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Unambiguous Structure Determination of Some Pyrazolo[1,5-*a*]pyrimidine Derivatives by Multinuclear NMR Spectroscopy

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The condensation of 3(5)-aminopyrazole and 5-amino-3-phenylpyrazole with ethyl 2,4-dioxopentanoate and 2-ethoxymethylidene-3-oxobutyrate has been re-investigated. Contrary to previous reports, the former reaction gives rise to both regioisomeric pyrazolo[1,5-*a*]pyrimidines (5-carbethoxy-7-methyl- and 7-carbethoxy-5-methyl-), the structures of which were determined by ^{1}H and ^{13}C NMR spectroscopy. The 6-carbethoxy-7-methyl- regioisomer is shown to be the only product in the reaction of the same aminopyrazoles with 2-ethoxymethylidene-3-oxobutyrate; the regiochemical assignment was independently achieved by multinuclear (^{13}C and ^{15}N) NMR spectroscopy.

KEY WORDS Pyrazolo[1,5-*a*]pyrimidines Structure determination Coupling constants ^{1}H, ^{13}C and ^{15}N NMR spectra

INTRODUCTION

The condensation reaction between aminoazoles and electrophiles such as β-keto esters, β-diketones, β-ketoaldehydes or their acetals can, in general, lead to regioisomeric mixtures of azolo[*a*]pyrimidines.[1–4] Structure determination of these products is often the major problem in this field. In continuation of our previous study on the pyrazolo[1,5-*a*]pyrimidine system,[5] we highlight the use of multinuclear NMR spectroscopy for the structural differentiation or determination of the compounds obtained by the reaction of 3(5)-aminopyrazoles **1** and **2** with 1,3-dicarbonyl compounds such as ethyl 2,4-dioxopentanoate (**3**) or ethyl 2-ethoxymethylidene-3-oxobutyrate (**16**) (for formulae, see Schemes 1–3).

EXPERIMENTAL

Chemicals

3(5)-Aminopyrazole (**1**) is commercially available (Aldrich) and was used without further purification; compounds **2**,[6] **3**[7] and **16**[8] were synthesized by literature procedures.

Reaction of 3(5)-Aminopyrazole with Ethyl 2,4-Dioxopentanoate

Ethyl 2,4-dioxopentanoate (ethyl acetylpyruvate) (**3**) (0.57 g; 3.6 mmol) was added to a solution of 3(5)-aminopyrazole (**1**) (0.27 g; 3.2 mmol) in EtOH (2 ml). The solution was refluxed for 30 min and removal of the solvent left a yellow solid (0.66 g, quantitative yield) consisting of ethyl 7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (**4**) and ethyl 5-methylpyrazolo[1,5-*a*]pyrimidine-7-carboxylate (**5**) in the ratio 73:27 (^{1}H NMR). The mixture was separated by column chromatography with ethyl acetate–*n*-hexane (1:1, v/v) as eluent; the fastest moving band gave **4** (0.39 g, yield 58%), m.p. 88–89 °C from light petroleum (b.p. 40–70 °C) (lit.[9] m.p. 91–92 °C). The second band afforded the ester **5** as a yellow solid (0.10 g, yield 15%), m.p. 74–75 °C from light petroleum (b.p. 40–70 °C). Calculated for $C_{10}H_{11}N_3O_2$ (205.2), C 58.53, H 5.40, N 20.48; found, C 58.64, H 5.37, N 20.24%.

Reaction of 5-Amino-3-phenylpyrazole with Ethyl 2,4-Dioxopentanoate

Ethyl 2,4-dioxopentanoate (**3**) (1.74 g; 11.0 mmol) was added to a solution of 5-amino-3-phenylpyrazole (**2**) (1.59 g; 10 mmol) in EtOH (10 ml). The solution was refluxed for 30 min and the precipitate was filtered off (2.58 g, yield 92%). The yellow precipitate, consisting of the two isomeric compounds ethyl 7-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (**6**) and ethyl 5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine-7-carboxylate (**7**) in the ratio 90:10 (^{1}H NMR spectrum), was recrystallized from EtOH to give **6** (1.65 g, yield 64%), m.p. 156–157 °C (lit.[10] m.p. 156–158 °C). Evaporation to dryness of the initial mother liquors afforded an orange solid (0.23 g) containing (^{1}H NMR spectrum) **6** and **7** in the ratio 30:70. This mixture was resolved by column chromatography with ethyl acetate-light pet-

