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The Reaction of 5-Amino-3-(cyanomethyl)-1H-pyrazol-4-carbonitrile with beta-Cycloketols †

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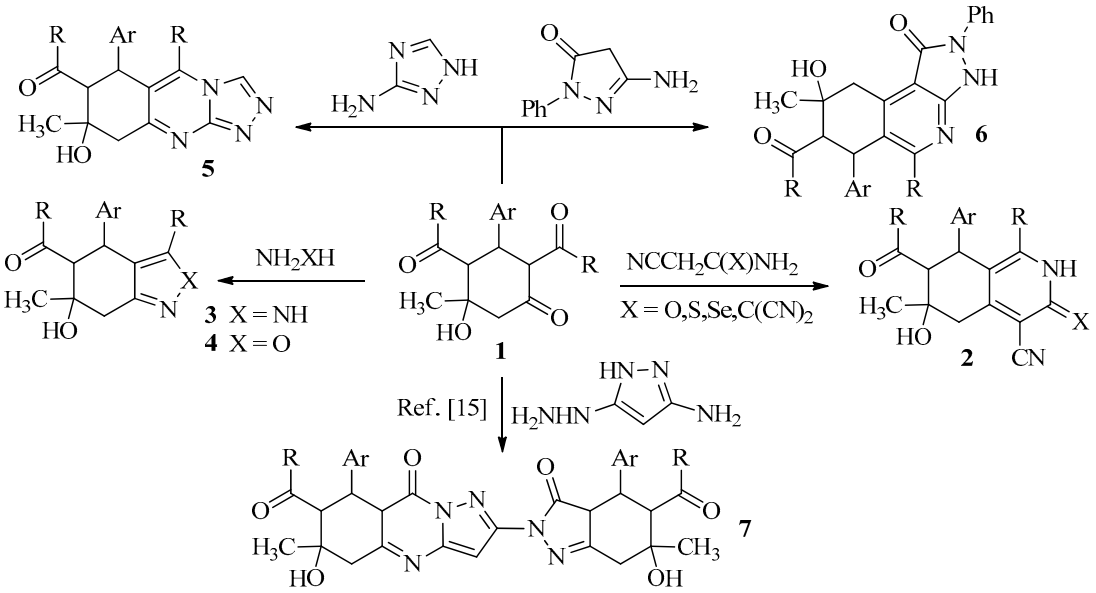
Abstract: The reaction of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile with 3-aryl-2,4-di (ethoxycarbonyl)-5-hydroxy-5-methylcyclohexanones in boiling acetic acid leads to the formation of new 4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolines. The mechanism is discussed. The structure of the products was confirmed by means of ^{1}H и ^{13}C (DEPTQ) NMR, as well as 2D NMR (NOESY, ^{1}H–^{13}C HSQC, HMBC).

Keywords: β-cycloketols; aminopyrazole; cyclocondensation; pyrazolo[1,5-a]quinazoline

