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SYNTHESIS OF 5-AMINO-4,5-DIHYDROPYRAZOLO [3,4-d] PYRIMIDIN-4-ONES AND RELATED ISOMERIC SYSTEMS.

PART I. SYNTHESIS AND CHARACTERIZATION OF POTENTIAL INTERMEDIATES.

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Abstract - Reactions between aminopyrazole-4-carboxylic acids derivatives and orthoesters or amide acetals lead, in most cases, to the introduction of a heteroalkylidene moiety on the amino group of ethyl aminopyrazole-4-carboxylates and on the β-hydrazide nitrogen atom of aminopyrazole-4-carboxhydrazides.

Several factors governing the course of these reactions are discussed.

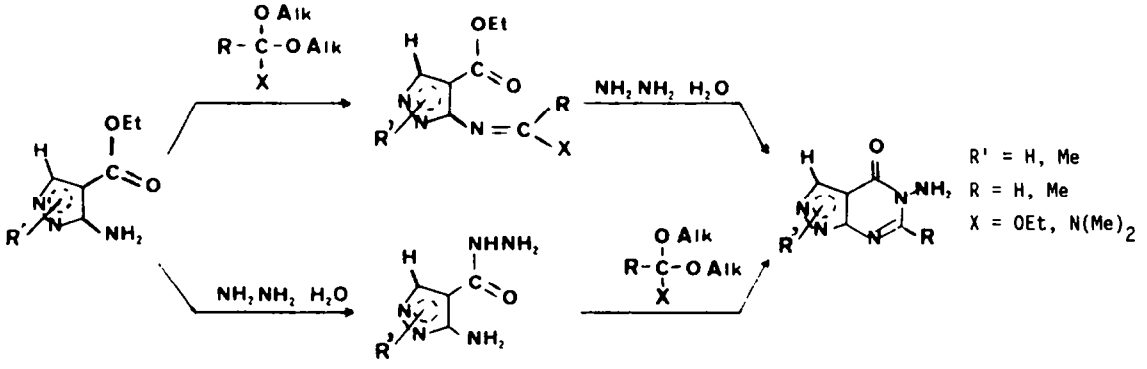
INTRODUCTION

The synthesis of 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones is of growing interest [1-3] because of their structural resemblance to various biologically active purines[4-6].

A priori, four synthetic strategies may be used to prepare these bicyclic compounds (scheme 1). Two of them consist in the introduction of a heteroalkylidene moiety on the amino group of aminopyrazole-4-carboxylic esters by means of an orthoester[3,7] or of an amide acetal[1,8,9] ; the so obtained derivatives are then treated with hydrazine hydrate to yield the expected fused heterocycles [1,3]. The two other strategies are the reverse sequences, i.e., preparation of an aminopyrazole-4-carboxhydrazide, first, and reaction with the orthoester[2,3] or the amide acetal in the second step.

Reactions between aminopyrazole-4-carboxhydrazides and amide acetals were never studied and 2-substituted-5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones have not been described previously.

Thus, the aim of this series of papers is to test the possibilities offered by the four synthetic strategies in view of the synthetis of some new 5-amino-4,5-dihydropyrazolo [3,4-d] pyrimidin-4-ones. In this first paper, the chemical behaviour of aminopyrazole-4-carboxylic esters and of aminopyrazole-4-carboxhydrazides towards aliphatic orthoesters and amide acetals will be studied. The cyclisation processes of the so isolated reaction intermediates will be discussed later[10].

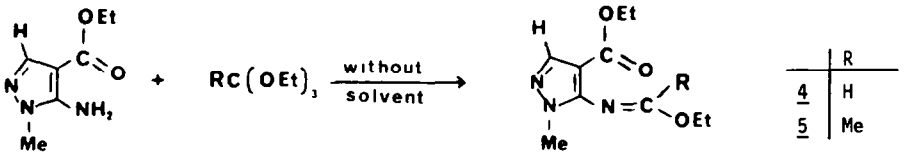


Scheme 1.

RESULTS AND DISCUSSION

Reactions between aminopyrazole-4-carboxylic esters and orthoesters.

Ethyl 5-amino-1-methylpyrazole-4-carboxylate (1) reacts with refluxing triethyl orthoformate[3] or triethyl orthoacetate (in the absence of solvent) to yield the corresponding 5-(ethoxyalkylidene)amino derivatives (4, 5 - scheme 2). No reaction occurs in refluxing methanol.



