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Reactions between isocyanides and dialkyl acetylenedicarboxylates in the presence of 1,2-diacylhydrazines. One-pot synthesis of highly functionalized pyrazoles

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Abstract—The reactive 1:1 intermediate produced in the reaction between isocyanides and dialkyl acetylenedicarboxylates was trapped with 1,2-diacylhydrazines to yield highly functionalized pyrazoles in good yields.

Nitrogen heterocycles are of synthetic interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[1] The interest in five-membered systems with two adjacent nitrogen atoms stems from the occurrence of saturated and partially saturated pyrazoles in biologically active compounds and natural products.[2,3] Some examples are used in supramolecular and polymer chemistry, pharmaceuticals, agrochemicals, food, cosmetic colorings, complexing agents for the synthesis of hydrogenation catalysts, and UV stabilizers, whilst some have liquid crystal properties.[3–9]

By far the most common synthetic methods for the preparation of pyrazole ring systems involve ring synthesis from non-heterocyclic precursors by formation of one bond (between the two heteroatoms [N–N], adjacent to a heteroatom [C–N], or β to a heteroatom [C–C]), and by formation of two bonds from [4+1] atom fragments ([CCNN+C] or [CCCN+N]), or from [3+2] atom fragments ([CCC+NN] or [CNN+CC]), and also by transformation of another ring.[3–16] To date, we know of no published report concerning the synthesis of pyrazole ring systems by formation of three new bonds. In this letter, we report a facile synthesis of highly functionalized pyrazoles by formation of three new bonds from [1+2+2] atom fragments [C+CC+NN]. Thus, isocyanides **1** and dialkyl acetylenedicarboxylates **2** in the presence of 1,2-diacylhydrazines **3** undergo a smooth 1:1:1 addition reaction in acetone at ambient temperature, to produce the highly functionalized pyrazoles **4** in 68–85% yields (Scheme 1).

The structure of **4a** was assigned on the basis of elemental analysis, IR, high-field ^{1}H and ^{13}C NMR spectra, and mass spectrometric data.[17] The mass spectrum of **4a** displayed the molecular ion (M^{+}) peak at 427 *m/z*, which is consistent with the 1:1:1 adduct of cyclohexyl isocyanide, dimethyl acetylenedicarboxylate, and diethyl hydrazine-1,2-dicarboxylate. The ^{1}H NMR spectrum of **4a** exhibited three sharp singlets readily recognized as arising from the two methoxy ($\delta = 3.53$ and 3.54 ppm) and methine ($\delta = 5.20$ ppm) protons. A broad signal ($\delta = 7.17$ ppm) corresponded to the NH proton, along with the characteristic multiplets with appropriate chemical shifts and coupling constants for the 11 protons of the cyclohexyl moiety and 10 protons of the two ethoxy groups. The proton decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances in agreement with the proposed structure.[17]

Although we have not established the mechanism of the reaction between isocyanides and acetylenic esters in the presence of hydrazine derivatives **3** in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,[18–22] it is reasonable to assume that the functionalized pyrazoles **4** may result from initial addition of the isocyanide to the acetylenic ester and subsequent

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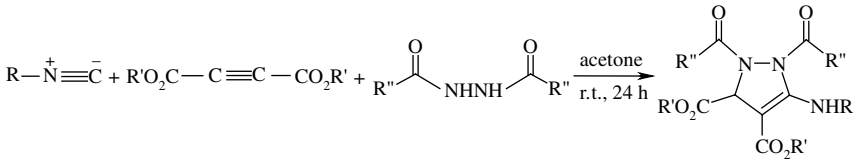