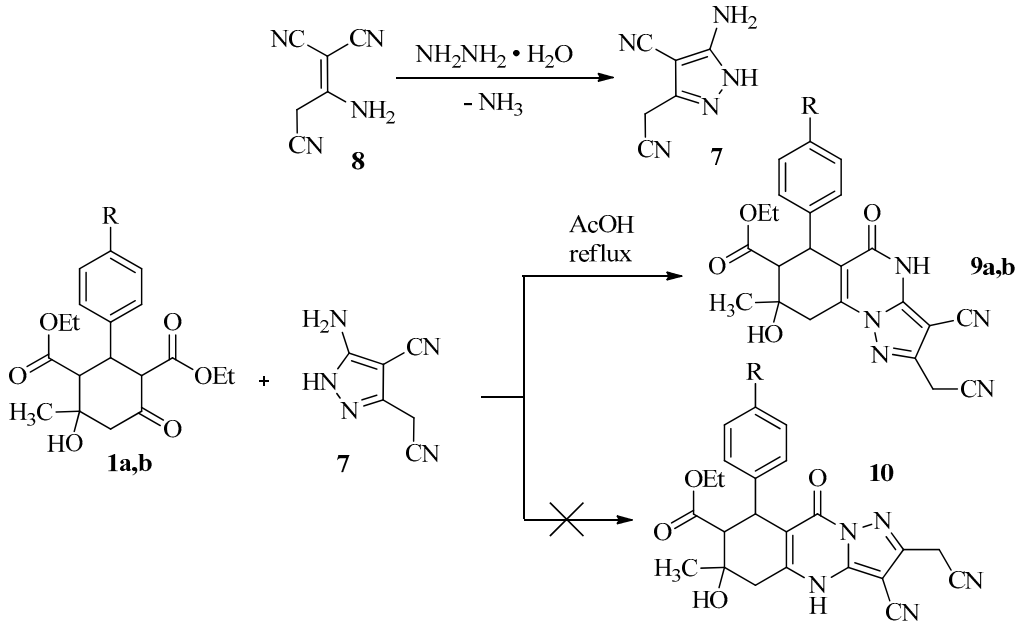
β-Cycloketols (2,4-di-(RC(O))-3-aryl-5-hydroxy-5-methylcyclohexano-nes) **1** which are easily accessible by the reaction of aromatic aldehydes with 1,3-dicarbonyls $RC(O)CH_2C(O)CH_3$, were recognized as promising reagents for organic synthesis. According to the literature [1,2], β-cycloketols are good precursors of a variety of carbocycles, enamine ketones and esters, etc. However, the heterocyclization reactions of β-cycloketols are not well studied. Thus, the literature describes the preparation of isoquinolines **2** [3–7], indazoles **3** [8–10], benzo[c]isoxazoles **4** [9,10], [1,2,4]triazolo[3–b]quinazolines **5** [11] and pyrazolo[3-c]isoquinolines **6** [12] (Scheme 1) by reactions of beta-cycloketols with various 1,2- and 1,3-dinucleophilic agents. Despite the large attention paid to reactions of aminoazoles with 1,3-dielectrophilic agents (see reviews [13,14]), only a few examples of reactions involving β-cycloketols were found in the literature. Thus, the reaction of cycloketols with 5-amino-3-hydrazinopiazole was reported to give 6,7,8,8a-tetrahydropyrazolo[5,1-b]quinazolin-9(5H)-one **7** [15] (Scheme 1).



Scheme 1. Heterocyclization reactions of β-cycloketols

In continuation of our studies in the chemistry of the malononitrile dimer [16–19], herein we report the reaction of 3-aryl-5-hydroxy-5-methyl-2,4-di (ethoxycarbonyl)cyclohexanones **1a,b** with 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **7** (Scheme 2). Aminopyrazole **7** can be easily prepared by the reaction of malononitrile dimer **8** with hydrazine hydrate [20].

We found that cycloketols **1a,b** react with 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **7** in boiling AcOH to give previously not described 4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolines **9a,b** in low yields (15–22%). The structure of compounds **9a,b** was confirmed by means of IR spectrophotometry, ^{1}H and ^{13}C NMR (DEPTQ), and by the results of 2D NMR experiments (NOESY, ^{1}H–^{13}C HSQC, HMBC) for **9a** (Figures 1–3). Presumably, the reaction proceeds through the initial attack of pyrazole NH group at C-1 followed by intramolecular attack of the NH_2 group to ester carbonyl.



1, 9: **a** R = OMe; **b** R = NO_2.

Scheme 2. The reaction of cycloketols **1a,b** with 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **7**.