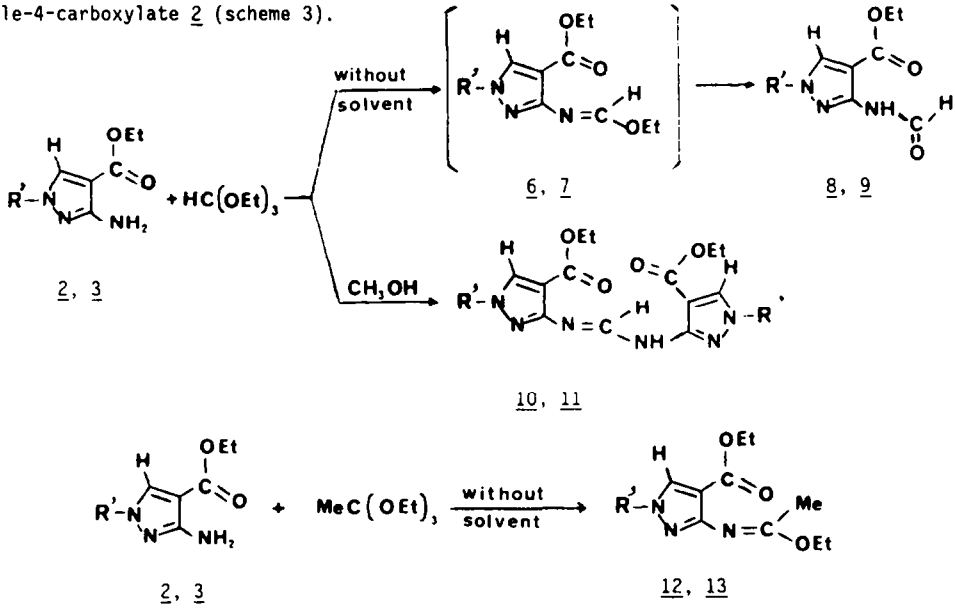
1 4, 5

Scheme 2.

In the absence of solvent, the heterocyclic precursor 2 also reacts with these orthoesters (scheme 3). However, starting from triethyl orthoformate, the expected ethoxymethylene compound 6 was not isolated ; instead the hydrolysis product was obtained : the (formylamino)pyrazolecarboxylate 8[7]. Compound 12 is less sensitive to hydrolysis because of both steric and electronic effects induced by the methyl group on the exocyclic N=C double bond[11,12].

Attempts to obtain 6 using less drastic conditions were unsuccesful. Instead, reaction between 2 and triethyl orthoformate in refluxing methanol leads to the (pyrazolylamino)methylene derivative 10. This latter probably arises from the substitution of the ethoxy group, on the exocyclic N=C double bond in 6, by a second molecule of the amine 2, as the formylamino compound 8 does not react with 2 in refluxing methanol.

At this stage of our study, it may be pointed out that most authors represent tautomeric 3(5)-aminopyrazoles as 5-amino compounds despite the results of Dorn[13,14] and recent investigation of Bruix[15] favouring formulation as 3-amino derivatives. Indeed, in our hands, the chemical behaviour of ethyl 3(5)-aminopyrazole-4-carboxylate (3) closely parallels that of 3-amino-1-methylpyrazole-4-carboxylate 2 (scheme 3).



2, 3 6, 7 8, 9

10, 11

2, 3 12, 13

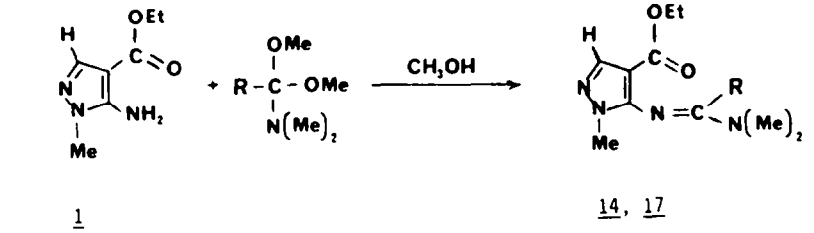
R' = Me : 2, 6, 8, 10, 12
R' = H : 3, 7, 9, 11, 13

Scheme 3.

Moreover, it appears that, due to conjugation with the carboethoxy function, 5-amino derivatives are less reactive than the 3-amino equivalents. For example, 1 does not react with triethyl orthoformate in alcoholic solution and 4 is more resistant towards hydrolysis.

Reactions between aminopyrazole-4-carboxylic esters and amide acetals.

