SYNTHESIS OF 4-ACETYL (OR CARBETHOXY) -5-METHYL-1-HETEROCYCLYLPYRAZOLES

Shiv P Singh* Jitander K Kapoor and Anil K Sadana
Department of Chemistry .
Kurukshetra University, Kurukshetra-136 119, INDIA

Abstract : Reaction of heterocyclylhydrazines (**1a-f**) with 3-ethoxymethylenepentane-2,4-dione (**2**) and ethyl 2-ethoxymethylene-3-oxobutyrate (**3**) yields exclusively 4-acetyl-5-methyl-1-heterocyclylpyrazoles (**4a-f**) and 4-carbethoxy-5-methyl-1-heterocyclylpyrazoles (**5a-f**), respectively, in good yields.

Introduction

3-Ethoxymethylenepentane-2,4-dione (**2**) and ethyl 2-ethoxymethylene-3-oxobutyrate (**3**) are useful synthons for the construction of heterocyclic systems such as pyrazoles (1,2), isoxazoles(3) and pyrimidines(4,5). In view of our continued interest in the reaction of heterocyclylhydrazines (**1**) with 1,3-dicarbonyl compounds (6,7), which led to the structure revision of the products in many cases, we now report the reaction of **1** with **2** and **3**.

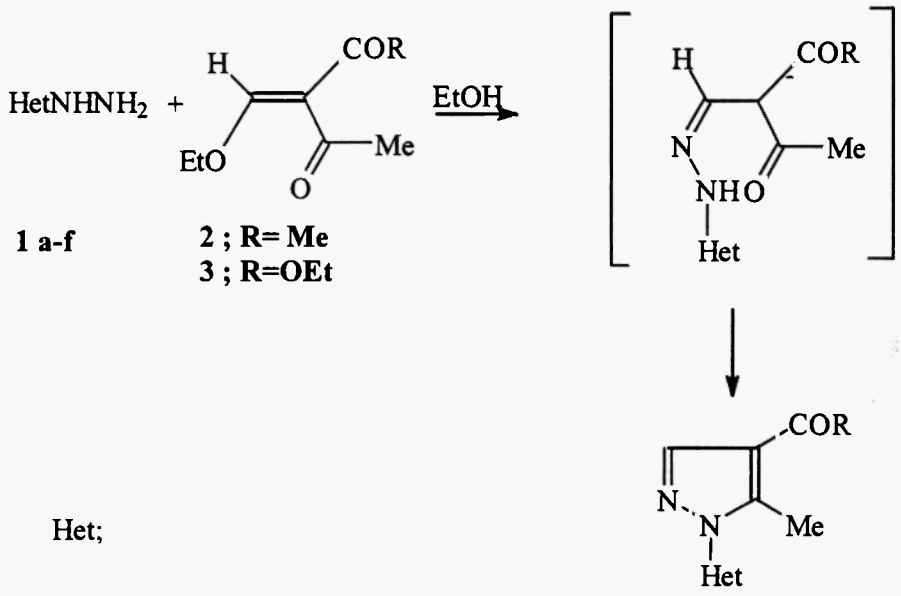
Discussion

Thus, 6-methyl-2-hydrazinobenzothiazole (**1a**) on reaction with **2** in ethanol, afforded a single crystalline compound, m.p 182^{0}C whose structure was established as 4-acetyl-5-methyl-1-(6-methylbenzothiazol-2-yl)pyrazole (**4a**) on the basis of elemental analysis, NMR (^{1}H & ^{13}C) spectral data and mass spectrometry (M^+, m/z 271.0789).

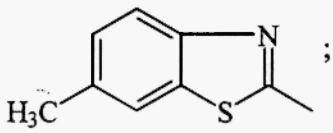
Attachment of methyl group at position -5 of pyrazole moiety was established by the appearance of a relatively downfield three proton singlet at δ ~3.00 assuming a planar geometry of the molecule (8). Further, a signal at δ 7.84 could be assigned to pyrazole C_3-H. An inspection of ^{13}C NMR spectrum of **4a** displayed signals at δ 143.50, 122.85 and 145.67 which are assigned to C_3, C_4 and C_5 carbon of pyrazole moiety, besides a downfield signal at δ 193.79 ($COCH_3$). These values are in complete agreement with those recorded with for similarly constituted molecules.

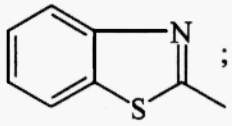
Generality of this reaction was established by treating several heteroclylhydrazines (**1b-f**) with **2** (**Scheme-1**). In all the cases, single isomers were obtained (**4b-f**) which were characterized by their ^{1}H NMR data (*vide* experimental). Reaction of **1a-f** with ethyl 2-ethoxymethylene-3-oxobutyrate (**3**) similarly provided 4-carhethoxy-5-methyl-1-heterocyclylpyrazoles (**5a-f**) exclusively in good yields.

