Reactions with Diethyl Acetonedicarboxylate: Novel Synthesis of Pyrazolo[3,4-*d*]pyridazine Derivatives

Reaktionen mit Azetondicarbonsäure-diethylester: Neue Synthese von Pyrazolo[3,4-*d*]pyridazinen

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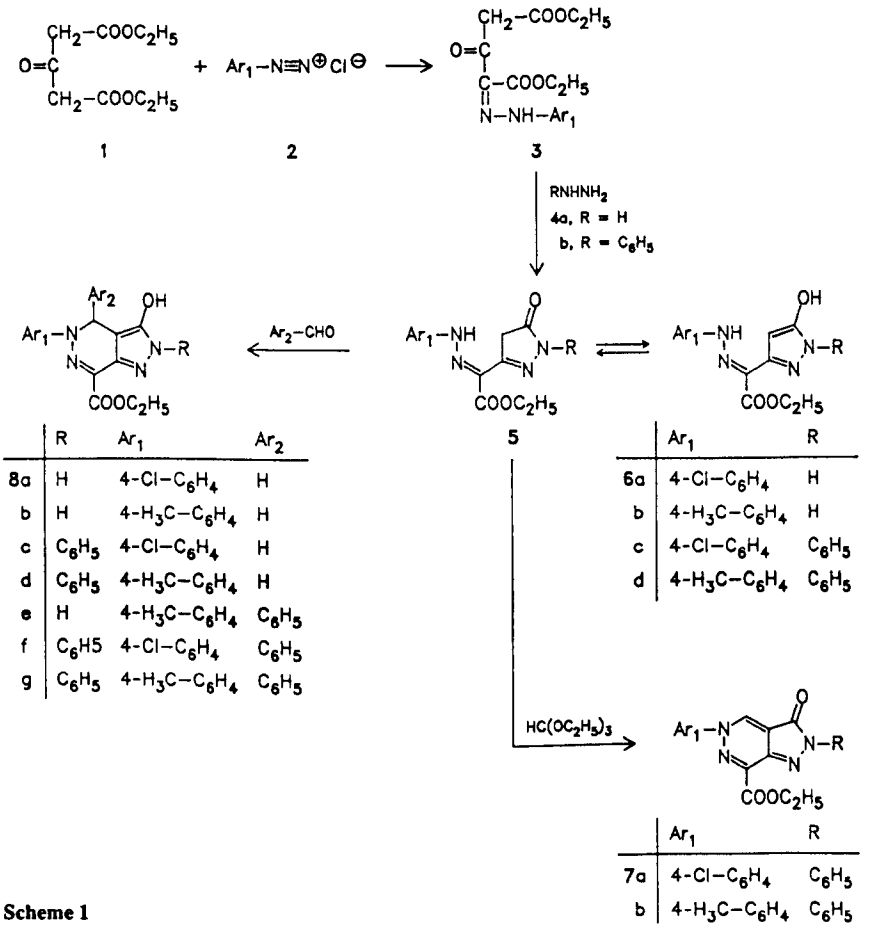
Continuing our interest in the synthesis of azoles and fused azoles as both potential CNS regulants and antimetabolites in purine biochemical reactions[1-4], we investigated the possible utility of the products obtained by coupling diethyl acetonedicarboxylate with diazotised arylamines for the synthesis of new pyrazolo[3,4-*d*]pyridazine derivatives. Thus, we developed a novel procedure for the synthesis of pyrazolo[3,4-*d*]pyridazines. Diethyl acetonedicarboxylate (**1**) couples with an equimolecular proportion of the appropriate arenediazonium salts **2** in sodium acetate buffered solution to give the corresponding hydrazone derivatives **3**. Attempted cyclization of the hydrazone **3** by reacting it with hydrazine or phenylhydrazine (**4b**) in glacial acetic acid led to the pyrazoles **5**. The ^{1}H-NMR-spectra revealed that the pyrazoles **5** are present in the tautomeric form **6**: **6a** reveals a singlet at δ 5.86 ppm (pyrazole H-4) and broad signals at δ 12.1 and 13.19 ppm assigned to NH and OH, respectively.

Compounds **5** reacted with triethyl orthoformate to yield annulated products, obtained by elimination of three moles of ethanol.