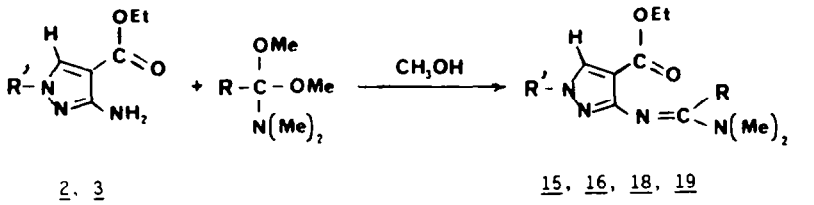
Dimethylformamide dimethyl acetal and dimethylacetamide dimethyl acetal are more reactive[16] than the orthoesters towards 1 - 3 ; indeed, it is possible to introduce a (dimethylamino)alkylidene group on the precursor molecules by performing the synthesis in refluxing methanol, even starting from 1 (scheme 4). Moreover, the enhanced reactivity of the amide acetals inhibits the formation of the (pyrazolylamino)alkylidene derivatives 10 and 11.



1

14, 17

	R
14	H
17	Me



2, 3

15, 16, 18, 19

	R	R'
2		Me
3		H
15	H	Me
16	H	H
18	Me	Me
19	Me	H

Scheme 4

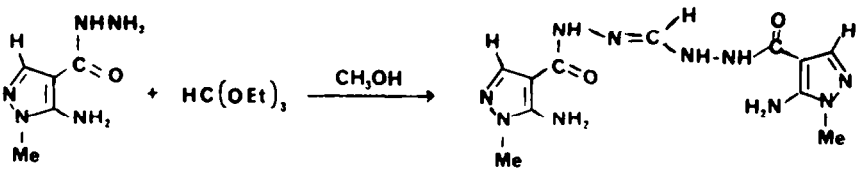
Structure of the ethyl [(heteroalkylidene)amino] pyrazole-4-carboxylates.

Comparison between the NMR spectra (see experimental) of the synthesized (heteroalkylidene) amino compounds shows that the chemical shift of the R group does not change when going from the series of the 3-amino derivatives to the series of the 5-amino derivatives. This observation suggests that all substances possess the same geometry around the exocyclic N=C double bond.

Examination of molecular models indicates that a Z geometry is unlikely in the case of compounds 14 and 17, and we thus assign the E geometry to all of them.

Reactions between aminopyrazole-4-carboxhydrazides and orthoesters.

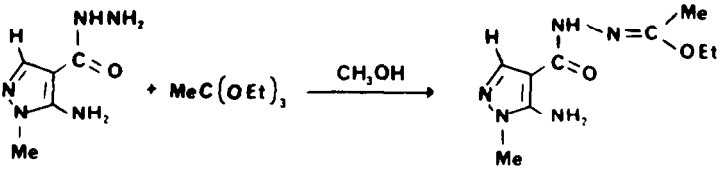
In refluxing methanol, 5-amino-1-methylpyrazole-4-carboxhydrazide 20 reacts with triethyl orthoformate but not to yield an ethoxymethylene compound (no ethoxy signal on the NMR spectrum).The obtained product rather arises from a further substitution by a second molecule of hydrazide (scheme 5). We propose structure 23 for this compound as in enaminocarboxhydrazide systems, the β-hydrazide nitrogen atom is generally considered as having the greater nucleophilic character[17]. Furthermore, the spectral data (see experimental) agree with the suggested structure : the free N-H vibration of the 5-amino group, observed around 3400 cm^{-1} in the infra-red spectra of the precursors 1 and 20 is still present in the infra-red spectrum of the reaction product ; in the NMR spectra, the peak attributed to the protons carried by the β-hydrazide nitrogen atom, and appearing at 4-4.5 ppm for 20 (and also 21, 22), is absent in the case of 23. For steric reasons, the E geometry around the exocyclic N=C double bond is assumed.



20 23

Scheme 5.

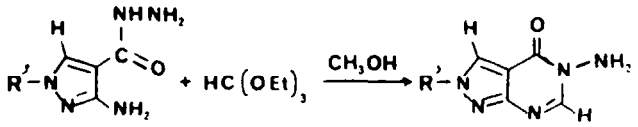
Starting from 20 and triethyl orthoacetate, in refluxing methanol, we isolated an ethoxyethylidene derivative (24 - scheme 6) whose structure is established as for 23. Once more (vide supra), it is probably the presence of the methyl group on the exocyclic N=C double bond that prevents further substitution of 24 by 20.



20 24

Scheme 6.

The 3-amino-1-methylpyrazole-4-carboxhydrazide 21 and compound 22 react differently to 20 with triethyl orthoformate in refluxing methanol (scheme 7). Indeed, these syntheses directly lead to the pyrazolo [3,4-d] pyrimidinones 25 and 26 which were identified by the criteria of Scheiner[18]. The intermediate compounds could not be isolated either by reducing the reaction time or by performing the reaction at room temperature ; the formation of 25, 26 will be discussed elsewhere[10].