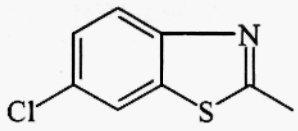
*To whom correspondence should be addressed.

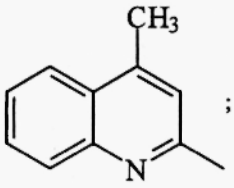


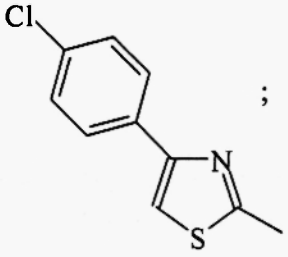
Het;

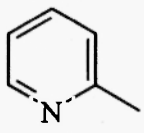
a, 

b, 

c, 

d, 

e, 

f, 

Scheme-1

The ^{1}H NMR spectrum of all these compounds (**4** and **5**) displayed a sharp singlet at ~δ 3.0, which is characteristic for C_5-CH_3 of pyrazole moiety. The ^{13}C NMR spectrum of **5a** exhibits signals for C_3 and C_5 at the same place as in **4a**, while C_4 appeared somewhat shielded at δ 115.36. This is understandable as carbethoxy group is less electron-withdrawing than an

acetyl group. It appears reasonable to assume that the reaction proceeds through the initial formation of a hydrazone by the attack of terminal NH_2 of hydrazine on the highly electrophilic extra chain carbon of **2** and **3** (1b,10). This is followed by ring closure of this intermediate via interaction of a carbonyl group with the other nucleophilic site (**Scheme-1**). It is interesting to mention here that alkylhydrazines react with **2** and **3** to give a mixture of 3-and 5-methyl-4-acyl-1-substituted pyrazoles with the predominance of former over the latter. On the other hand, arylhydrazines generate the 5-methyl derivative as the major product (2). Formation of an exclusive product is now observed with heterocylcylhydrazines.

This difference in reactivity can be explained by taking into account the nucleophilicities of the two nitrogen atoms in different hydrazines. It can be surmised that whereas alkylhydrazines react predominantly through secondary nitrogen atoms, heterocyclylhydrazines attack only *via* terminal primary -NH_2. Arylhydrazines provide the intermediate case where the major product is obtained by reaction through terminal-NH_2 and minor one *via* secondary nitrogen atom.

Conclusions

Finally, the following conclusions may be drawn from the present study.

i). Heterocyclylhydrazines react with **2** and **3** yielding pyrazoles instead of diazepines or triazepines as reported in several related cases(11).

ii). These compounds (**4** and **5**) have planar geometry and consequently isomeric pairs having methyl group at positions -3 and –5 can easily be distinguished by ^{1}H NMR spectroscopy.

iii). Many 4-acylpyrazoles have found application in the synthesis of biologically important compounds (1c,12). Incorporation of a heterocyclic ring in such compounds is thus significant.

Experimental

Melting points were taken in a sulfuric acid bath and are uncorrected. The IR (nujol) and ^{1}H NMR spectra were recorded on Perkin Elmer IR-842, R-32 (90MH_Z), Bruker (300 MHz) spectrometers, respectively. ^{13}C NMR spectra were recorded on a JEOL JNM GSX 400 instrument, Mass spectra were measured on a Kratos MS-50 mass spectrometer. 2-Hydrazinopyridine (**1f**) was obtained from Aldrich and other hydrazines (**1a-e**) were synthesized using literature procedures (13).

Synthesis of 4-acetyl-5-methyl-1-heterocyclylpyrazoles (4a-e)

General Procedure: 3-Ethoxymethylenepentane-2-4-dione (**2**, 0.78g, 5mmol) in ethanol (10ml) was slowly added with stirring to a solution or suspension of an appropriate hydrazine I (5mmol) in ethanol (50 ml). The resulting solution was stirred at room temperature for 30 minutes. The solvent was evaporated in vacuuo and the residue was recrystallized from a suitable solvent to give 4.