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roleum (b.p. 40–70 °C) (1:2.5, v/v) as eluent; the first band afforded a yellow solid (0.06 g, yield 26%) which was easily identified as **6** and the second band gave the derivative **7** (0.14 g, yield 61%). An analytical sample of the latter compound obtained by recrystallization from EtOH–H_2O (1:1, v/v) had m.p. 119–120 °C. Calculated for $C_{16}H_{15}N_3O_2$ (281.3), C 68.31, H 5.37, N 14.94; found, C 68.15, H 5.55, N 14.67%.

Reaction of 3(5)-Aminopyrazole with Ethyl 2-Ethoxymethylidene-3-oxobutyrate

Ethyl 2-ethoxymethylidene-3-oxobutyrate (ethyl 2-ethoxymethyleneacetoacetate) (**16**) (2.87 g; 15.4 mmol) was added to a solution of 3(5)-aminopyrazole (**1**) (1.16 g; 14.0 mmol) in EtOH (7 ml). The solution was refluxed for 30 min and the precipitate (2.64 g) was filtered off. Evaporation to dryness of the mother liquors gave a second crop (0.23 g; quantitative yield) of the same product (TLC and ^{1}H NMR spectrum). An analytical sample of ethyl 7-methylpyrazolo[1,5-*a*] pyrimidine-6-carboxylate (**19**), obtained by recrystallization from EtOH, had m.p. 89–90 °C (lit.[11] m.p. 94.5–95.5 °C).

Reaction of 5-Amino-3-phenylpyrazole with Ethyl 2-Ethoxymethylidene-3-oxobutyrate

Operating as described for the preparation of **19**, from ethyl 2-ethoxymethylidene-3-oxobutyrate (**16**) (2.05 g; 11.0 mmol) and 5-amino-3-phenylpyrazole (**2**) (1.59 g; 10.0 mmol) in EtOH (10 ml), a precipitate (2.80 g; quantitative yield) of ethyl 7-methyl-2-phenylpyrazolo[1,5-*a*] pyrimidine-6-carboxylate (**20**) was obtained. Recrystallization from EtOH afforded crystals with m.p. at 151 °C (lit.[12] m.p. 150–151 °C).

General

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{13}C and ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer in the Fourier transform mode. All carbon spectra were recorded at 75.43 MHz in 10 mm o.d. tubes at 25 ± 0.5 °C for 0.5 M solutions in $CDCl_3$. Proton coupled spectra were obtained in the 'gated decoupling' mode. Typical conditions were spectral width 16000 Hz, 64K data points (digital resolution of 0.49 Hz per point, i.e. 0.01 ppm), quadrature phase detection and pulse width 7 μs (*ca.* 30°). Chemical shifts are reported in ppm to high frequency from TMS as a secondary reference; coupling constants are given in Hz. Natural abundance ^{15}N spectra were measured at 60.83 MHz in 10 mm o.d. tubes at 25 ± 0.5 °C for 0.5 M solutions in $CDCl_3$ on a Bruker AMX-600 spectrometer (University of Zürich); chemical shifts are reported in ppm from nitromethane as internal standard. Silica gel plates (Merck, F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for analytical TLC and for flash chromatography, respectively. Solvents were removed under reduced pressure.

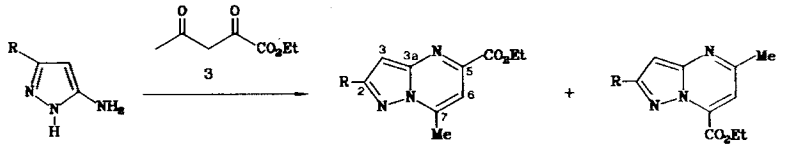
RESULTS AND DISCUSSION

It has been reported previously that the reaction between 3(5)-aminopyrazole (**1**)[9] or 5-amino-3-phenylpyrazole (**2**)[10] and ethyl 2,4-dioxopentanoate in refluxing acetic acid, or without solvent, furnishes the 7-methyl derivative **4** or **6**, respectively, (Scheme 1) as the sole reaction product in high yield. However, when we repeated this reaction by refluxing a solution of the aminopyrazole **1** or **2** with the β-diketone **3** in ethanol, we obtained the 7-methyl derivative **4** or **6** accompanied by the regioisomeric 5-methyl compound **5** or **7**, contrary to the earlier reports.