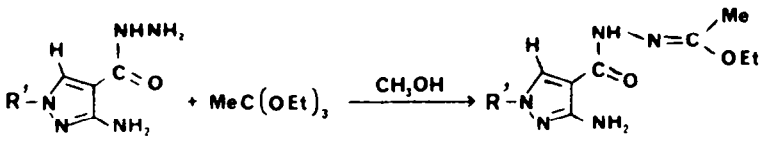


21, 22 25, 26

R' = Me : 21, 25
R' = H : 22, 26

Scheme 7.

Starting from triethyl orthoacetate, however, we obtained the ethoxyethylidene derivatives 27 and 28 (scheme 8). Subsequent cyclization appears to be a higher energy step and is not observed under the present experimental conditions.



21, 22 27, 28

R' = Me : 21, 27
R' = H : 22, 28

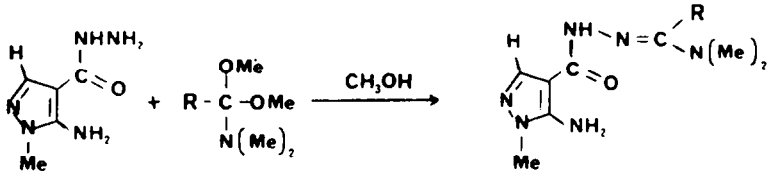
Scheme 8.

Reactions between aminopyrazole-4-carboxhydrazides and amide acetals.

The hydrazides 20-22 readily react with dimethylformamide and dimethylacetamide dimethyl acetals, in refluxing methanol, to yield compounds resulting from the introduction of a (dimethylamino) alkylidene moiety on the precursors (scheme 9).

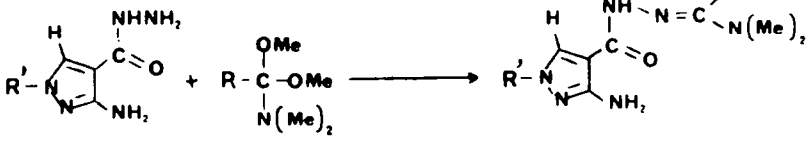
The site of attachment of these moieties is the β-nitrogen atom of the carboxhydrazide function as can be deduced from a detailed analysis of the spectral data (see experimental). In addition to the arguments advanced in the case of 23 (scheme 5), it can be seen, from the NMR spectra, that the methylene and ethylidene protons in 29-34 are less deshielded than in the ethyl 3-[(dimethylamino)alkylidene] aminopyrazole-4-carboxylates 15-19, because these protons are no more in the close vicinity of the carbonyl group.

It may also be emphasized that the structural resemblance between 34 and 28 has been confirmed by the conversion of 28 into 34 upon treatment with dimethylamine (scheme 9).



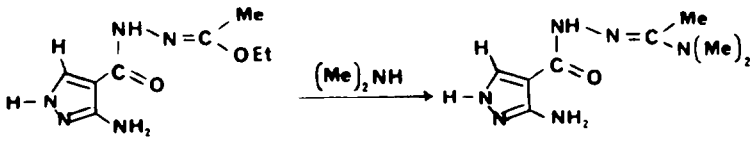
	R
29	H
30	Me

20 29, 30



	R	R'
21		Me
22		H
31	H	Me
32	Me	Me
33	H	H
34	Me	H

21, 22 31-34



28 34

Scheme 9.

In these syntheses, amide acetals still appear to be more reactive than the orthoesters ; indeed, a trimolecular process is never observed (contrary to the reaction carried out from 20 and triethyl orthoformate). Moreover, the dimethylamino group in 31 and 33 exerts a highly deactivating effect on the carbon atom of the exocyclic N=C double bond (when compared with an ethoxy group) as intramolecular cyclization of 31 and 33 does not occur in refluxing methanol.

CONCLUSIONS

The chemical behaviour of aminopyrazole-4-carboxylic acids derivatives towards triethyl orthoformate is highly dependent upon the position of the amino group on the heterocyclic precursor. In these reactions, the tautomeric parent pyrazole can be considered as a 3-aminopyrazole.

On the other hand, the 3- or 5- position of the amino group does not affect the course of the synthesis performed with triethyl orthoacetate, dimethylformamide dimethyl acetal or dimethylacetamide dimethyl acetal,with the amide acetals appearing to be more reactive than the corresponding orthoesters.

