A Facile Synthesis of 3,5-Diaminopyrazole-4-carbothioamides and 3,5-Diaminopyrazole-4-carboxylates

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Simple and convenient synthesis of hitherto unknown 3,5-diaminopyrazole-4-carbothioamides **3** as well as new ethyl 3,5-diaminopyrazole-4-carboxylates **7** is reported. The key intermediates were 2-cyanopropenethioamides **2** and 2-(ethoxycarbonyl)propenethioamides **5** which were readily obtained by reaction of phenyl isothiocyanate with 3-(2-acylhydrazino)-3-aminopropenenitriles **1** and ethyl 3-(2-acylhydrazino)-3-aminopropenoates **4** respectively. Intramolecular cyclization of compounds **2** afforded pyrazole-4-carbothioamides **3** while propenethioamides **5** gave pyrazole-4-carboxylates **7**.

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3-Amino- or 5-aminopyrazole-4-carboxylic acid derivatives have been employed as a convenient starting material for the preparation of purine analogues as pyrazolo[3,4-*d*]pyrimidine nucleosides [1,2], many of which show cytostatic activity, or pyrazolo[1,5-*a*]pyrimidine derivatives as anti-inflammatory agents [3,4] and angiotensin antagonists [5,6]. Recently 3,5-diaminopyrazole-4-carboxylates have attracted considerable attention due to their good antioxidant activity [7,8] and their use as intermediates for magenta couplers [9].

Although much work has been devoted to the synthesis of 3-amino- or 5-aminopyrazole-4-carboxylates, on scanning the literature, we found only a few methods to obtain 3,5-diaminopyrazole-4-carboxylates. One of these procedures consists in the condensation of ethyl 3-amino-2-cyano-4,4,4-trihalo-2-butenoates with hydrazine and subsequent cyclization in *N,N*-dimethylformamide or ethyl phenyl ether [10]. In an alternative approach ethyl 2-cyano-3,3-(dimethylmercapto)acrylate was reacted with aniline to afford ethyl 3-anilino-2-cyano-3-(methylmercapto)acrylate that was finally reacted with hydrazine hydrate to give the expected pyrazole derivatives [11]. However the above synthetic pathways employ multistep reactions and furthermore they required the use of expensive reactants. On the contrary, to the best of our knowledge, 3,5-diaminopyrazole-4-carbothioamide derivatives have not yet been reported.

Pursuing our interest in the chemistry of 3-(2-acylhydrazino)-3-aminopropenenitriles **1** and ethyl 3-(2-acylhydrazino)-3-aminopropenoates **4**, as useful intermediates for the preparation of biologically interesting heterocyclic compounds [12,13], in this paper we report that the synthesis of 2-cyanopropenethioamides **2** and 2-(ethoxycarbonyl)propenethioamides **5** from the reaction of compounds **1** and **4** with phenyl isothiocyanate constitute an easier route to 3,5-diaminopyrazole derivatives **3**, **7**.

We previously reported that 3-(2-acylhydrazino)-3-aminopropenenitriles **1** and ethyl 3-(2-acylhydrazino)-3-aminopropenoates **4** react with electrophiles, through their C-2 due to its higher nucleophilicity in comparison to that of the amino groups [12]. As expected by reacting compounds **1** and **4** with phenyl isothiocyanate the propenethioamides **2** and **5** were obtained in satisfactory yields. After screening different reaction conditions we found that treatment of **1** and **4** with an equimolecular amount of phenyl isothiocyanate in dry *N,N*-dimethylformamide at room temperature, afforded the propenethioamides **2** and **5** almost pure for subsequent reactions (Table 1). Any attempt of further purification gave rise to partial decomposition of the thioamides.

Many problems are involved in the structural assignment of propenethioamides **2** and **5** because of the possibility of existence of tautomeric species (amide hydrazone, hydrazide imide and enamine) and the *E/Z* isomerism. The ^{1}H nmr spectra (Table 2), recorded in hexadeuteriodimethyl sulfoxide solution, provided evidence for the presence of the enamine tautomer, while for the absence of a methine proton the amide hydrazone and hydrazide imide tautomers should not be considered.

The new propenethioamides, so easily obtained, were submitted to cyclocondensation to give the target 3,5-diaminopyrazole derivatives **3** and **7**. When equimolecular amounts of propenethioamides **2** and triethylamine were allowed to react in chloroform solution at room temperature high yields of 3,5-diaminopyrazole-4-carbothioamide derivatives **3** were obtained (Tables 3 and 4).