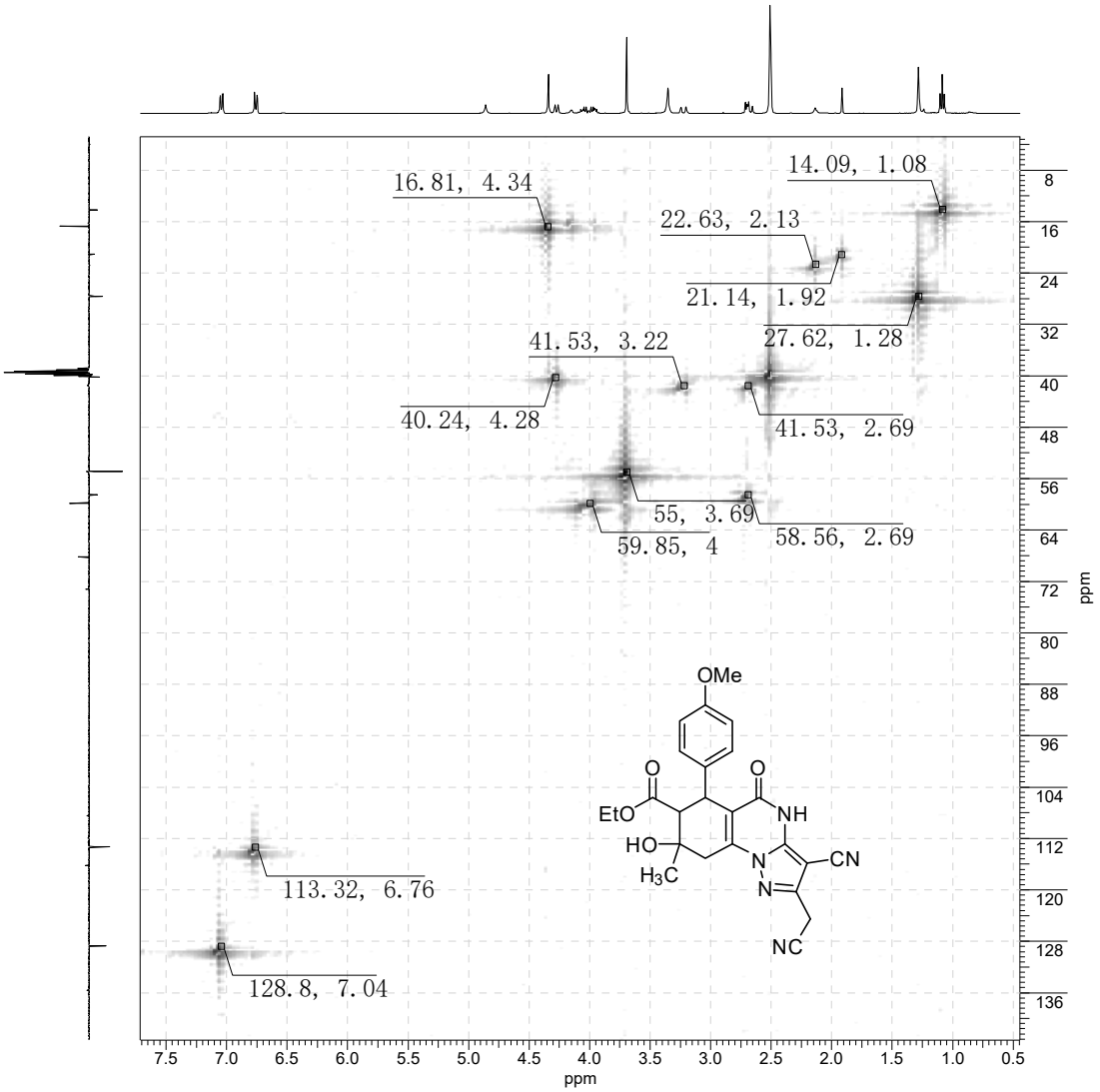


Figure 1. HSQC ^{1}H–^{13}C NMR (400/101 MHz, DMSO-d_6) spectrum of **9a**.