EXPERIMENTAL

All melting points are uncorrected. The I.R. spectra were recorded on a Perkin-Elmer 577 spectrophotometer, NMR spectra on a Varian EM-360 L spectrometer (TMS as internal reference) and mass spectra on a Varian 311 A spectrometer.

Compounds 1[19], 2[19], 3[20], 4[3], 8[7], 16[1,8,9], 19[8,9], 20[3], 22[21] and 26[2] are described.

- Ethyl 5-(1'-ethoxyethylidene)amino-1-methylpyrazole-4-carboxylate (5). A mixture of 1 (10 mmoles) and triethyl orthoacetate (4 ml) was refluxed for 5 h. After cooling, excess of orthoester was eliminated by washing with petroleum ether. Yield : 70 % ; b.p. : 165-7°C/20 mm.

  I.R. (film) : 1690 (C=O) cm^{-1} ; $M^{+\cdot}$ = 239 u.m.a.

  N.M.R. (DMSO d_6-δ) : 7.8 (s, 3-H), 4.2 (2q, CH_2, J = 7 Hz), 3.5 (s, N-CH_3), 1.9 (s, CH_3), 1.3 (2t, CH_3) ppm.

  $C_{11}H_{17}N_3O_3$ (239.3) Calc. C 55.22, H 7.16, N 17.56 ; Found C 55.19, H 7.04, N 17.30.

- Ethyl 3-formylamino-1-methylpyrazole-4-carboxylate (8). Prepared from 2 and triethyl orthoformate as described for 5. Reaction time : 3 h. Yield : 80 %, m.p. (petroleum ether ; 40-60°C) :127-8°C.

  I.R. (KBr) : 3340 (NH), 1690, 1670 cm^{-1} (C=O) ; $M^{+\cdot}$ = 197 u.m.a.

  N.M.R. (DMSO d_6-δ) : 9.8 (br, NH), 8.6 (s, CHO), 8.2 (s, 5-H), 4.3 (q, CH_2, J = 7 Hz), 3.9 (s, N-CH_3), 1.3 (t, CH_3) ppm.

  $C_8H_{11}N_3O_3$ (197.2) Calc. C 48.73, H 5.62, N 21.31 ; Found C 48.81, H 5.53, N 21.55.

- Ethyl 3-[(4-carboethoxy-1-methyl-3-pyrazolyl)aminomethylene]amino-1-methylpyrazole-4-carboxylate (10). A solution of 2 (10 mmoles) and triethyl orthoformate (12 mmoles) in 10 ml of methanol was refluxing for 6 h. After cooling, the precipitate was filtered off. Yield : 70 % ; m.p.(CH_3OH) : 73-4°C.

  I.R. (KBr) : 3340 (N-H), 1690 (C=O) cm^{-1} ; $M^{+\cdot}$ = 348 u.m.a.

  N.M.R. (DMSO d_6-δ) : 9.5 (br, N-H) , 8.6 (s, H), 8.2 (s, 5-H), 4,2 (2q, CH_2, J = 7 Hz), 3,7 (s, N-CH_3), 1.2 (2t, CH_3) ppm.

  $C_{15}H_{20}N_6O_4$ (348.4) Calc. N 24.12 ; Found N 23.79.

- Ethyl 3(5)-[(4-carboethoxy-3(5)-pyrazolyl)aminomethylene]aminopyrazole-4-carboxylate (11). Prepared from 3 as described for 10. Yield : 75 % ; m.p. (CH_3OH) : 182-3°C.

  I.R. (KBr) : 3340, 3220 (N-H), 1690 (C=O) cm^{-1} ; $M^{+\cdot}$ = 320 u.m.a.

  N.M.R. (DMSO d_6-δ) : 12.4 (br, N-H), 9.5 (br, N-H), 8.6 (s, H), 8.0 (s, 3(5)-H), 4.2 (q, CH_2, J = 7 Hz), 1.2 (t, CH_3) ppm.

  $C_{13}H_{16}N_6O_4$ (320.3) Calc. C 48.75, H 5.04, N 26.24 ; Found C 48.27, H 5.48, N 25.63.

- Ethyl 3-(1'-ethoxyethylidene)amino-1-methylpyrazole-4-carboxylate (12). Prepared from 2 as decribed for 5. Yield : 90 % ; m.p. (petroleum ether ; 40-60°C): 56-7°C.

  I.R. (KBr) : 1680 (C=O) cm^{-1} ; $M^{+\cdot}$ = 239 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.1 (s, 5-H), 4.1 (2q, CH_2, J = 7 Hz), 3.6 (s, N-CH_3), 1.7 (s, CH_3), 1.2 (2t, CH_3) ppm.