The cyclization involves nucleophilic attack by the N-2 of the hydrazine function of compounds **2** at the cyano group, through 5-*exo-dig* cyclization as confirmed by the disappearance of the CN strecthing vibration in the ir spectra of pyrazoles **3**. The conditions for the cyclization of **2** to **3** were very strict. Poor yields of compounds **3** and/or a complex mixture of products were obtained by

Table 1

Physical and Analytical Data of Propenethioamides **2** and **5**

Compound No.	X	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd./Found C	H	N
2a	CN	CH_3	95	209-210	$C_{12}H_{18}N_5OS$	52.35	4.76	25.44
						52.31	4.73	25.47
2b	CN	*i*-Pr	61	214-215	$C_{14}H_{17}N_5OS$	55.43	5.65	23.08
						55.47	5.66	23.09
2c	CN	Ph	79	198-200	$C_{17}H_{15}N_5OS$	60.52	4.48	20.76
						60.60	4.50	20.72
2d	CN	$PhCH_2$	57	223-225	$C_{18}H_{17}N_5OS$	61.52	4.88	19.93
						61.46	4.87	19.90
2e	CN	4-$ClC_6H_4CH_2$	98	204-205	$C_{18}H_{16}ClN_5OS$	56.03	4.18	18.15
						56.08	4.20	18.09
5a	COOEt	CH_3	60	140-141	$C_{14}H_{18}N_4O_3S$	52.16	5.63	17.38
						52.23	5.65	17.35
5b	COOEt	*i*-Pr	76	129-130	$C_{16}H_{22}N_4O_3S$	54.84	6.33	15.99
						54.86	6.30	16.03
5c	COOEt	Ph	80	138-140	$C_{19}H_{20}N_4O_3S$	59.36	5.24	14.57
						59.33	5.26	14.50
5d	COOEt	$PhCH_2$	40	130-131	$C_{20}H_{22}N_4O_3S$	60.28	5.56	14.06
						60.33	5.55	13.99
5e	COOEt	4-$ClC_6H_4CH_2$	45	134-135	$C_{20}H_{21}ClN_4O_3$	55.49	4.89	12.94
						55.42	4.91	12.97

Table 2

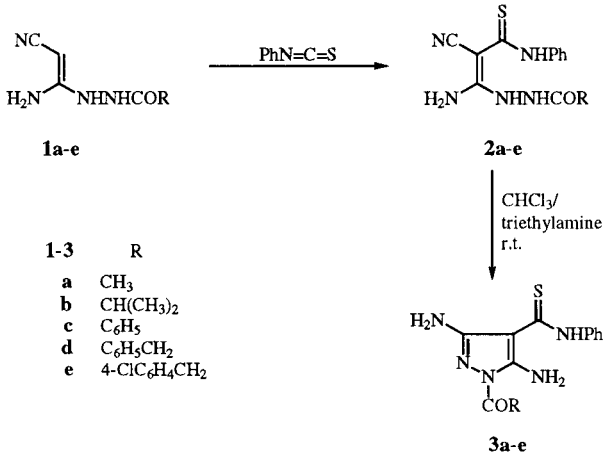
IR and ^1H NMR Data of Compounds **2** and **5**

