Chemistry of Heterocyclic Compounds, Vol. 47, No. 6, September 2011 (Russian original Vol. 47, No. 6, June, 2011)

MODIFIED METHOD FOR THE SYNTHESIS OF ISOMERIC N-SUBSTITUTED (1*H*-PYRAZOLYL)PROPANE-1,3-DIONES

I. V. Taydakov[1*] and S. S. Krasnoselsky[2]

The condensation reaction of isomeric N-substituted (1H-pyrazol-4-yl)ethanones with the ethyl esters of pyrazole carboxylic acids and fluoroacetic acids has been studied using NaH as the base. Under optimized conditions, it proved to be a convenient and preparative method for the synthesis of N-substituted (1H-pyrazolyl)propane-1,3-diones and (1H-pyrazolyl)-4-polyfluorobutane-1,3-diones.

Keywords: 1,3-diketones, pyrazoles, Claisen condensation.

Heterocyclic 1,3-diketones are important intermediate compounds in organic synthesis and find widespread use as extracting agents, analytical reagents, and as ligands in coordination chemistry [1, 2]. In terms of our current scientific plan in searching for novel heterocyclic ligands there arose the need to prepare a series of dibenzoylmethane analogs which contain different pyrazole substituents.

A few reports are in the literature on these compounds synthesis. Most of the publications relate to the preparation of acyl pyrazolone derivatives [3, 4] but reported methods cannot be used for the preparation of the target compounds. The reaction of 1,3,4,6-tetracarbonyl compounds with hydrazines to give 1,3-diketones has also been reported [5] but this method is not universal and requires hardly obtainable starting materials.

The most obvious route to synthesis of the pyrazole-containing diketones is a Claisen condensation of the corresponding carbonyl compounds in the presence of a base. This method has been little studied because of the relatively poor availability of pyrazole ketones. Data existing in the literature is restricted, in all, to a few examples, *viz*. the condensation of 1-(1,3,5-trimethyl-1H-pyrazol-4-yl)ethanone with ethyl acetate in the presence of sodium ethylate [6] and the reaction of ethyl 1-alkylacetyl-4-methyl-1H-pyrazole-5-carboxylates, also with ethyl acetate [7].

We have previously reported a general method for the synthesis of isomeric pyrazolyl ketones. This work now relates to the reaction of compounds **1** with the pyrazole carboxylates **2** and with certain other esters in the presence of bases.

*To whom correspondence should be addressed; e-mail: taidakov@gmail.com.

[1]G. S. Petrov Institute of Plastics, 35 Perovskij Pr., Moscow 111024, Russia.

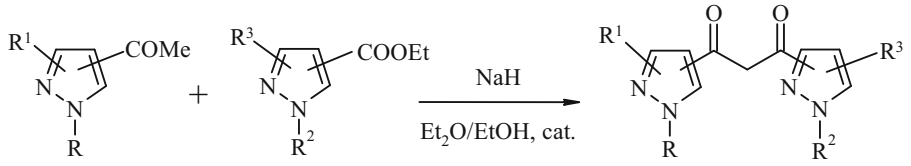
[2]People's Friendship University of Russia, 6 Miklukho-Maklaya St., Moscow 117198, Russia, e-mail: taidakov@gmail.com.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 843–848, June, 2011. Original article submitted October 29, 2010.

0009-3122/11/4706-0695

The right choice of solvent and base is often critical for the achievement of high and steady yields in the condensation reactions. On the basis of preliminary experiments it was found that the best results were obtained using sodium hydride in ether as the base. Sodium ethylate in ethanol, ether, or toluene gave the poorest results as did the use of sodium suspension in toluene or benzene.

A commercially available 60% suspension of NaH in oil was used and, if the reaction product is a relatively low boiling, oil does not have to be washed out. Alternatively, the hydride before reaction is washed several times with dry hexane and suspended in ether directly in the reaction flask.