  $C_{11}H_{17}N_3O_3$ (239.3) Calc. C 55.22, H 7.16, N 17.56 ; Found C 54.87, H 7.23, N 18.02.

- Ethyl 3(5)-(1'-ethoxyethylidene)aminopyrazole-4-carboxylate (13). Prepared from 3 as described for 5. Yield : 75 % ; oil.

  I.R. (film) : 3240 (N-H), 1690 (C=O) cm^{-1}, $M^{+\cdot}$ = 225 u.m.a.

  N.M.R. (DMSO d_6-δ) : 12.5 (br, NH), 7.8 (s, 3(5)-H),4.2 (2q, CH_2, J = 7 Hz), 1.7 (s, CH_3),

1.2 (2t, CH_3) ppm.

This product was used without further purification.

- Ethyl 5-[(dimethylamino)methylene]amino-1-methylpyrazole-4-carboxylate (14). Prepared from 1 and N,N-dimethylformamide dimethyl acetal as described for 10. Reaction time : 2 h. Yield : 90 % ; m.p. (petroleum ether ; 40-60°C) : 36-7°C.

  I.R. (KBr) : 1680 (C=O) cm^{-1} ; $M^{+\cdot}$ = 224 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.2 (s, H), 7.5 (s, 3-H), 4.1 (q, CH_2, J = 7 Hz), 3.5 (s, N-CH_3), 3.0 (2s, N-$(CH_3)_2$), 1.2 (t, CH_3) ppm.

  $C_{10}H_{16}N_4O_2$ (224.3) Calc. C 53.56, H 7.19, N 24.98 ; Found C 53.91, H 6.86 , N 25.10.

- Ethyl 3-[(dimethylamino)methylene]amino-1-methylpyrazole-4-carboxylate (15). A solution of 1 (10 mmoles) and N,N-dimethylformamide dimethyl acetal (12 mmoles) in 10 ml of methanol was refluxed for 2 h. The volatile materials were evaporated under reduced pressure. Yield : 95 % ; oil.

  I.R. (film) : 1680 (C=O) cm^{-1} ; $M^{+\cdot}$ = 224 u.m.a.

  N.M.R. (DMSO d_6-δ) : 7.9 (s, H), 7.8 (s, H), 4.2 (q, CH_2, J = 7 Hz), 3.8 (s, N-CH_3), 2.9 (s, $N(CH_3)_2$), 1.2 (t, CH_3) ppm.

  This product was used without further purification.

- Ethyl 5-[1'-(dimethylamino)ethylidene]amino-1-methylpyrazole-4-carboxylate (17). Prepared from 1 and N,N-dimethylacetamide dimethyl acetal as described for 15. Yield : 90 % ; m.p. (petroleum ether ; 40-60°C) : 66-7°C.

  I.R. (KBr) : 1680 (C=O) cm^{-1} ; $M^{+\cdot}$ = 238 u.m.a.

  N.M.R. (DMSO d_6-δ) : 7.6 (s, 3-H), 4.1 (q, CH_2, J = 7 Hz), 3.4 (s, N-CH_3), 3.0 (s, N-$(CH_3)_2$), 1.8 (s, CH_3), 1.2 (t, CH_3) ppm.

  $C_{11}H_{18}N_4O_2$ (238.3) Calc. C 55.45, H 7.61, N 23.51 ; Found C 55.65, H 7.89, N 23.87.

- Ethyl 3-[1'-(dimethylamino)ethylidene]amino-1-methylpyrazole-4-carboxylate (18). Prepared from 2 and N,N-dimethylacetamide dimethyl acetal as described for 15. Yield : 90 % ; m.p. (petroleum ether ; 40-60°C): 78-9°C.

  I.R. (KBr) : 1690 (C=O) cm^{-1} ; $M^{+\cdot}$ = 238 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.0 (s, 5-H), 4.0 (q, CH_2, J = 7 Hz), 3.6 (s, N-CH_3), 3.0 (s, N-$(CH_3)_2$), 1.8 (s, CH_3), 1.2 (t, CH_3) ppm.

  $C_{11}H_{18}N_4O_2$ (238.3) Calc. C 55.45, H 7.61, N 23.51 ; Found C 55.83, H 7.91, N 23.76.

- 3-amino-1-methylpyrazole-4-carboxhydrazide (21). A solution of 2 (20 g) and hydrazine hydrate (40 ml) was refluxed for 2 h. After cooling, the precipitated material was filtered off and washed with cold water. Yield : 90 % , m.p. (H_2O) : 257-8°C.