Compound No.	IR (Nujol) ν (cm^{-1})	^1H NMR (tetramethylsilane/dimethyl-d_6 sulfoxide) δ, J (Hz)
2a	3260, 3090, 2170, 1700	1.89 (*s*, 3H, CH_3), 7.13-7.61 (m, 7H, ArH and NH_2), 9.53, 9.94, 10.38 (*s*, 3H, NH)
2b	3280, 2160, 1670, 1610	1.03 (d, J = 6.3 Hz, 6H, CH_3), 2.40 (m, 1H, CH), 7.10-7.38 (m, 7H, ArH and NH_2), 9.50, 9.83, 10.22 (*s*, 3H, NH)
2c	3350, 3270, 2150, 1670, 1610	7.15-7.98 (m, 12H, ArH and NH_2), 9.60, 10.60, 10.64 (*s*, 3H, NH)
2d	3420, 3240, 2190, 1705, 1610	3.48 (*s*, 2H, CH_2), 7.16-7.32 (m, 12H, ArH and NH_2), 9.49, 10.17, 10.37 (*s*, 3H, NH)
2e	3320, 3230, 3150, 3050, 2180, 1700, 1620	3.48 (*s*, 2H, CH_2), 7.12-7.36 (m, 11H, ArH and NH_2), 9.49, 10.16, 10.36 (*s*, 3H, NH)
5a	3310, 3220, 1635, 1590	1.06 (t, J = 7.1 Hz, 3H, CH_3), 1.85 (*s*, 3H, CH_3), 3.89 (q, J = 7.1 Hz, 2H, CH_2), 7.03-7.56 (m, 5H, ArH), 8.35 (br s, 2H, NH_2), 9.94, 10.42, 11.60, (*s*, 3H, NH)
5b	3350, 3290, 3230, 1675, 1660, 1640, 1600	1.00-1.05 (m, 9H, CH_3), 2.38-2.43 (m, 1H, CH), 3.87 (q, J = 7.1 Hz, 2H, CH_2), 7.02-7.55 (m, 5H, ArH), 8.06 (br s, 2H, NH_2), 9.87, 10.41, 11.56 (*s*, 3H, NH)
5c	3460, 3260, 3190, 1670, 1635	1.07 (t, J = 6.8 Hz, 3H, CH_3), 3.90 (q, J = 6.8 Hz, 2H, CH_2), 7.07-7.91 (m, 10H, ArH), 8.35 (br *s*, 2H, NH_2), 10.56, 10.67, 11.51 (*s*, 3H, NH)
5d	3350, 3200, 1675, 1650, 1600	1.04 (t, J = 6.8 Hz, 3H, CH_3), 3.47 (*s*, 2H, CH_2), 3.86 (q, J = 6.8 Hz, 2H, CH_2), 7.14-7.29 (m, 10H, ArH), 8.40 (br *s*, 2H, NH_2), 10.23, 10.46, 11.60 (*s*, 3H, NH)
5e	3430, 3340, 3200, 1725, 1660, 1610	1.04 (t, J = 7.3 Hz, 3H, CH_3), 3.48 (*s*, 2H, CH_2), 3.86 (q, J = 7.3 Hz, 2H, CH_2), 7.15-7.30 (m, 9H, ArH), 8.40 (br *s*, 2H, NH_2), 10.23, 10.45, 11.60 (*s*, 3H, NH)

carrying out the reaction under acidic conditions. The reaction did not occur at lower temperature but gave complicated product mixture upon reflux.

Under the same reaction conditions propenethioamides **5**, in which an ethoxycarbonyl group replaces the cyano group, the cyclocondensation followed a completely different course. As a matter of fact thioamides **5** produced ethyl pyrazole-4-carboxylate derivatives **7** (Table 5).

Scheme 1



1a-e **2a-e** **3a-e**

1-3	R
a	CH_3
b	$CH(CH_3)_2$
c	C_6H_5
d	$C_6H_5CH_2$
e	4-$ClC_6H_4CH_2$

The structure of compounds **7** was deduced by microanalyses, ir, nmr and mass spectral data. The nmr spectra of **7** revealed that compounds **7a,c** exist as 2,5-dihydro-3-amino-5-(phenylimino)-1*H*-pyrazoles, **7b,d** as 3-amino-5-(phenylamino)-1*H*-pyrazoles, while only in the case of **7e** a mixture of the two tautomers was detected (10:1 ratio by integration of the ^1H nmr signals) (Table 6). From the above it seems that the existence of pyrazole tautomers **7** is affected by the nature of the acylic moiety on the N-1 position. From the comparative analysis of the ^1H nmr of the two tautomers we note that there are significant differences in all the chemical shifts values of the NH_2 group (~5.8 ppm for **7a,c** and ~7.5 ppm for **7b,d**) and NH groups (~9.4 for NH of pyrazole ring and ~8.3 ppm for the exocyclic NH). Another interesting feature of the ^1H nmr spectra of pyrazoles **7a,c** is an upfield shift of 0.5-0.6 ppm of the signals for the ethyl protons of the carboxylic group, compared with **7b,d**, probably due to the presence of an exocyclic double bond that constrains the phenyl

Table 3

Physical and Analytical Data of 3,5-Diaminopyrazole-4-carbothioamide Derivatives **3**