In particular, after reaction of **1** with ethyl 2,4-dioxopentanoate we isolated in high yield a solid consisting of two pyrazolo[1,5-*a*]pyrimidine carboxylates in the ratio 73:27, as revealed by the ^{1}H NMR spectrum of the crude reaction product, which showed complete duplication of all signals. The two regioisomers were separated by flash chromatography and their ^{1}H (Table 1) and ^{13}C NMR spectra (Tables 2 and 3) were carefully examined. The most convincing diagnostic data for the regiochemical assignment of the methyl group on the pyrimidine ring came from the ^{1}H NMR spectra, the pyrazolo[1,5-*a*]pyrimidines **8–13** being used as model compounds (Scheme 2).[5]

The presence of a small coupling (0.9 Hz) between the methyl group in position 7 and H-6 led us to assign the structure ethyl 7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (**4**) to the predominant reaction product. The regioisomers can also be easily distinguished on the basis of the ^{13}C chemical shift of the methyl carbon atom; in fact, as for the model compounds **8–13**, this substituent exhibits a diagnostic low-frequency shift on going from position 5 to 7 (δ 24.70 *vs.* 16.60–17.50 ppm, respectively).[5]

Moreover, in the coupled carbon spectra the carbonyl carbon shows a small coupling to H-6 when it is in position 5 [J(5-CO,H-6) = 1.4–1.5 Hz] compared with when it is in position 7 [J(7-CO,H-6) = 3.6–3.7 Hz]. The same spectroscopic considerations hold for the 3-chloro- (**14**) and 3-bromo- (**15**) derivatives, which were obtained as reported in the literature.[13]



1 R = H
2 R = Ph

4 R = H
6 R = Ph

5 R = H
7 R = Ph

Scheme 1

Table 1. Selected ^{1}H NMR ($CDCl_3$, 300 MHz) chemical shifts (δ, ppm) of pyrazolo[1,5-*a*]pyrimidine derivatives[a]

Compound	H-2	H-3	H-5	H-6	5-CH_3	7-CH_3
4	8.24[d, J(2,3) 2.4]	6.96[d, J(3,2) 2.4]	—	7.47[q, J(6, 7-CH_3) 0.9]	—	2.86[d, J(7-CH_3-6) 0.9]
5	8.21[d, J(2,3) 2.4]	6.69[d, J(3,2) 2.4]	—	7.19 (s)	2.66 (s)	—
6	—	7.22 (s)	—	7.46[q, J(6,7-CH_3) 0.9]	—	2.92[d, J(7-CH_3-6) 0.9]
7	—	6.97 (s)	—	7.15 (s)	2.66 (s)	—
14	—	—	—	7.50[q, J(6,7-CH_3) 0.9]	—	2.89[d, J(7-CH_3-6) 0.9]
15	—	—	—	7.52[q, J(6,7-CH_3) 0.9]	—	2.90[d, J(7-CH_3-6) 0.9]
19	8.22[d, J(2,3) 2.3]	6.73[d, J(3,2) 2.3]	8.94 (s)	—	—	3.20 (s)
20	—	7.02 (s)	8.93 (s)	—	—	3.26 (s)

[a] Multiplicity: s = singlet, d = doublet, q = quartet. J(H,H) values in Hz.

