An Efficient Synthesis of Isomeric 1-(1-Alkyl-1*H*-pyrazolyl) Ethanones

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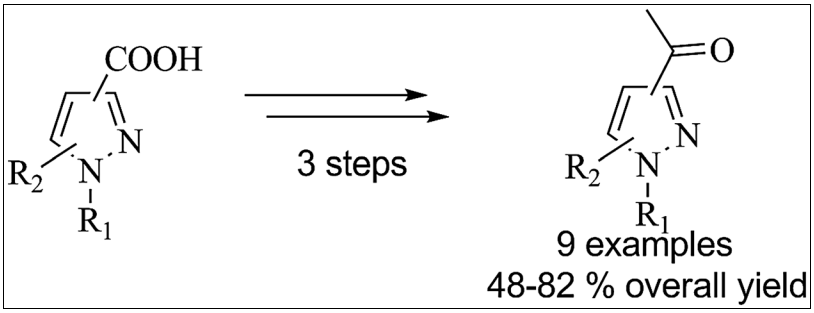

A simple and versatile general method for the preparation of *N*-substituted 3-, 4-, or 5-acetylpyrazoles from corresponding acids via hydrolysis and decarboxylation of substituted diethyl [(1-alkyl-1*H*-pyrazolyl)carbonyl] malonates was developed. Title compounds were prepared in three steps without isolation of intermediates in 48–82% overall yield.

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Acylpyrazoles are the important intermediates in the synthesis of pyrazole derivatives. The described methods of their synthesis are: interaction of organomethallic (Li or Mg) derivatives of pyrazole with nitriles [1], acyl chlorides [2], or anhydrides of carbonic acids [3], decarboxylation of pyrazol ketoacids [4,5], by oxidation of alcohols or propenyl substituted pyrazoles [6], by condensation of polycarbonyl compounds with hydrazines [7–9], by multistep synthesis started from substituted alkynes [10,11], by catalytic carbonilation of pyrazoles in the presence of $Ru_3(CO)_{12}$ [12] and by other methods. 4-Acylpyrazoles were also obtained [13,14] by direct acylation of pyrazoles by acyl chlorides under drastic conditions (150–200°C).

The major disadvantages of the specified methods are: multistage process, not readily available starting materials, and, very often, low yields of target compounds. Besides, not all of the methods can be easily scale-up.

Within the framework of our research project, there was a necessity to develop a convenient and versatile method of preparation of various *N*-substituted acetylpyrazoles. Besides, this method should be applicable for preparation of multigram quantities of target compounds. A simple and general, three-step approach to synthesis of the title compounds based on the ketonic degradation of substituted acylmalonates have been developed (Scheme 1).

N-Substituted pyrazolecarboxylic acid **1** were used as starting materials. Many of these compounds are commercially available, other could be prepared in any required quantities by oxidation of alkylpyrazoles [15,16] or by means of *N*-alkylation of ethyl 3-pyrazolecarboxylate with the subsequent separation of isomers and hydrolysis [17,18].

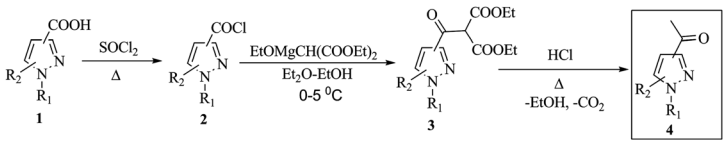
Acids **1** were converted to corresponding acyl chlorides by interaction with $SOCl_2$ (2 equiv.) in the presence of catalytic amounts of DMF. Compounds **2** were obtained in quantative yields.

To the best of our knowledge, the only one example of acylation of diethyl malonate with the compound **2** was described [17], but no further investigations were made.

Preliminary experiments have shown, that the highest yields of the acylated compounds **3** could be achieved if mixed magnesium (EtOMg) derivative of diethyl malonate was used instead of sodium salt. The best results were obtained when Et_2O-EtOH (5–6%) mixture was used as a solvent and reaction was performed in the sufficiently diluted solutions at 0–5°C. Other solvents such as pure EtOH, dioxane, Et_2O, THF are much less effective due to formation of gummy precipitate and considerable yields decrease.

Saponification of the compounds **3** and subsequent decarboxylation were performed by the refluxing of crude **3** with the excess of 20% aqueous HCl solution until CO_2 evolution have ceased. The typical reaction time is 2–6 h, depending uploads and the nature of the substitutients. As pyrazoles are rather soluble in the acidic media, the acid should be neutralized before extraction of the target ketone. The best results were obtained, when pH was maintained at 7.5–8. To prevent too large dilution, the most part of HCl was neutralized by the carefully addition of 50% KOH solution to pH 4–5 with external cooling, and only after

Scheme 1



that solid K_2CO_3 was added to reach necessary pH. After usual workup crude ketones **4** were purified by crystallization or distillation.