1 **2** **3** **4**

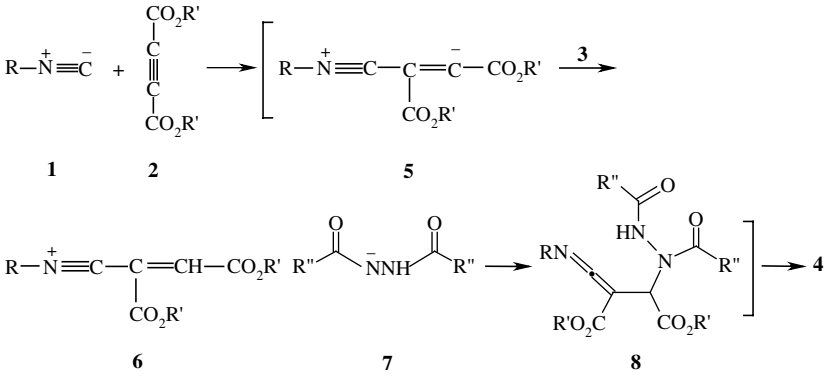
1	R
a	Cyclohexyl
b	^{t}Bu

2	R′
a	Me
b	Et

3	R″
a	OEt
b	Me

4	R	R′	R″	% Yield
a	Cyclohexyl	Me	OEt	82
b	Cyclohexyl	Me	Me	85
c	Cyclohexyl	Et	OEt	68
d	Cyclohexyl	Et	Me	72
e	^{t}Bu	Me	OEt	80
f	^{t}Bu	Me	Me	84
g	^{t}Bu	Et	OEt	70
h	^{t}Bu	Et	Me	75

Scheme 1.



1 **2** **5** **6** **7** **8**

Scheme 2.

protonation of the 1:1 adduct **5** by compound **3**, followed by attack of the anion of the NH-acid **7** on the positively charged ion **6** to form the ketenimine **8**. The ketenimine intermediate **8** can then isomerize to produce the heterocyclic system **4**.

In summary, the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of acyl hydrazines provides a simple one-pot entry into the synthesis of polyfunctional pyrazoles of potential synthetic and pharmaceutical interest. The present method carries the advantage of being performed under neutral conditions and requires no activation or modification of the educts.

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17. The procedure for the preparation of 1,2-diethyl-3,4-dimethyl 5-(cyclohexylamino)-1*H*-pyrazole-1,2,3,4(3*H*)-tetracarboxylate **4a** is described as an example. To a magnetically stirred solution of diethyl hydrazine-1,2-dicarboxylate (0.176 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in acetone (6 mL) was added dropwise a solution of cyclohexyl isocyanide (0.109 g, 1 mmol) in acetone (2 mL) at −5 °C for 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. The solvent was removed and the product was purified by column chromatography using hexane–ethyl acetate (1:1) as eluent. The solvent was removed and the product was obtained as a colorless oil 0.35 g, yield 82%. IR (KBr) (ν_{max}/cm^{-1}): 3290 (NH), 1739, and 1668 (C=O), 1611, 1451, 1368, 1300, 1256, 1162, 1095, 1020, 784. MS, *m*/*z* (%): 428 (M^++1, 3), 427 (M^+, 1), 396 (2), 368 (40), 324 (10), 296 (100), 268 (8), 252 (12), 224 (20), 170 (10), 138 (29), 110 (23), 83 (7), 55 (10), 41 (8), 29 (38). Anal. Calcd for $C_{19}H_{29}N_3O_8$ (427.45): C, 53.39; H, 6.84; N, 9.83. Found: C, 53.5; H, 6.8; N, 9.7. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.14 and 1.17 (6H, 2t, $J = 7.1$ Hz, $2OCH_2CH_3$), 1.15–1.95 [10H, m, $CH(CH_2)_5$], 3.53 and 3.54 (6H, 2s, $2OCH_3$), 4.07–4.10 [2H: q ($J = 7.1$ Hz) and 1H: m, OCH_2CH_3, and $NHCH$], 4.12 and 4.19 (2H, 2dq, ABX_3 system, $^2J = 10.6$ Hz and $^3J = 7.1$ Hz, $OCH_AH_BCH_3$), 5.20 (1H, s, NCH), 7.17 (1H, br, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.32 and 14.41 ($2OCH_2CH_3$), 24.32, 24.60, 25.49, 32.62, and 34.46 (5 CH_2), 50.79 and 52.38 ($2OCH_3$), 54.81 (NHCH), 62.26 (NCH), 63.38 and 63.85 ($2OCH_2CH_3$), 82.71 ($N_2C=C$), 154.18, 154.20, and 156.47 ($N_2C=C$ and 2ONC=O), 165.74 and 170.02 (2C=O, ester).
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