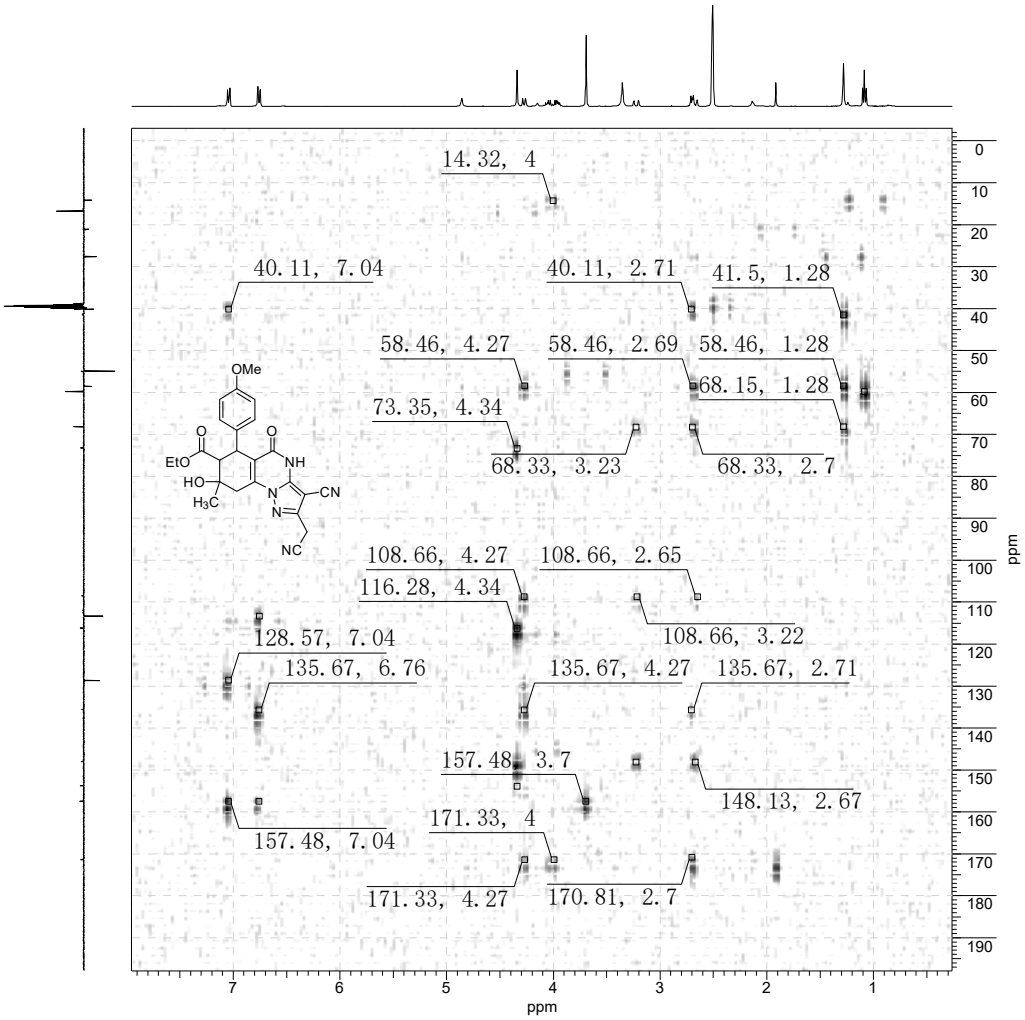


Figure 2. HMBC ^{1}H–^{13}C NMR (400/101 MHz, DMSO-d_6) spectrum of **9a**.