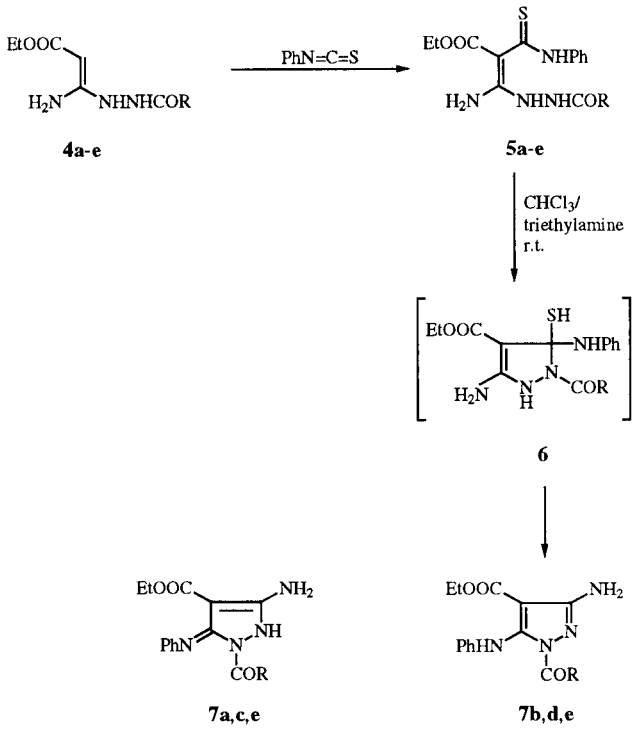
Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd./Found C	H	N
3a	Me	97	219-220	$C_{12}H_{13}N_5OS$	52.35	4.76	25.44
					52.29	4.77	25.45
3b	*i*-Pr	85	220-221	$C_{14}H_{17}N_5OS$	55.43	5.65	23.08
					55.37	5.66	23.02
3c	Ph	98	179-180	$C_{17}H_{15}N_5OS$	60.52	4.48	20.76
					60.58	4.46	20.81
3d	$PhCH_2$	89	199-200	$C_{18}H_{17}N_5OS$	61.52	4.88	19.93
					61.47	4.85	19.92
3e	4-$ClC_6H_4CH_2$	63	209-210	$C_{18}H_{16}ClN_5OS$	56.03	4.18	18.15
					56.10	4.22	18.22

Table 4

Ir and ^1H NMR Data of Compounds **3**

Compound No.	IR (Nujol) ν (cm^{-1})	^1H NMR (tetramethylsilane/dimethyl-d_6 sulfoxide) δ, J (Hz)
3a	3480, 3370, 3310, 1700, 1590	2.43 (*s*, 3H, CH_3), 5.80 (*s*, 2H, NH_2), 7.17-7.61 (m, 5H, ArH), 8.28 (*s*, 2H, NH_2), 10.45 (*s*, 1H, NH)
3b	3480, 3270, 1700, 1620	1.10 (d, J = 6.3 Hz, 6H, CH_3), 3.37-3.44 (m, 1H, CH), 5.77 (*s*, 2H, NH_2), 7.15-7.56 (m, 5H, ArH), 8.27 (*s*, 2H, NH_2), 10.41 (*s*, 1H, NH)
3c	3400, 3320, 3190, 1665, 1620	5.80 (*s*, 2H, NH_2), 7.15-7.90 (m, 10H, ArH), 8.42 (*s*, 2H, NH_2), 10.50 (*s*, 1H, NH)
3d	3420, 3240, 1705, 1610	4.18 (*s*, 2H, CH_2), 5.83 (*s*, 2H, NH_2), 7.13-7.56 (m, 10H, ArH), 8.23 (*s*, 2H, NH_2), 10.43 (*s*, 1H, NH)
3e	3380, 3330, 3160, 1710, 1615	4.29 (*s*, 2H, CH_2), 5.85 (*s*, 2H, NH_2), 7.15-7.59 (m, 9H, ArH), 8.23 (*s*, 2H, NH_2), 10.43 (*s*, 1H, NH)

Scheme 2



4-7 R

- **a** CH_3
- **b** $CH(CH_3)_2$
- **c** C_6H_5
- **d** $C_6H_5CH_2$
- **e** $4\text{-}ClC_6H_4CH_2$

ring in a position such that it can exert a remarkable shielding effect on the neighboring ethyl protons of the ester group. Furthermore in the ^{13}C nmr spectrum of the same compounds we note, respectively, a difference of about 6 ppm and about 3 ppm for the chemical shifts of C-4 and C-1' between the two tautomers. The nmr spectra of pyrazole **7e** show two sets of signals due to the contemporary presence of the two tautomers.