  I.R. (KBr) : 3420, 3390, 3320, 3300 (N-H), 1630 (C=O) cm^{-1} ; $M^{+\cdot}$ = 155 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.9 (br, N-H), 7.8 (s, 5-H), 5.2 (br, NH_2), 4.2 (br, 3-NH_2), 3.5 (s, N-CH_3) ppm.

  $C_5H_9N_5O$ (155.2) Calc. C 38.70, H 5.85, N 45.14 ; Found C 38.84, H 6.34, N 44.97.

- β-[β-(5-amino-1-methyl-4-pyrazolecarboxy)hydrazinomethylene] 5-amino-1-methylpyrazole-4-carboxhydrazide (23). Prepared from 20 and triethyl orthoformate as described for 10. Reaction time : 2 h. Yield : 90 % ; m.p. (CH_3OH) : 245-7°C.

  I.R. (KBr) : 3340, 3300 (N-H), 1630 (C=O) cm^{-1} ; $M^{+\cdot}$ = 320 u.m.a.

  N.M.R. (DMSO d_6-δ) : 9.8 (br, N-H), 7.8 (s), 6.2 (br, NH_2), 3.5 (s, N-CH_3) ppm.

  This product was used without further purification.

- β-(1'-ethoxyethylidene) 5 amino-1-methylpyrazole-4-carboxhydrazide (24). Prepared from 20 and triethyl orthoacetate as described for 10. Reaction time : 4 h. Yield : 90 % ; m.p. (CH_3OH) : 195-6°C.

  I.R. (KBr) : 3400, 3280, 3120 (N-H), 1620 (C=O) cm^{-1} ; $M^{+\cdot}$ = 225 u.m.a.

  N.M.R. (DMSO d_6-δ) : 9.5 (br, N-H), 7.6 (s, 3-H), 6.2 (br, NH_2), 4.0 (q, CH_2, J = 7 Hz), 3.5 (s, N-CH_3), 1.8 (s, CH_3), 1.2 (t, CH_3) ppm.

  This product was used without further purification.

- 5-amino-4,5-dihydro-2-methylpyrazolo [3,4-d] pyrimidin-4-one (25). Prepared from 21 and triethyl orthoformate as described for 10. Reaction time : 2 h. Yield : 75 % ; m.p. (H_2O) : 264-5°C.

  I.R. (KBr) : 3400, 3300, 3200 (N-H), 1700 (C=O) cm^{-1} ; $M^{+\cdot}$ = 165 u.m.a.

  N.M.R. (DMSO d_6-δ) : 8.5 (s, 3-H), 8.2 (s, 6-H), 5.5 (br, NH_2), 4.0 (s, N-CH_3) ppm.

  $C_6H_7N_5O$ (165.2) Calc. N 42.41 ; Found N 42.35.

- β-(1'-ethoxyethylidene) 3-amino-1-methylpyrazole-4-carboxhydrazide (27). Prepared from 21 and triethyl orthoacetate as described for 15. Reaction time : 2 h. Yield : 85 % ; m.p. (CH_3CN) : 163-4°C.

  I.R. (KBr) : 3400, 3250, 3150 (N-H), 1610 (C=O) cm^{-1} ; $M^{+\cdot}$ = 225 u.m.a.

N.M.R. (DMSO d_6-δ) : 9.8 (br, N-H), 7.9 (s, 5-H), 5.4 (br, NH_2), 4.1 (q, CH_2, J = 7 Hz), 3.8 (s, $N-CH_3$), 2.0 (s, CH_3), 1.2 (t, CH_3) ppm.

This product was used without further purification.

- β-(1'-ethoxyethylidene) 3(5)-aminopyrazole-4-carboxhydrazide (28). Prepared from 22 and triethyl orthoacetate as described for 10. Reaction time : 4 h. Yield : 75 % ; m.p. (CH_3OH) : 197-9°C.

I.R. (KBr) : 3420, 3380, 3250, 3150 (N-H), 1620 (C=O) cm^{-1} ; $M^{+\cdot}$ = 211 u.m.a.

N.M.R. (DMSO d_6-δ) : 9.2 (br, N-H), 8.0 (s, 3(5)-H), 5.9 (br, NH_2), 4.1 (q, CH_2, J = 7 Hz), 2.1 (s, CH_3), 1.2 (t, CH_3) ppm.

This product was used without further purification.

- β-[(dimethylamino)methylene] 5-amino-1-methylpyrazole-4-carboxhydrazide (29). Prepared from 20 and N,N-dimethylformamide dimethyl acetal as described for 10. Reaction time : 2 h. Yield : 90 % ; m.p. (CH_3OH) : 219-20°C.