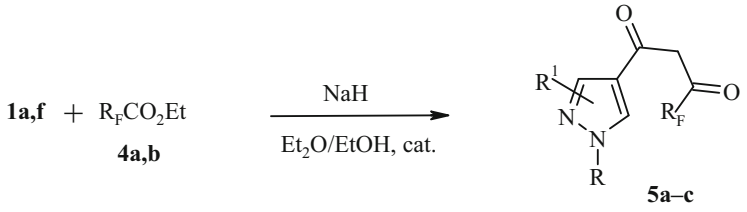
1a–e **2a–e** **3a–f**

1a, **3a,e** R = Me, R^1 = H-3, H-5; **2a, 3a,d** R^2 = Me, R^3 = H-3, H-4; **1b**, **3b** R = Me, R^1 = H-4, H-5; **2b, 3b** R^2 = Me, R^3 = H-4, H-5; **1c**, **3c** R = *i*-Pr, R^1 = H-4, H-5; **2c, 3c** R^2 = *i*-Pr, R^3 = H-4, H-5; **1d**, **3d** R = Me, R^1 = H-3, H-4; **2d, 3e** R^2 = Me, R^3 = H-3, H-5; **1e, 3f** R = Me, R^1 = H-3, H-5; **2e**, **3f** R^2 = Me, R^3 = 3-Me, H-5

The addition of a small amount of absolute ethanol to the NaH before the process start is a necessary condition for a smooth reaction. The traces of sodium ethylate formed catalyze the reaction and decrease its induction period. In the opposite case (particularly for large loading) the reaction may go out of control.

The temperature regime and the time of the reaction markedly depend on the activity of the ester used. Most of the reactions were carried out at room temperature without external cooling but the condensation involving poorly active esters of 1-methyl-1H-pyrazole-4-carboxylic acid needed refluxing for several days and a change to xylene or toluene as solvent in order to increase the reaction temperature.

We have also studied the possibility of carrying out the condensation of acetyl pyrazoles with the ethyl esters of difluoro- or trifluoroacetic acids. Under these conditions the reaction occurs smoothly, even at room temperature, and leads to the expected 1,3-diketone with fluorinated substituents. The yields of compounds **3a–f** and **5a–c** are generally good (see Table 1).



5a–c

4a, **5a**,**b** R_F = CF_3, **4b**, **5c** R_F = CHF_2; **1f**, **5a**–**c** R = Me; **5a** R^1 = H-5, 3-Me; **1f**, **5b**,**c** R^1 = H-3, 5-Me

The highest yields were obtained when condensing the ketones **1** with the esters of 3- or 5-pyrazole carboxylic acids or with fluorinated esters. However, in this case, a clear dependence between ketone structure and product yield was not seen.

Modest yields of the diketones were obtained using, as ester component, the poorly active esters of the pyrazole carboxylic acids **3e** and **3f**. Completion of the reaction needs prolonged refluxing of the reaction mixture in toluene or xylene as a high boiling solvent.

TABLE 1. N-Substituted (1H-Pyrazolyl)propane-1,3-diones **3a–f** and (1H-Pyrazolyl)-4-polyfluorobutane-1,3-diones **5a**–**c**

Product	Ketone	Ester	Time, h	T, °C	Yield, %
3a	**1a**	**2a**	5	40	57
3b	**1b**	**2b**	5	40	87
3c	**1c**	**2c**	5	40	76
3d	**1d**	**2a**	5	40	59
3e	**1a**	**2d**	30	110	51
3f	**1e**	**2e**	24	110	64
5a	**1a**	**4a**	3	30	82
5b	**1f**	**4a**	3	30	78
5c	**1f**	**4b**	3	30	75

Analysis of the ^{1}H NMR spectra showed that compounds **3** are significantly enolized in the solution. In $CDCl_3$ signals can be observed which correspond to both the ketone and enol form but transition to the more polar DMSO-d_6 solvent showed signals virtually only corresponding to the enol form. Thus, the ^{1}H NMR spectrum of compound **3d** in $CDCl_3$ showed signals at 6.80 and 6.45 ppm for the H-4 protons of the pyrazole fragment in the keto and enol forms respectively (the signals for the H-3 proton fell together). In addition, the signals at 6.95 (enol double bond CH) and at 3.25 ppm (ketone CH_2 fragment protons) were present. The intensities of the signals for both forms related to one proton indicate a ratio of 1:2.25 (keto:enol). The spectrum of the same compound in DMSO-d_6 (at the same concentration and temperature) showed only one set of signals, *viz*. at 7.32 and 6.82 (pyrazole fragment CH) and 7.65 ppm (double bond CH). A similar dependence was observed for the other compounds **3**.