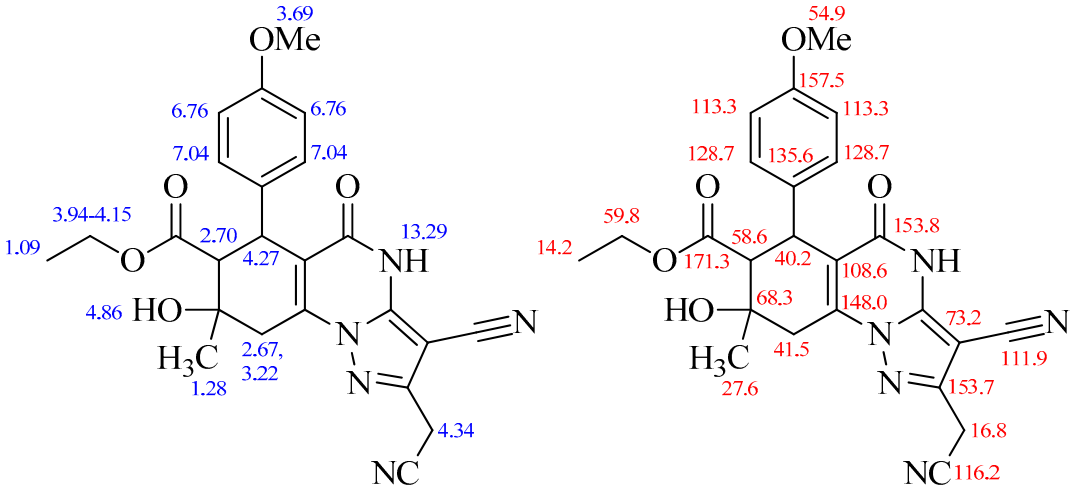


Figure 3. The chemical shifts in the ^{1}H NMR (**left**) and ^{13}C NMR (**right**) spectra of **9a**.

Experimental

IR spectra were recorded on a Bruker Vertex 70 spectrometer. NMR spectra were recorded on a Bruker Avance III HD (400 MHz) in DMSO-d_6 using TMS as an internal standard. Selected experimental procedures are given.

Ethyl 3-cyano-2- (cyanomethyl)-8-hydroxy-6-(4-methoxyphenyl)-8-methyl-5-oxo-4,5,6,7,8,9-hexahydropyrazolo[1,5-a]quinazolin-7-carboxylate (9a). A mixture of 380 mg (1 mmol) of diethyl 5-hydroxy-5-methyl-3- (4-methoxyphenyl)cyclohexanone-2,4-dicarboxylate (1a), 5 ml of glacial AcOH and 150 mg (1 mmol) of pyrazole 7 was heated under reflux for 4 h (TLC control). The precipitate was filtered off and washed with EtOH. Yield 22%, beige amorphous powder.

IR spectrum, ν, cm^{-1}: 3476 (O–H), 3182, 3076 (N–H), 2262, 2226 (2 C≡N), 1720 (C=O ester), 1688 (C=O amide), 1649, 1593 (C=C).

^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.09 t (3H, $C\underline{H}_3CH_2O$, ^3J 7.1 Hz), 1.28 s (3H, $C^8C\underline{H}_3$), 2.65–2.71 two d overlapped (2H, H^9 and H^7), 3.22 d (1H, H^9, ^2J 17.1 Hz), 3.69 s (3H, CH_3O), 3.94–4.15 m (ABX$_3$) (2H, $CH_3C\underline{H}_2O$), 4.27 d (1H, H^6, ^3J 10.2 Hz), 4.34 s (2H, CH_2CN), 4.86 br.s (1H, OH), 6.76 d (2H, H^3 and H^5 Ar, ^3J 8.4 Hz), 7.04 d (2H, H^2 and H^6 Ar, ^3J 8.4 Hz), 13.29 br.s (1H, NH). NMR ^{13}C DEPTQ (101 MHz, DMSO-d$_6$), δ$_C$, ppm.: 14.5* ($\underline{C}H_3CH_2O$), 16.7 ($\underline{C}H_2CN$), 27.6* ($C^8\underline{C}H_3$), 40.2* (C^6), 41.5 (C^9), 54.9* (CH_3O), 58.6* (C^7), 59.8 ($CH_3\underline{C}H_2O$), 68.2 (C^8), 73.2 (C^3), 108.5 (C^{5a}), 111.9 (CN), 113.3* (C^3, C^5 Ar), 116.2 ($CH_2\underline{C}N$), 128.7* (C^2, C^6 Ar), 135.6 (C^1 Ar), 148.0 (C^{9a}), 148.1 (C^{3a}), 153.7 (C^2), 153.8 (C^5), 157.5 (C^4 Ar), 171.4 ($\underline{C}O_2Et$). *Opposite signals.

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