Structural evidence for compounds **7** resulted from their mass spectra that are characterized by the initial loss of the acylic group from the molecular ion, while the subsequent fragmentation pattern is the same for all pyrazoles **7** and like that reported for ethyl 5(3)-amino-3(5)-(phenylamino)-1*H*-pyrazole-4-carboxylate [11]. The above compound was also obtained by submitting pyrazoles **7** to hydrolysis with tricholoroacetic acid.

It is likely that the mechanism of formation of **7** involves the addition of N-2 of hydrazine moiety of **5** on the thioamidic carbon atom to give cyclic intermediate **6**, that subsequently loses H_2S to afford pyrazoles **7**.

Melting points were determined with a Kofler hot stage and are uncorrected. The ir spectra were recorded on Nujol mulls between salt plates in a Perkin-Elmer 398 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded with a Varian Unity 300 spectrometer. Mass spectra were recorded with Fisons QMD 1000 spectrometer in EI mode at 70 eV. Elemental analyses were carried with a Carlo Erba Model 1106 Elemental Analyser. 3-(2-Acylhydrazino)-3-aminopropenenitriles **1** and ethyl 3-(2-acylhydrazino)-3-aminopropenoates **4** were prepared as described in the literature [13].

Table 5

Physical and Analytical Data of Ethyl 3,5-Diaminopyrazole-4-carboxylate Derivatives **7**

Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd./Found C	H	N
7a	Me	98	158-160	$C_{14}H_{16}N_4O_3$	58.32	5.59	19.43
					58.33	5.57	19.47
7b	*i*-Pr	83	87-88	$C_{16}H_{20}N_4O_3$	60.75	6.37	17.71
					60.79	6.38	17.65
7c	Ph	96	165-167	$C_{19}H_{18}N_4O_3$	65.13	5.18	15.99
					65.17	5.16	16.04
7d	$PhCH_2$	89	132-133	$C_{20}H_{20}N_4O_3$	65.92	5.53	15.37
					65.97	5.55	15.34
7e	$4\text{-}ClC_6H_4CH_2$	95	153-154	$C_{20}H_{19}ClN_4O_3$	60.23	4.80	14.05
					60.14	4.78	14.09

Table 6

Spectral Data of Compounds **7**

Compound No.	IR (Nujol) ν (cm^{-1})	^1H NMR (tetramethylsilane/dimethyl-d_6 sulfoxide) δ, J (Hz)	^{13}C NMR (tetramethylsilane/dimethyl-d_6 sulfoxide) δ	MS (70 eV) m/z (%)
7a	3440, 3310, 1685, 1630	0.65 (t, J = 7.0 Hz, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.71 (q, J = 7.0 Hz, 2H, CH_2), 5.86 (br s, 2H, NH_2), 7.00-7.21 (m, 5H, ArH), 9.45 (s, 1H, NH)	11.2 (CH_3), 21.9 ($COCH_3$), 57.4 (CH_2), 86.8 (C-4), 117.2, 120.9, 126.7 (ArC), 138.8 (C-5), 145.2 (C-1'), 153.8 (C-3), 160.9 (CO)	288 (M^+, 6), 246 (12), 200 (50), 171 (6), 145 (16), 117 (15), 104 (6), 77 (31), 51 (24), 43 (100)
7b	3430, 3380, 3300, 1700, 1670	1.16 (d, J = 6.8 Hz, 6H, CH_3), 1.28 (t, J = 7.3 Hz, 3H, CH_3), 3.57 (m, 1H, CH), 4.25 (q, J = 7.3 Hz, 2H, CH_2), 6.88-7.55 (m, 7H, ArH and NH_2), 8.20 (s, 1H, NH)	14.2 (CH_3), 18.1 (CH_3), 32.8 (COCH), 59.6 (CH_2), 82.9 (C-4), 117.0, 128.7 (ArC), 140.2 (C-5), 151.0 (C-1'), 152.2 (C-3), 163.6 (CO)	316 (M^+, 5), 246 (12), 200 (13), 171 (1), 145 (2), 117 (1), 104 (1), 77 (3), 51 (1), 43 (18)
7c	3400, 3280, 1675, 1600	0.81 (t, J = 7.0 Hz, 3H, CH_3), 3.85 (q, J = 7.0 Hz, 2H, CH_2), 5.81 (s, 2H, NH_2), 6.92-7.86 (m, 10H, ArH), 9.38 (s, 1H, NH)	13.4 (CH_3), 59.4 (CH_2), 89.3 (C-4), 118.7, 122.6, 127.8, 128.6, 130.2, 132.2, 133.1 (ArC), 141.1 (C-5), 148.4 (C-1'), 155.6 (C-3), 162.9 (CO)	350 (M^+, 9), 246 (1), 200 (1), 171 (1), 145 (6), 117 (1), 104 (1), 105 (100), 77 (9), 51 (2), (43 (2)
7d	3420, 3400, 3310, 1700, 1655	1.27 (t, J = 6.8 Hz, 3H, CH_3), 4.24 (q, J = 6.8 Hz, 2H, CH_2), 4.27 (s, 2H, CH_2), 6.89-7.58 (m, 12H, ArH and NH_2), 8.22 (s, 1H, NH)	14.3 (CH_3), 41.4 ($COCH_2$), 59.7 (CH_2), 83.1 (C-4), 117.2, 120.8, 126.8, 128.2, 128.8, 129.7, 133.9 (ArC), 140.1 (C-5), 151.1 (C-1'), 152.2 (C-3), 163.6 (CO)	364 (M^+, 5), 246 (12), 200 (13), 171 (1), 145 (7), 117 (2), 104 (1), 91 (3), 77 (3), 51 (1), 28 (100)
7e	3380, 3250, 3160, 1670, 1605	0.81, 1.27 (t, J = 6.8 and 7.3 Hz, 3H, CH_3), 3.34, 4.28 (s, 2H, CH_2), 3.86, 4.24 (q, J = 6.8 and 7.3 Hz, 2H, CH_2), 5.81, 7.40 (s, 2H, NH_2), 6.83-7.89 (m, 9H, ArH), 9.38, 8.23 (s, 1H, NH)	14.3, 13.4 (CH_3), 40.7 ($COCH_2$), 59.7, 59.4 (CH_2), 83.1, 89.2 (C-4), 117.2, 118.7, 120.8, 122.6, 131.6, 132.1, 130.2, 131.6, 128.8, 128.6, 128.1, 127.7, 133.1 (ArC), 140.1, 141.0 (C-5), 151.1, 148.4 (C-1'), 152.1, 155.7 (C-3), 163.6, 163.0 (CO)	401 (M^++2, 1), 364 (M^+, 3), 246 (11), 200 (11), 171 (1), 145 (9), 125 (3), 117 (2), 104 (1), 77 (3), 51 (1), 28 (100)