Compounds **5** are fully in the enolic form, even in $CDCl_3$. Hence the ^{1}H NMR spectrum of compound **5a** in $CDCl_3$ or DMSO-d_6 (values for the chemical shifts for DMSO-d_6 solutions given in brackets) shows one set of signals, *viz*. for the protons of the enol multiple bond at 7.91 ppm (8.85), the pyrazole fragment at 6.15 (6.56), and the protons of the NCH_3 and CH_3 groups at 3.92 (3.83) and 2.50 (2.33) ppm respectively.

Hence it was found, that condensation of pyrazole type ketones with 1-alkyl-1H-pyrazole carboxylic acid esters in the presence of NaH is an efficient method for the synthesis of different substituted 1,3-bis(pyrazolyl)propane-1,3-diones. Condensation of ethyl trifluoroacetate or ethyl difluoroacetate with ketones gave 1,3-dicarbonyl compounds which contained fluorinated substituents.

EXPERIMENTAL

^{1}H and ^{19}F NMR spectra were recorded on Bruker AC-300 or AM-300 instruments (300 and 283 MHz respectively) at 298 K for solutions in $CDCl_3$ or DMSO-d_6. TMS was used as internal standard for ^{1}H NMR spectra and $CFCl_3$ for ^{19}F NMR spectra (δ 0.00). ^{13}C NMR spectra were taken on a Varian 400-MR instrument (100 MHz) at 328 K with TMS as internal standard. Mass spectra were recorded on a Finnigan Incos 50 instrument (direct sample injection, EI, 70 eV ionization energy). Melting points were taken in open capillaries on an MRM-1HV instrument (Shorpp, Germany).

The starting ketones **1a–f** were bought from the ART-Chem company, the esters **2a–e** from Art-Chem Gmbh (Berlin-Buch Campus, Germany), and the remaining reagents from Aldrich (USA) and were used without additional purification. Diethyl ether, toluene, xylene, and hexane were initially distilled over metallic sodium. All of the reactions with NaH were carried out in an argon atmosphere.

Synthesis of Compounds 3 and 5 (General Method). Sodium hydride (4.7 g, 195 mmol, 30% excess, as a 60% suspension in vaseline oil) was washed by decanting with dry hexane (3×50 ml). Dry ether (200 ml)

was added (in the synthesis of compounds **3e** and **3f** an equivalent volume of dry toluene). Absolute ethanol (1.5 ml, 27 mmol) was added dropwise with stirring and mixed for 5 min. A mixture of ketone **1** (150 mmol) and the ester **2** or **4** (150 mmol) was added dropwise with the necessary amount of the solvent. After addition of the first drops the reaction mixture sometimes needed some heating for the evolution of gas to begin. The remainder of the reagents was added at such a rate that produced a steady evolution of hydrogen. At the end of the addition the mixture was stirred for 1 h and heated under the conditions indicated in Table 1. The product was cooled in an ice bath, ethanol (96%, 5 ml) was added carefully to decompose the excess NaH, and diluted acetic acid (15 ml of glacial acetic acid were diluted by water to 100 ml) was added dropwise. The mixture was extracted with CH_2Cl_2 (3×100 ml) and the organic phase was washed with saturated NaCl solution (100 ml), dried over $MgSO_4$, and evaporated *in vacuo*. In this process the diketones usually crystallized and could be filtered off. If the product is a liquid the solvent was evaporated and the residue was distilled *in vacuo*.

1-(1-Methyl-1H-pyrazol-4-yl)-3-(1-methyl-1H-pyrazol-5-yl)propane-1,3-dione (3a). Yellowish crystalline material; mp 139–140ºC (benzene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 14.51 (1H, s, OH); 8.55 (1H, s, CH); 8.10 (1H, s, CH); 7.55 (1H, s, CH=); 7.23 (1H, s, CH); 6.81 (1H, s, CH); 4.21 (3H, s, CH_3); 3.92 (3H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 187.63; 177.21; 140.25; 139.10; 138.30; 132.63; 123.21; 110.33; 94.85; 39.90; 38.91. Mass spectrum, *m/z* (I_{rel}, %): 232 $[M]^+$ (24), 109 $[M–CF_3]^+$ (100), 82 (46), 69 (27), 42 (73). Found, %: C 57.13; H 5.67; N 24.19. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