4a: m.p. 182°C (from ethanol), Yield 75%: IR : 1675 (CO) cm^{-1}, ^1H NMR ($CDCl_3$): δ 2.34 (s, 6H, $COCH_3$ and C_6–CH_3), 3.00 (s, 3H, C_5-CH_3, pyrazole), 7.12 (dd, 1H, J=8.5 & 1.5Hz, C_5-H), 7.46 (d, 1H, J=1.5Hz, C_7-H), 7.66 (d, 1H, J=8.5Hz. C_4-H), 7.84 (s, 1H, C_3-H pyrazole), ^{13}C NMR ($CDCl_3$): δ 13.21 (C_5-CH_3, pyrazole), 21.58(C_6-CH_3), 9.18 ($COCH_3$), 121.20 (C-7), 122.77 (C-4), 122.85 (C-4, pyrazole), 128.22 (C-5), 133.36 (C-7a). 135.84(C-6), 143.50(C-3. pyrazole), 145.67 (C-5. pyrazole), 149.13 (C-3a), 159.63 (C-2), 193.79 (CO) : MS: M^+, m/z 271.0789. (Found N. 15.38.$C_{14}H_{13}N_3OS$ requires N. 15.50%).

4b: m.p. 186°C (from ethanol). Yield 78%: IR :1678 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 2.40 (s, 3H, $COCH_3$), 3.10 (s, 3H, C_5-CH_3, pyrazole), 7.15-7.52 (m,2H, C'$_5$-H and C'$_6$-H), 7.70-8.00 (m, 3H, C'$_4$-H, C'$_7$-H and C_3-H. pyrazole) : MS : M^+, m/z 257.0626. (Found N. 16.30. $C_{13}H_{11}N_3OS$ requires N. 16.34%).

4c: m.p.205°C (from methanol). Yield 70%: IR: 1680 (CO) cm^{-1}: ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H, $COCH_3$), 3.12 (s, 3H, C_5-CH_3. pyrazole), 7.45 (dd, 1H, J=8.0 & 1.5Hz, C'$_5$–H), 7.64 (d, 1H, J=1.5Hz, C'$_7$-H), 7.86 (d, 1H, J=8.0 Hz, C'$_4$-H), 8.06 (s,1H, C_3-H, pyrazole), (Found N. 14.35. $C_{13}H_{10}ClN_3OS$ requires N, 14.41%).

4d: m.p. 148°C (from ethanol). Yield 75%: IR: 1672 (CO) cm^{-1}: ^1H NMR ($CDCl_3$): δ 2.35 (s, 3H, $COCH_3$), 2.72 (s, 3H, C'$_4$-CH_3), 3.02 (s, 3H, C'$_5$-CH_3), 7.40-8.07 (m, 6H, ArH and C_3-H. pyrazole) : MS: M^+, m/z 265.1211. (Found N. 15.74 $C_{16}H_{15}N_30$ requires N. 15.85%).

4e: m.p. 189-90 °C (from ethanol), Yield 70%; IR: 1675 (CO) cm^{-1}: ^1H NMR ($CDCl_3$) : δ2.50 (s, 3H, $COCH_3$), 3.14 (s, 3H, C_5-CH_3, pyrazole), 7.32 (s,1H,C_5-H, thiazole), 7.40 (dd, 2H, J=8.6 Hz, p-chlorophenyl), 7.81 (dd, 2H, J=8.6Hz p-chlorophenyl), 7.98 (s, 1H, C_3-H pyrazole), (Found N 12.43. $C_5H_{12}N_3O_2SCl$ requires N. 12.59%).

4f: m.p. 78°C (from ethanol). Yield 70%; IR: 1660 (CO) cm^{-1}: ^1H NMR ($CDCl_3$) : δ 2.50 (s, 3H, $COCH_3$), 2.93 (s, 3H, C_5-CH_3, pyrazole), 7.16-7.38 (m,1H, C'$_5$-H), 7.69-7.94 (m, 2H, C'$_3$-H and C'$_4$-H), 8.01 (s, 1H, C_3-H, pyrazole), 8.51 (d, 1H, J=5.0 Hz. C'$_6$-H), (Found N. 20.75, $C_{11}H_{11}N_3O$ requires N. 20.89%).

Synthesis of 4-carbethoxy-5-methyl-1-heterocyclylpyazoles(5a-f)

General procedure: To a stirred solution of **1** (5mmol) in ethanol (50ml) was added a solution of ethyl 2-ethoxymethylene-3-oxobutyrate (**3** 0.93g, 5mmol) in ethanol (10ml) during 10 minutes. After stirring the resulting solution for 15-30 minutes the solvent was removed in vacuuo. The residue so obtained was recrystallized from a suitable solvent to give **5**.

