyrazoles rely on the 1,3-dipolar cycloaddition of diazoalkanes with alkynes and related [3+2] cycloadditions.[4] The cyclization of 1,3-diketones with hydrazine also constitutes an important approach to pyrazoles.[5] In addition, the Michael reaction of hydrazines with α,β-unsaturated ketones is widely used.[6] Pyrazoles have been prepared by cyclization[7] of hydrazone dianions with esters,[8] acid chlorides[9] and nitriles.[10] Pyrazolines are available by cyclization of hydrazone dianions with α-haloketones.[11] Recently, an efficient approach to pyrazole carboxylates from Weinreb amides, hydrazines and propiolates has been reported.[12] We reported the synthesis of 1,2-oxazines and oxazolo[3,4-*b*]pyridazin-7-ones by cyclization of oxime and hydrazone dianions with epibromohydrin, respectively.[13] We also reported the synthesis of isoxazole-5-carboxylates by cyclization of oxime dianions with diethyl oxalate.[14] Herein, we report a new and convenient approach to pyrazole-5-carboxylates by what are, to the best of our knowledge, the first one-pot cyclizations of hydrazone dianions with diethyl oxalate.

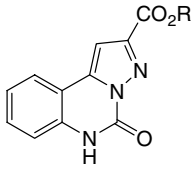

Figure 1.

The reaction of diethyl oxalate (**2**) with the dianion of acetophenone hydrazone **1a**, generated by *n*-butyllithium (2.5 equiv), and subsequent aqueous work-up resulted in the formation of ethyl *N*-ethoxycarbonyl-4,5-dihydropyrazol-5-ol-5-carboxylate. Stirring of a toluene solution of the latter in the presence of *p*-toluenesulfonic acid (PTSA) under reflux resulted in dehydration and cleavage of the ester protective group to give the pyrazole-5-carboxylate **3a** (Scheme 1).[15] Based on these findings, we successfully developed a one-pot procedure for the synthesis of **3a**. Best results were obtained when the reaction mixture was allowed to slowly warm from −78 to 20 °C. The solvent was removed in vacuo without aqueous work-up and a toluene solution of the residue was simply refluxed in the presence of PTSA for 10 h. Notably, the use of diethyl oxalate proved to be important; oxalyl chloride or ethyl 2-chloro-2-oxoacetate gave unsatisfactory results, due to polymerization. The use of the hydrazone containing a tosyl protective group was not successful (formation of complex mixtures). The formation of **3a** can be

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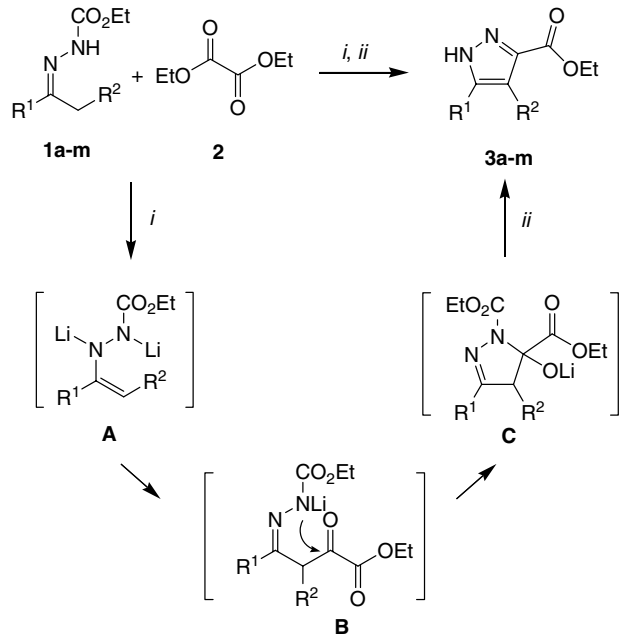


Scheme 1. Synthesis of pyrazole-5-carboxylates **3a**–**m**. Reagents and conditions: (i) (1) *n*-BuLi (2.5 equiv), THF, 45 min, −78 °C; (2) 15 min, 20 °C; (3) **2**, −78 → 20 °C, 16 h; (ii) *p*-TsOH (4.0 equiv), toluene, reflux, 10 h.

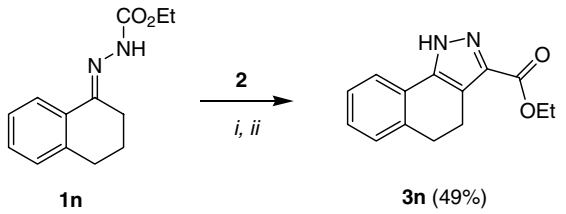
explained by attack of the carbon atom of the dianion (intermediate **A**) onto the ester group to give intermediate **B**, subsequent cyclization by attack of the nitrogen atom onto the keto group to give intermediate **C** and subsequent aromatization (Scheme 1).