1,3-Bis(1-methyl-1H-pyrazol-3-yl)propane-1,3-dione (3b). Yellowish crystalline material; mp 131–132ºC (a mixture of ether and hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.40 (2H, s, CH); 7.05 (1H, s, CH=); 6.75 (2H, s, CH); 3.95 (6H, s, $2CH_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 189.81; 179.42; 150.11; 147.35; 133.43; 133.12; 106.22; 92.70; 39.31. Mass spectrum, *m/z* (I_{rel}, %): 232 $[M]^+$ (56), 204 $[M–CO]^+$ (20), 109 (100), 54 (31), 42 (76). Found, %: C 57.09; H 5.48; N 24.51. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

1,3-Bis(1-isopropyl-1H-pyrazol-3-yl)propane-1,3-dione (3c). Light-yellow solid material; mp 74–75ºC (a mixture of ether and hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.52 (2H, s, CH); 7.13 (1H, s, CH=); 6.71 (2H, s, CH); 4.62 (2H, sept, *J* = 6.9, C<u>H</u>$(CH_3)_2$); 1.52 (12H, d, *J* = 6.8, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 189.71; 179.60; 149.54; 146.73; 130.41; 129.91; 106.08; 105.93; 92.51; 54.12; 53.94; 22.61; 22.40. Mass spectrum, *m/z* (I_{rel}, %): 288 $[M]^+$ (17), 137 (76), 95 (100), 43 (54). Found, %: C 62.81; H 7.05; N 20.03. $C_{15}H_{20}N_4O_2$. Calculated, %: C 62.48; H 6.99; N 19.43.

1,3-Bis(1-methyl-1H-pyrazol-5-yl)propane-1,3-dione (3d). Mp 111–112ºC (benzene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 13.23 (1H, br. s, OH); 7.65 (1H, s, CH=); 7.32 (2H, s, CH); 6.82 (2H, s, CH); 4.10 (6H, m, $2CH_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 185.55; 176.61; 160.74; 138.29; 138.18; 137.70; 137.43; 136.41; 132.96; 113.40; 111.02; 40.22; 39.81. Mass spectrum, *m/z* (I_{rel}, %): 232 $[M]^+$ (29), 109 (100), 82 (24), 69 (22), 54 (36). Found, %: C 56.99; H 5.34; N 24.31. $C_{15}H_{20}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12

1,3-Bis(1-methyl-1H-pyrazol-4-yl)propane-1,3-dione (3e). Light-yellow, microcrystalline powder; mp 212–213ºC (acetonitrile). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.33 (2H, s, CH); 7.92 (1H, s, CH=); 6.52 (2H, s, CH); 3.94 (6H, s, $2CH_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 179.53; 163.81; 140.40; 138.91; 134.25; 132.55; 119.80; 114.82; 93.43; 39.01; 38.80. Mass spectrum, *m/z* (I_{rel}, %): 232 $[M]^+$ (56), 204 $[M–CO]^+$ (17), 109 (100), 95 (17), 42 (76). Found, %: C 56.99; H 5.63; N 24.73. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

1,3-Bis(1,3-dimethyl-1H-pyrazol-4-yl)propane-1,3-dione (3f). Light-yellow crystals; mp 148–149ºC (a mixture of ether and hexane). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.91 (1H, s, CH=); 7.61 (1H, s, CH); 6.83 (1H, s, CH); 3.91 (6H, s, $2NCH_3$); 2.35 (6H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 188.40; 180.59; 149.34; 148.41; 136.70; 133.83; 119.91; 116.51; 38.55; 38.44; 14.1; 13.60. Mass spectrum, *m/z* (I_{rel}, %): 260 $[M]^+$ (28), 123 (100), 96 (22), 42 (14). Found, %: C 60.34; H 6.71; N 21.13. $C_{13}H_{16}N_4O_2$. Calculated, %: C 59.99; H 6.20; N 21.52.