I.R. (KBr) : 3420, 3300, 3220 (N-H), 1640 (C=O) cm^{-1} ; $M^{+\cdot}$ = 210 u.m.a.

N.M.R. (DMSO d_6-δ) : 9.1 (br, N-H), 7.8 (s, H), 7.6 (s, 3-H), 6.1 (br, NH_2), 3.6 (s, $N-CH_3$), 2.7 (s, $N(CH_3)_2$)ppm.

This product was used without further purification.

- β-[1'-(dimethylamino)ethylidene] 5-amino-1-methylpyrazole-4-carboxhydrazide (30). Prepared from 20 and N;N-dimethylacetamide dimethyl acetal as described for 10. Reaction time : 2 h. Yield : 90 % ; m.p. ($CH_3CO_2C_2H_5$) : 162-3°C.

I.R. (KBr) : 3410, 3200 (N-H), 1620 (CO) cm^{-1} ; $M^{+\cdot}$ = 224 u.m.a.

N.M.R. (DMSOd_6-δ) : 9.5 (br, N-H), 7.6 (s, 3-H), 6.1 (br, NH_2), 3.5 (s, $N-CH_3$), 2.8 (s, $N(CH_3)_2$), 1.8 (s, CH_3) ppm.

This product was used without further purification.

- β-[(dimethylamino)methylene] 3-amino-1-methylpyrazole-4-carboxhydrazide (31). Prepared from 21 and N;N-dimethylformamide dimethyl acetal as described for 10. Reaction time : 1 h. Yield : 75 %; m.p. (CH_3OH) : 190-1°C.

I.R. (KBr) : 3400, 3280 (N-H), 1620 (C=O) cm^{-1} ; $M^{+\cdot}$ = 210 u.m.a.

N.M.R. (DMSO d_6-δ) : 9.9 (br, N-H), 7.7 (br, H and 5-H), 5.3 (br, NH_2) ; 3.5 (s, $N-CH_3$), 2.7 (s, $N(CH_3)_2$) ppm.

This product was used without further purification.

- β-[1'-(dimethylamino)ethylidene] 3-amino-1-methylpyrazole-4-carboxhydrazide (32). Prepared from 21 and N,N-dimethylacetamide dimethyl acetal as described for 15. Reaction time : 1 h. Yield : 85 % ; m.p. (CH_3IOH) : 184-5°C.

I.R. (KBr) : 3400, 3260, 3180 (N-H), 1610 (C=O) cm^{-1} ; $M^{+\cdot}$ = 224 u.m.a.

N.M.R. (DMSO d_6-δ) : 9.6 (br, N-H), 7.9 (s, 5-H), 5.4 (br, NH_2), 3.7 (s, $N-CH_3$), 2.8 (s,$N(CH_3)_2$), 1.8 (s, CH_3) ppm.

This product was used without further purification.

- β-[(dimethylamino)methylene] 3(5)-aminopyrazole-4-carboxhydrazide (33). Prepared from 22 and N,N-dimethylformamide dimethyl acetal as described for 10. Reaction time : 2 h. Yield : 80 % ; m.p. (H_2O) : 207-9°C.

I.R. (KBr) : 3420, 3300, 3200 (N-H), 1640 (C=O) cm^{-1} ; $M^{+\cdot}$ = 196 u.m.a.

N.M.R. (DMSO d_6-δ) : 9.8 (br, NH), 7.8 (br, H and 3(5)-H),5.6 (br, NH_2), 2.7 (s, $N(CH_3)_2$)ppm.

This product was used without further purification.

- β-[1'-(dimethylamino)ethylidene] 3(5)-aminopyrazole-4-carboxhydrazide (34). Prepared from 22 and N,N-dimethylacetamide dimethyl acetal as described for 10. Reaction time : 2 h. Yield : 85 % ; m.p. (CH_3OH) : 197-8°C.

I.R. (KBr) : 3400, 3280, 3200 (N-H), 1640 (C=O) cm^{-1} ; $M^{+\cdot}$ = 210 u.m.a.

N.M.R. (DMSO d_6-δ) : 9.6 (br, N-H), 7.7 (s, 3(5)-H), 5.5 (br, NH_2), 2.8 (s, $N(CH_3)_2$), 1.8 (s, CH_3) ppm.

This product was used without further purification.

- Conversion of 28 to 34. 0,4 g of 28 and 1 ml of dimethylamine in aqueous solution were refluxed for 1 h. Concentration of the solution yielded 0.3 g of 34.

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