Table 2. ^{13}C NMR ($CDCl_3$, 75 MHz) chemical shifts (δ, ppm) of pyrazolo[1,5-*a*]pyrimidine derivatives[a]

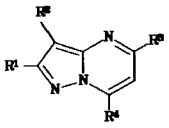
Compound	C-2	C-3	C-3a	C-5	C-6	C-7	5-CH_3	7-CH_3	C-*ipso*	C-*ortho*	C-*meta*	C-*para*	CO	OCH_2	CH_2CH_3
4	145.91 (dd)	99.72 (dd)	147.77 (dd)[b]	145.65 (s)	106.95 (dq)	146.75 (qd)	—	17.48 (qd)	—	—	—	—	164.12 (td)	62.56 (tq)	14.29 (qt)
5	145.69 (dd)	96.72 (dd)	149.76 (dd)[b]	158.09 (qd)	110.62 (dq)	135.10 (s)	24.72 (qd)	—	—	—	—	—	160.21 (dt)[c]	63.02 (tq)	14.16 (qt)
6	156.54 (dt)[c]	95.51 (d)	148.55 (d)	145.37 (s)	106.65 (dq)	146.14 (qd)	—	17.05 (qd)	132.17	128.42	126.26	128.85	163.37 (td)	62.10 (tq)	13.98 (qt)
7	156.82 (dt)	93.33 (d)	150.88 (d)	158.08 (qd)	110.24 (dq)	135.10 (d)	24.70 (qd)	—	132.62	128.69	126.68	129.07	160.38 (dt)[c]	62.92 (tq)	14.17 (qt)
14	151.81 (t)	100.12 (s)	144.34 (s)	146.26 (s)	107.68 (dq)	146.79 (qd)	—	16.64 (qd)	130.94	128.40	127.91	129.21	163.66 (td)	62.39 (tq)	14.03 (qt)
15	153.52 (t)	85.60 (s)	145.75 (s)	146.62 (s)	107.82 (dq)	146.93 (qd)	—	16.73 (qd)	131.37	128.34	128.26	129.20	163.69 (td)	62.39 (tq)	14.03 (qt)
19	146.60 (dd)	98.07 (dd)	148.61 (ddd)	149.77 (d)	110.58 (dq)	151.44 (dq)[d]	—	15.02 (q)	—	—	—	—	164.74 (m)	61.57 (tq)	14.26 (qt)
20	157.55 (dt)[c]	94.67 (d)	149.58 (dd)	149.71 (d)	110.22 (dq)	151.12 (qd)	—	14.89 (q)	132.21	128.64	126.54	129.27	164.63 (m)	61.31 (tq)	14.13 (qt)

[a] Multiplicity: s = singlet, d = doublet, t = triplet, q = quartet.
[b] Appears as triplet.
[c] Appears as quartet.
[d] Appears as quintet.

Table 3. Selected ^nJ(C,H) values (Hz) of pyrazolo[1,5-*a*]pyrimidine derivatives