5a : m.p. 168°C (from ethanol), Yield 78%: IR: 1710 (CO) cm^{-1} : ^1H NMR ($CDCl_3$) : δ 1.25 (t, 3H, J=7.0 Hz, $-CH_2CH_3$), 2.34 (s, 3H, C'$_6$-CH_3), 2.97 (s, 3H, C_5-CH_3, pyrazole), 4.19 (q, 2H, J=7.0 Hz,-CH_2CH_3), 7.13 (dd, 1H, J=8.0 & 1.5 Hz, C'$_5$-H), 7.48 (d, 1H, J=1.5 Hz, C'$_7$-H), 7.65 (d, 1H, J=8.0 Hz, C'$_4$-H), 7.87 (s, 1H, C_3-H, pyrazole) : ^{13}C NMR ($CDCl_3$) : δ 12.97 (C_5-CH_3, pyrazole), 14.38 (-CH_2CH_3), 21.56 (C_6-CH_3), 60.39 (-CH_2CH_3), 115.36 (C-4 pyrazole), 121.15 (C-7), 122.59 (C-4), 128.01(C-5), 133.24 (C-7a), 135.50 (C-6), 143.59 (C-3, pyrazole), 146.20 (C-5, pyrazole), 149.17 (C-3a), 159.91 (C-2), 163.15 (CO): MS: M^+. m/z 301.0888. (Found N. 13.87. $C_{15}H_{15}N_3O_2S$ requires N. 13.95%).

5b : m.p. 143°C (from methanol). Yield 75%: IR: 1715 (CO) cm^{-1} : ^1H NMR ($CDCl_3$+DMSO-d_6): δ 1.33 (t, 3H, J=7.0 Hz, -CH_2CH_3), 3.10 (s, 3H, C_5-CH_3 pyrazole), 4.29 (q, 2H, J=7.0 Hz, -CH_2CH_3), 7.20-7.43 (m, 2H, C'$_5$-H and C'$_6$-H), 7.70-7.93 (m, 2H, C'$_4$-H and C'$_7$-H), 7.97 (s, 1H, C_3-H, pyrazole): MS : M^+, m/z 287.0728. (Found N. 14.58 $C_{14}H_{13}N_3O_2S$ requires N. 14.63%).

5c : m.p. 190°C (from methanol). Yield 70% : IR : 1718 (CO) cm^{-1} : ^1H NMR ($CDCl_3$) :δ 1.24 (t, 3H, J=7.O Hz, $-CH_2CH_3$), 2.96 (s, 3H, C_5-CH_3, pyrazole), 4.18 (q, 2H, J=7.0 Hz, -CH_2CH_3),7.30 (dd, 1H, J=8.5 & 2.0 Hz, C_5-H), 7.57-7.73 (m, 2H, C_4-H and C_7-H), 7.97 (s, 1H. C_3-H. pyrazole). (Found N. 13.09. $C_{14}H_{12}ClN_3O_2S$ requires N. 13.06%).

5d : m.p.108°C (from methanol) , Yield 72%; IR : 1720 (CO) cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 1.32 (t, 3H, J=7.0 Hz, -CH_2CH_3), 2.71 (s, 3H, C_4-CH_3), 3.02 (s, 3H, C_5-CH_3, pyrazole), 4.26 (q, 2H, J=7.0 Hz, -CH_2CH_3), 7.44-7.92 (m, 5H, ArH), 7.99 (s, 1H, C_3-H, pyrazole) : MS : M^+ , m/z 295.1322. (Found N, 14.18, $C_{17}H_{17}N_3O_2$ requires N, 14.24%).

5e m.p. 144-45 °C (from ethanol), Yield 78%; IR : 1716 (CO) cm^{-1}, ^1H NMR ($CDCl_3$) : δ 1.39 (t, 3H, J=7.25Hz, -CH_2CH_3), 3.12(s, 3H, C_5-CH_3 pyrazole), 4.35 (q, 2H, J=7.25 -CH_2CH_3) 7.30 (s, 1H, C_5-H thiazolyl), 7.41 (d, 2H, C_2-H, C_6-H J=8.6 Hz, p-chlorophenyl) 7.41 (d, 2H, C_2-H, C_6-H, J=8.6 Hz, p-chlorophenyl) 7.82 (d, 2H, C_3-H, C_5-H, J=8.6 Hz, p-chlorophenyl), 8.01 (s, 1H, C_3-H pyrazolyl) (Found N 11.83 , $C_{16}H_4N_3O_2SCl$ requires N, 12.08%).

5f : m.p. 53°C (from ethanol), Yield 70%; IR : 1715 (CO) cm^{-1} ; ^1H NMR ($CDCl_3$) : δ 1.35 (t, 3H, J=7.0 Hz, -CH_2CH_3), 2.91 (s, 3H, C_5–pyrazole), 4.31 (q, 2H, J=7.0H_2, -CH_2CH_3). 7.02-7.35 (m, 1H, C'$_5$H) 7.87-7.92 (m, 2H, C'$_3$–H and C'$_4$-H), 8.02 (s, 1H,C_3-H, pyrazole), 8.52 (dd, 1H, J=5.0 & 1.2Hz, C'$_6$-H), (Found N, 18.12, $C_{12}H_{13}N_3O_2$ requires N,18.18%).:

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