The one-pot procedure was successfully applied to the synthesis of the aryl-substituted pyrazole-5-carboxylates **3a**–**j** which were isolated in moderate to good yields (Table 1). The cyclization of **2** with the dilithiated hydrazone of *p*-nitroacetophenone was unsuccessful. The cyclization of diethyl oxalate with the dianions of hydrazones **1k** and **1l**, prepared from 3-methylbutane-2-one and pentane-2-one, afforded alkyl-substituted pyrazole-5-carboxylates **3k** and **3l** in good yields, respectively. Pyrazole-5-carboxylate **3m**, containing a phenyl and a methyl substituent, was prepared by cyclization

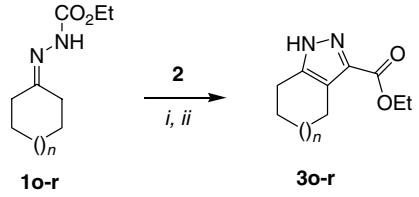
Table 1. Yields of **3a**–**m**

3	R^1	R^2	% (3)[a]
a	C_6H_5	H	53
b	4-MeC_6H_4	H	57
c	3-MeC_6H_4	H	61
d	2-MeC_6H_4	H	41
e	4-(MeO)C_6H_4	H	45
f	2-(MeO)C_6H_4	H	41
g	1-Naphthyl	H	45
h	2-Naphthyl	H	38
i	4-ClC_6H_4	H	42
j	4-FC_6H_4	H	45
k	*i*-Pr	H	69
l	*n*-Pr	H	72
m	C_6H_5	Me	62

[a] Yields of isolated products.



Scheme 2. Synthesis of **3n**. Reagents and conditions: (i) (1) *n*-BuLi (2.5 equiv), 1 h, −78 °C; (2) 10 min, 20 °C; (3) **2**, −78 → 20 °C, 16 h; (ii) *p*-TsOH (4.0 equiv), toluene, reflux, 6 h.



Scheme 3. Synthesis of **3o**–**r**. Reagents and conditions: (i) (1) *n*-BuLi (2.5 equiv), 1 h, −78 °C; (2) 10 min, 20 °C; (3) **2**, −78 → 20 °C, 16 h; (ii) concd H_2SO_4, toluene, reflux, 8 h.

Table 2. Products and yields

3	*n*	% (3)[a]
o	1	43
p	2	40
q	3	38
r	7	31

[a] Yields of isolated products.

of **2** with hydrazone **1m** (available from propiophenone). The structure of **3b** was independently confirmed by crystal structure analysis.[16]

The cyclization of the dianion of tetralone hydrazone **1n** with diethyl oxalate afforded the tricyclic pyrazole **3n** (Scheme 2).

The cyclization of diethyl oxalate with the dianion of cyclohexanone hydrazone gave 4,5,6,7-tetrahydro-1*H*-indazole **3o** (Scheme 3, Table 2). Likewise, 5,7-, 5,8- and 5,12-bicyclic pyrazoles **3p**–**r** were prepared from the corresponding hydrazones **1p**–**r**. The reaction of diethyl oxalate with the hydrazones of cyclopentanone and *N*-Boc-4-piperidone resulted in the formation of complex mixtures.

In conclusion, we have reported a convenient and regioselective synthesis of pyrazole-5-carboxylates by cyclization of hydrazone dianions with diethyl oxalate.

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15. *Typical procedure for the synthesis of pyrazole-5-carboxylates* **3**: To a THF solution of hydrazone **1b** (2.0 mmol, 0.46 g) was added *n*-butyllithium (2 mL, 2.5 M solution in hexane) at −78 °C. After stirring for 45 min at −78 °C, the mixture was stirred for 15 min at 20 °C and, subsequently, diethyloxalate (2.2 mmol) was added at −78 °C. After warming of the reaction mixture to 20 °C within 16 h, the solvent (THF) was removed in vacuo. To the residue were added *p*-TsOH (8.0 mmol, 1.52 g) and 30 mL of toluene. The mixture was stirred under reflux for 8 h. After cooling to 20 °C, a saturated solution (20 mL) of $NaHCO_3$ was added and the mixture was stirred for 15 min at 20 °C. The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc = 3:1) to give **3b** (57%, 262 mg) as a colourless solid, mp 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.21$ (t, $^3J = 7.2$ Hz, 3H, OCH_2CH_3), 2.37 (s, 3H, CH_3), 4.25 (q, $^3J = 7.2$ Hz, 2H, OCH_2CH_3), 6.95 (s, 1H, C*H*), 7.18 (d, 2H, Ar*H*), 7.59 (d, 1H, Ar*H*), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.08$ (CH_2CH_3), 19.34 (CH_3), 58.84 (OCH_2CH_3), 102.7 (CH), 123.52, 123.52, 127.48, 127.48 (CH, ArH), 125.06, 136.47 (2C, Ar), 139.18, 145.12 (C, pyrazole), 159.30 (CO). IR (KBr, cm^{-1}): $\tilde{\nu} = 3215$ (w), 2922 (w), 1728 (s), 1412 (w), 1242 (s), 1131 (s), 986 (m), 816 (m), 782 (w), 506 (w). MS (EI, 70 eV): m/z (%) = 230 (M^+, 100), 185 (13), 158 (9), 128 (86), 131 (8), 69 (21), 57 (8). HRMS (EI, 70 eV): calcd for $C_{13}H_{14}O_2N_2$ (M^+): 230.1139; found, 230.1134.
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