General Procedure for the Synthesis of Propenethioamides **2**, **5**.

A mixture of compound **1** or **4** (5 mmoles) and phenyl isothiocyanate (0.68 g, 5 mmoles) in dry dimethylformamide (10 ml) was stirred at room temperature. After 24 hours water (30 ml) was added and the resulting precipitate was filtered, washed with ethyl acetate (2 x 15 ml) and dried to give compounds **2** and **5** in analytically pure form without additional purification by recrystallization or by chromatography.

General Procedure for the Synthesis of 3,5-Diaminopyrazole-4-carbothioamide Derivatives **3**.

A mixture of propenethioamide **2** (2.5 mmoles) and triethylamine (0.25 g, 2.5 mmoles) in dry chloroform (100 ml) was stirred at room temperature for 48 hours. Then the solution was concentrated *in vacuo* and ice-water was poured onto the residue at once. The resulting solid was filtered by suction, dried and recrystallized from 2-propanol in the case of **3a** and from ethanol in the other cases.

General Procedure for the Synthesis of Ethyl 3,5-Diaminopyrazole-4-carboxylate Derivatives **7**.

A mixture of propenethioamide **5** (2.5 mmoles) and triethylamine (0.25 g, 2.5 mmoles) in dry chloroform (100 ml) was stirred at room temperature for 48 hours. Then the solution was concentrated *in vacuo* and ice-water was poured onto the residue at once. The resulting solid was filtered by suction, dried and recrystallized from *n*-hexane in the case of **7b** and from 2-propanol in the other cases.

Hydrolysis of Pyrazole Derivatives **7**.

A mixture of pyrazole **7** (1.5 mmoles) and trichloroacetic acid (0.5 g, 3 mmoles) in ethanol (5 ml) was heated at reflux for 2 hours. The solvent was evaporated *in vacuo*, and the residue was mixed with 40% aqueous potassium carbonate (20 ml) and then extracted with chloroform (3 x 20 ml). The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to give ethyl 5(3)-amino-3(5)-(phenylamino)-1*H*-pyrazole-4-carboxylate in quantitative yield, mp 164-165° (lit [11] 166°).

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