	R	Ar_1	Ar_2
8a	H	4-Cl–C_6H_4	H
b	H	4-H_3C–C_6H_4	H
c	C_6H_5	4-Cl–C_6H_4	H
d	C_6H_5	4-H_3C–C_6H_4	H
e	H	4-H_3C–C_6H_4	C_6H_5
f	C_6H5	4-Cl–C_6H_4	C_6H_5
g	C_6H_5	4-H_3C–C_6H_4	C_6H_5

	Ar_1	R
6a	4-Cl–C_6H_4	H
b	4-H_3C–C_6H_4	H
c	4-Cl–C_6H_4	C_6H_5
d	4-H_3C–C_6H_4	C_6H_5

	Ar_1	R
7a	4-Cl–C_6H_4	C_6H_5
b	4-H_3C–C_6H_4	C_6H_5

Scheme 1

  0365-6233/91/0909-0585 $ 3.50+.25/0

The pyrazolo[3,4-*d*]pyridazine structure was established based on elemental analyses and spectral data (IR, ^{1}H-NMR and MS). Thus, the MS of compound **7a** supports a molecular formula of $C_{20}H_{15}ClN_4O_3$ (M^+: m/z = 394; ^{35}Cl). The IR-spectrum reveales bands at 1740 and 1715 cm^{-1} (two CO). The ^{1}H-NMR-spectrum shows the pyridazine-H at δ 9.65 ppm.

Also, compounds **5** react with formaldehyde (*Mannich* reaction) and with aromatic aldehydes to yield the pyrazolo[3,4-*d*]pyridazine derivatives **8**. Structures **8a-g** were inferred from analytical and spectral data. The ^{1}H-NMR-spectrum reveals the pyridazine-H at δ 6.8 ppm and the IR-spectrum shows no carbonyl absorption. Although, one may argue that the reaction of **5** with aromatic aldehydes may lead to the formation of (coloured) 4-arylidene derivatives. However, all products are colourless and the IR spectra revealed no NH hydrazone group.

These results indicate that diethyl acetonedicarboxylate is an excellent starting material for the synthesis of pyrazoles and different pyrazolo[3,4-*d*]pyridazines.

Experimental Part

Melting points: uncorrected.- IR spectra (KBr disc): Pye Unicam Spectra-1000 or Shimadzu IR 200.- ^{1}H-NMR spectra: Wilmad 270 MHz spectrometer in $(CD_3)_2SO$, $SiMe_4$ as internal standard.- Analytical data: Microanalytical Centre at Cairo University.

Diethyl α-arylhydrazonoacetonedicarboxylates

21 g of **1** and 20 g of sodium acetate were dissolved in 300 ml of ethanol and cooled in an ice bath. The cold solution was treated gradually, with stirring, with 0.1 mole of the appropriate diazotised aromatic amine pre-

Table 1: List of compounds **6a-d, 7a-b and 8a-g**

Compd. No.	m.p. °C	Yield %	Molec. Form. (Mol.Wt.)	Analysis Calc. /Found C	H	N	Cl
6a [1]	180	65	$C_{13}H_{13}N_4ClO_3$ (308.71)	50.5 50.3	4.24 4.0	18.1 18.5	11.4 11.1
6b	183	68	$C_{14}H_{16}N_4O_3$ (288.30)	58.3 57.9	5.59 5.2	19.4 19.0	
6c	163	73	$C_{19}H_{17}N_4ClO_3$ (384.81)	59.3 59.7	4.45 4.0	14.5 14.2	9.2 8.8
6d	172	82	$C_{20}H_{20}N_4O_3$ (364.39)	65.9 65.5	5.53 5.9	15.3 15.5	
7a [2]	238	62	$C_{20}H_{15}N_4ClO_3$ (394.98)	60.8 61.3	3.83 4.1	14.19 14.5	8.9 9.0
7b	168	66	$C_{21}H_{18}N_4O_3$ (374.38)	67.3 66.9	4.85 5.2	14.9 15.4	
8a	171	52	$C_{14}H_{13}N_4ClO_3$ (320.72)	52.4 52.7	4.09 3.9	17.4 17.0	11.0 10.7
8b	180	58	$C_{15}H_{16}N_4O_3$ (300.31)	60.0 60.2	5.37 5.2	18.6 18.5	
8c	152	63	$C_{20}H_{17}N_4ClO_3$ (396.84)	60.5 61.0	4.32 4.8	14.1 13.7	8.93 9.2
8d	155	64	$C_{21}H_{20}N_4O_3$ (376.40)	67.0 66.6	5.36 4.9	14.8 15.1	
8e	162	73	$C_{21}H_{20}N_4O_3$ (376.40)	67.0 67.2	5.36 5.0	14.8 14.6	
8f	144	63	$C_{26}H_{21}N_4ClO_3$ (472.91)	66.0 66.2	4.48 4.2	11.85 11.5	7.5 7.2
8g	125	58	$C_{27}H_{24}N_4O_3$ (452.49)	71.6 72.0	5.35 5.3	12.3 12.1	