Compound	C-2	C-3	C-3a	C-5	C-6	C-7	5-CH_3	7-CH_3	CO
4	^1J(C-2,H-2) = 186.0 ^2J(C-2,H-3) = 5.4	^1J(C-3,H-3) = 182.2 ^2J(C-3,H-2) = 9.7	^2J(C-3a,H-3) = 6.8 ^3J(C-3a,H-2) = 6.8	—	^1J(C-6,H-6) = 172.4 ^3J(C-6,7-CH_3) = 4.6	^2J(C-7,7-CH_3) = 6.5 ^2J(C-7,H-6) = 3.1	—	^1J(7-CH_3) = 130.9 ^3J(7-CH_3,H-6) = 3.7	^3J(CO,OCH_2) = 3.3 ^3J(CO,H-6) = 1.5
5	^1J(C-2,H-2) = 186.4 ^2J(C-2,H-3) = 5.5	^1J(C-3,H-3) = 181.3 ^2J(C-3,H-2) = 9.7	^2J(C-3a,H-3) = 6.8 ^3J(C-3a,H-2) = 6.8	^2J(C-5,5-CH_3) = 6.6 ^2J(C-5,H-6) = 2.0	^1J(C-6,H-6) = 171.3 ^3J(C-6,5-CH_3) = 3.7	—	^1J(5-CH_3) = 128.2 ^3J(5-CH_3,H-6) = 1.6	—	^3J(CO,OCH_2) = 3.6 ^3J(CO,H-6) = 3.6
6	^2J(C-2,H-3) = 4.4 ^3J(C-2,H-*ortho*) = 4.4	^1J(C-3,H-3) = 180.2	^2J(C-3a,H-3) = 6.7	—	^1J(C-6,H-6) = 172.4 ^3J(C-6,7-CH_3) = 4.5	^2J(C-7,7-CH_3) = 6.6 ^2J(C-7,H-6) = 3.2	—	^1J(7-CH_3) = 130.8 ^3J(7-CH_3,H-6) = 3.6	^3J(CO,OCH_2) = 3.2 ^3J(CO,H-6) = 1.4
7	^2J(C-2,H-3) = 4.3 ^3J(C-2,H-*ortho*) = 4.3	^1J(C-3,H-3) = 179.6	^2J(C-3a,H-3) = 6.9	^2J(C-5,5-CH_3) = 6.6 ^2J(C-5,H-6) = 2.0	^1J(C-6,H-6) = 171.1 ^3J(C-6,5-CH_3) = 3.7	^2J(C-7,H-6) = 1.5	^1J(5-CH_3) = 128.2 ^3J(5-CH_3,H-6) = 1.8	—	^3J(CO,OCH_2) = 3.4 ^3J(CO,H-6) = 3.4
14	^3J(C-2,H-*ortho*) = 4.0	—	—	—	^1J(C-6,H-6) = 172.8 ^3J(C-6,7-CH_3) = 4.6	^2J(C-7,7-CH_3) = 6.6 ^2J(C-7,H-6) = 3.2	—	^1J(7-CH_3) = 131.1 ^3J(7-CH_3,H-6) = 3.6	^3J(CO,OCH_2) = 3.2 ^3J(CO,H-6) = 1.5
15	^3J(C-2,H-*ortho*) = 4.1	—	—	—	^1J(C-6,H-6) = 172.8 ^3J(C-6,7-CH_3) = 4.5	^2J(C-7,7-CH_3) = 6.6 ^2J(C-7,H-6) = 3.3	—	^1J(7-CH_3) = 131.1 ^3J(7-CH_3,H-6) = 3.6	^3J(CO,OCH_2) = 3.2 ^3J(CO,H-6) = 1.4
19[a]	^1J(C-2,H-2) = 185.8 ^2J(C-2,H-3) = 5.4	^1J(C-3,H-3) = 181.5 ^2J(C-3,H-2) = 9.7	^3J(C-3a,H-5) = 13.8 ^2J(C-3a,H-3) = 6.9 ^3J(C-3a,H-2) = 6.9	^1J(C-5,H-5) = 187.9	^2J(C-6,H-5) = 7.8 ^3J(C-6,7-CH_3) = 3.6	^2J(C-7,7-CH_3) = 6.2 ^3J(C-7,H-5) = 6.2	—	^1J(7-CH_3) = 131.9	^3J(CO,OCH_2) = 3.2 ^3J(CO,H-5) = 1.6 ^4J(CO,7-CH_3) = 0.8
20[a]	^2J(C-2,H-3) = 4.4 ^3J(C-2,H-*ortho*) = 4.4	^1J(C-3,H-3) = 179.7	^3J(C-3a,H-5) = 14.4 ^2J(C-3a,H-3) = 6.9	^1J(C-5,H-5) = 187.7	^2J(C-6,H-5) = 7.7 ^3J(C-6,7-CH_3) = 3.5	^2J(C-7,7-CH_3) = 6.7 ^3J(C-7,H-5) = 5.2	—	^1J(7-CH_3) = 132.0	^3J(CO,OCH_2) = 3.2 ^3J(CO,H-5) = 1.6 ^4J(CO,7-CH_3) = 0.8

[a] Coupling constants, for the CO group, obtained by simulation, LAOCH 3.[14]