4,4,4-Trifluro-1-(1,3-dimethyl-1H-pyrazol-4-yl)butane-1,3-dione (5a). Yellow solid material; mp 55–56ºC (a mixture of ether and pentane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.91 (1H, s, CH=); 6.15 (1H, s, CH); 3.92 (3H, s, CH_3); 2.50 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (J_{CF}, Hz): 185.51; 173.20 (q, J = 35.8); 150.90; 117.30 (q, J = 283.0); 116.22; 93.11; 39.10; 14.23. ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –77.15 (3F, s). Mass spectrum, *m/z* (I_{rel}, %): 234 $[M]^+$ (4), 165 $[M–CF_3]^+$ (11), 123 (21), 97 $[Pyr+H]^+$ (100). Found, %: C 46.49; H 4.16; N 11.81. $C_9H_9F_3N_2O_2$. Calculated, %: C 46.16; H 3.87; N 11.96.

4,4,4-Trifluro-1-(1,5-dimethyl-1H-pyrazol-4-yl)butane-1,3-dione (5b). Light-yellow crystals; mp 140–141ºC (a mixture of ether and hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.80 (1H, s, CH=); 6.20 (1H, s, CH); 3.81 (3H, s, NCH_3); 2.65 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (J_{CF}, Hz): 184.93; 171.62 (q, J = 35.8); 143.44; 139.68; 117.20 (q, J = 285.0); 116.11; 113.43; 93.61; 36.42; 11.40. ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –76.7 (3F, s). Mass spectrum, *m/z* (I_{rel}, %): 234 $[M]^+$ (11), 165 $[M–CF_3]^+$ (18), 123 (100), 97 $[Pyr+H]^+$ (19), 69 (48), 42 (41). Found, %: C 46.38; H 4.17; N 12.31. $C_9H_9F_3N_2O_2$. Calculated, %: C 46.16; H 3.87; N 11.96.

4,4-Difluro-1-(1,5-dimethyl-1H-pyrazol-4-yl)butane-1,3-dione (5c). Yellowish oil; bp 182–183ºC (12 mmHg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 7.54 (1H, s, CH=); 6.10 (1H, s, CH); 5.91 (1H, t, J_{CF} = 54.5, CHF_2); 3.83 (3H, s, CH_3); 2.52 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (J_{CF}, Hz): 185.83; 175.31; 142.91; 139.45; 116.66; 109.40 (t, J = 245.0); 94.10 (t, J = 3.9); 36.12; 10.91. ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (J_{CF}, Hz): –127.8 (2F, d, J = 55). Mass spectrum, *m/z* (I_{rel}, %): 216 $[M]^+$ (4), 165 $[M–CHF_2]^+$ (81), 123 (81), 97 $[Pyr+H]^+$ (100), 69 (32), 51 (22). Found, %: C 50.41; H 4.55; N 13.23. $C_9H_{10}F_2N_2O_2$. Calculated, %: C 50.00; H 4.66; N 12.96.

REFERENCES

1. V. V. Skopenko, V. M. Amirkhanov, T. Yu. Sliva, I. S. Vasil'chenko, E. L. Anpilova, and A. D. Garnovskii, *Usp. Khim.*, **73**, 797 (2004).
2. C. Pettinari, F. Marchetti, and A. Drozdov, in: *Comprehensive Coordination Chemistry II*, Vol. 1, 2003, Chap. 1.6, p. 97.
3. V. Colotta, D. Catarzi, F. Varano, F. Melani, G. Filacchioni, L. Cecchi, L. Trincavelli, C. Martini, and A. Lucacchini, *Farmaco*, **53**, 189 (1998).
4. M. A. Khan, G. P. Ellis, and C. M. Pagotto, *J. Heterocycl. Chem.*, **38**, 193 (2001).
5. S. Kovac, V. Rapic, and M. Lacan, *Liebigs Ann. Chem.*, 1755 (1984).
6. M. S. Shvartsberg, S. F. Vasilevskii, V. G. Kostrovskii, and I. L. Kotlyarevskii, *Khim. Geterotsikl. Soedin.*, 1055 (1969). [*Chem. Heterocycl. Comp.*, **5**, 797 (1969)].
7. E. G. Brain and I. L. Finar, *J. Chem. Soc.*, 2486 (1958).