* 1) M^+ = 308; 2) M^+ = 394

Table 2: ^{1}H-NMR data for compounds listed in table 1.

Compound	^{1}H-NMR (δ ppm)
6a	1.35 (t, 3H, CH_3); 4.37 (q, 2H, CH_2); 5.86 (s, 1H, pyrazole H-4); 7.33-7.61 (m, 4H, C_6H_4); 9.8 (s,br, 1H, NH), 12.11 (s, br, 1H, NH); 13.19 (s, br, 1H,OH).
6c	1.33 (t, 3H, CH_3); 4.28 (q, 2H, CH_2), 6.24 (s, 1H, pyrazole H-4); 7.29-7.88 (m, 9H, C_6H_5 and C_6H_4) ; 12.27 (s, br, 1H, NH); 13.15 (s, br, 1H, OH).
6d	1.33 (t, 3H, CH_3); 2.27 (s, 3H, CH_3); 4.22 (q, 2H, CH_2), 6.30 (s, 1H, pyrazole H-4); 7.19-7.88 (m, 9H, C_6H_5 and C_6H_4); 12.3 (s, br, 1H, NH); 13.19 (s, br, 1H, OH).
7a	1.39 (t, 3H, CH_3); 4.48 (q, 2H, CH_2); 7.06-8.17 (m, 9H, C_6H_5 and C_6H_4); 9.65 (s, 1H, pyridazine-H).
8f	1.36 (t, 3H, CH_3); 4.37 (q, 2H, CH_2); 6.82 (s, 1H, pyridazine-H); 7.27-7.99 (m, 14H, $2C_6H_5$ and C_6H_4)

*) I-values for C_2H_5 = 7Hz
[Justus]

pared in the usual way. The mixture was left for 1 h, diluted with H_2O and the precipitate **3** was collected and crystallized from pet. ether 80-100°C.

Ethyl α-arylhydrzono-α-(5-hydroxypyrazol-3-yl)acetates **6**

0.01 mole of diethyl arylhydrazonoacetonedicarboxylate **3** was dissolved in a least amount of glacial acetic acid by warming to about 50°C if necessary. 0.01 mole of hydrazine or phenylhydrazine were added gradually to the cold solution with stirring. The reaction mixture was left for 24-72 h and the precipitate **6** was filtered, washed with water/ethanol and crystallized from ethanol.

Pyrazolo[3,4-d]pyridazines **7**

0.01 mole of pyrazole derivative **6** was mixed with 0.001 mole of triethyl orthoformate and 1-2 drops of piperidine. The reaction mixture was heated in an oil bath at 170-180°C for 1 h, then dissolved in acetic acid and poured on water. The precipitate was crystallized from dilute acetic acid.

Pyrazolo[3,4-d]pyridazines **8a-d**

0.01 mole of pyrazole derivative **6** was dissolved in a least amount of ethanol, 2-5 ml of formalin and 0.011 mole of piperidine were added. The reaction mixture was left overnight, then heated for about 30 min and acidified with conc. HCl. The precipitate that formed after dilution was collected and crystallized from ethanol.

*Pyrazolo[3,4-d]*pyridazines **(8e-g)**

1 g of **6** was mixed with the appropriate aromatic aldehyde and 1-2 drops of piperidine. The reaction mixture was fused in an oil bath 140-160 for 30 min. Then, the product was dissolved in acetic acid and poured into water with stirring. The precipitate was crystallized from dilute acetic acid.

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