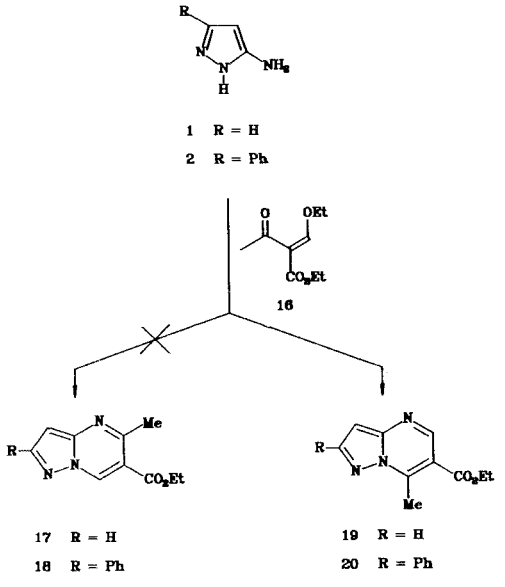


8 $R^1 = R^2 = R^3 = H$, $R^4 = Me$
9 $R^1 = R^2 = R^4 = H$, $R^3 = Me$
10 $R^1 = R^2 = H$, $R^3 = R^4 = Me$
11 $R^1 = Ph$, $R^2 = R^3 = H$, $R^4 = Me$
12 $R^1 = Ph$, $R^2 = R^4 = H$, $R^3 = Me$
13 $R^1 = Ph$, $R^2 = H$, $R^3 = R^4 = Me$
14 $R^1 = Ph$, $R^2 = Cl$, $R^3 = CO_2Et$, $R^4 = Me$
15 $R^1 = Ph$, $R^2 = Br$, $R^3 = CO_2Et$, $R^4 = Me$

Scheme 2

Finally, it is noteworthy that the reaction of **1** with ethyl 2,4-dioxopentanoate at room temperature (24 h) gave rise quantitatively to the same products **4** and **5**, in the ratio 88 : 12 (^{1}H NMR spectrum).

Next, in the light of the previous results, we investigated the nature of the products arising from the reaction of **1** or **2** with ethyl 2-ethoxymethylidene-3-oxobutyrate (**16**). It has been reported previously[9,12] that these reactions yield **19** or **20**, respectively, as the sole product but no diagnostic spectroscopic data were given (Scheme 3).



1 R = H
2 R = Ph

16

17 R = H
18 R = Ph
19 R = H
20 R = Ph

Scheme 3

We found that the reaction between the aminopyrazole **1** or **2** and **16** in ethanol carried out under various conditions (reflux or at room temperature) afforded a single product in every case. In particular, starting from **2**, the ^{1}H NMR spectrum of the crude reaction product displayed two singlets at 8.93 (1H) and 3.26 ppm (3H) in addition to a singlet at 7.02 ppm from the pyrazolic proton H-3. However, these data, in addition to those derived from the fully decoupled ^{13}C spectrum, can be accounted for by both theoretically possible regioisomers, namely **18** and **20**. In the coupled ^{13}C NMR spectrum, whereas C-6 will appear as a doublet of quartets in both structures, the C=O signal is a multiplet due to long-range couplings not only with the OCH_2 and H-5 or H-7 protons but also with the methyl protons. The latter coupling was confirmed by a selective decoupling experiment: on irradiation of the methyl protons, the C=O signal appears as a triplet of doublets.

The long-range coupling $^4J(CO,Me) = 0.8$ Hz and the value of $^3J(CO,H) = 1.6$ Hz, as evaluated from the simulated spectrum (LAOCOON III),[14] are in better agreement with a structure of type **20** than with one of type **18**. The latter value is in fact analogous to those previously observed for ^3J(CO,H-6) in **4** and **6** (σ–"σ"–σ situation), whereas the more σ–π–σ situation present in **5** and **7** should lead to a larger coupling (see Table 3). Nevertheless, it was necessary to seek more diagnostic proof.

The distinction between the two regioisomers **18** *vs.* **20** was unambiguously established by means of ^{15}N NMR (natural abundance) spectroscopy. Thus, the decoupled spectrum of the isolated ester shows three signals at δ −110.8, −111.3 and −156.8 ppm. The lowest frequency resonance was easily attributed to N-7a on the basis of chemical shift considerations. However, diagnostic structural information came from the proton coupled spectrum. The latter shows, in addition to a multiplet for N-7a, one singlet at δ −110.8 and a doublet at δ −111.3 ($|J| = 11.1$ Hz). Considering its size, this ^{15}N,^{1}H coupling must be a geminal coupling, thus unequivocally calling for a situation which is only present in isomer **20**. These results, in addition to confirming the previous hypothesis, allowed us unambiguously to assign the 7-methylpyrazolo[1,5-*a*]pyrimidine structures **19** and **20** to the derivatives obtained.

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