To investigate limitations of the developed method, substituted acyl chlorides were additionally prepared and tested for the acylation. Good results were obtained with *N*-alkylated acids, bearing Cl, Br, NO_2, CF_3 substitutions, but our attempts to use 1*H*-pyrazole-3-carbonyl chloride or 1*H*-pyrazole-4-carbonyl chloride were failed. No purification was needed for intermediates, and all reactions can be easily scaled-up to at least to 1.5 moles of starting compounds without decrease of the yield (Table 1).

Thus, a simple and a versatile general method for the preparation of *N*-substituted 3-, 4-, or 5-;acetylpyrazoles from corresponding acids via hydrolysis and decarboxylation of substituted diethyl [(1-alkyl-1*H*-pyrazolyl)carbonyl]malonates **3** was reported.

EXPERIMENTAL

General. Compounds **1(a-i)** were purchased from Art-Chem GmbH (Campus Berlin Buch, Germany). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-300 and Bruker AM-300 instruments (300 and 75.5 MHz, respectively). Mass-spectra were recorded on a Finnigan INCOS-50 instrument (EI, 70eV, direct insertion).

1-(1-Alkyl-1*H*-pyrazolyl)ethanones (4a-i): General procedure. To a stirred suspension of acid **1** (1 mol) in 100 mL of CCl_4 0.5 mL of dry DMF and 146 mL of thionyl chloride (238 g, 2 mol) were subsequently added. The resulted mixture was carefully refluxed for 2 h until all the acid dissolved and vigorous gas evolution ceased. The mixture was cooled to the room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in 300 mL of dry benzene and evaporated to dryness once again. This procedure was repeated in order to remove unreacted $SOCl_2$. Crude **1**-alkyl-1*H*-pyrazole-carbonyl chlorides (**2**) thus obtained in quantative yield, were used at the next step without further purification.

To a mechanically stirred suspension of magnesium (8g, 330 mmol) in the mixture of 250-mL anhydrous Et_2O and 30 mL of absolute EtOH 1 mL of CCl_4 was added, and the reaction mass was stirred under argon atmosphere until reaction started. The beginning of the reaction could be easily detected by gas evolution and warming of the mixture. At this moment, the solution of 50.3 mL (52.9 g, 330 mmol) of diethyl malonate and 10 mL of ethanol in 150 mL of Et_2O was added dropwise at a such rate to maintained vigorous reflux. After addition had been completed, solution was refluxed for 2 h. During this period of time, all magnesium was completely dissolved and dark clear solution was obtained. It was cooled to 0°C, diluted by 200 mL of Et_2O and solution of 300 mmol of acyl chloride (**2**) in 150 mL was added dropwise with stirring. The resulted suspension was stirred at the room temperature for 3 h and left overnight. Then it was poured into the ice-HCl mixture (300 g of ice and 50 mL of conc. HCl), stirred until all solid matter was dissolved and organic phase was separated. Water phase was extracted with CH_2Cl_2 (2 × 200 mL). Combined extracts were washed with brine and evaporated at a reduced pressure. The resulted oil was used at the next step without purification.

Crude compound **3** was refluxed with the 600 mL of 20% HCl until decarboxylation was completed (no bubbles was obtained in the bubble counter connected to the condenser) and cooled to a room temperature. Acid was firstly neutralized by slowly addition of 50% solution of NaOH with external cooling (the temperature was maintained below +30°C) and finally pH was adjusted to 8 by solid K_2CO_3. (**Do not use** NaOH for the compound **4i,** acid should be neutralized only by K_2CO_3). Mixture was extracted with EtOA (3 × 150 mL), organic phases were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by distillation or crystallization.

1-(1-Methyl-1H-pyrazol-3-yl)ethanone (4a). Colorless oil, bp112–115°C /11 Torr; ^{1}H NMR ($CDCl_3$): δ 7.3 (s, 1H, CH), 6.7 (s, 1H, CH), 3.9 (s, 3H, N—CH_3), 2.5 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 193.3, 151.0, 131.5, 106.3, 39.1, 26.1; ms (EI, 70Ev): *m/z* (%) 124 (27, M^+), 109 (100, M^+—CH_3), 44 (22), 43 (16, CH_3CO^+); Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H,6.50; N, 22.57. Found: C, 58.14; H, 6.63; N, 23.01.

1-(1-Ethyl-1H-pyrazol-3-yl)ethanone (4b). Colorless oil, bp 116–117°C/18 Torr; ^{1}H NMR ($CDCl_3$): δ 7.4 (s, 1H, CH), 6.7 (s, 1H, CH), 4.1 (q, 2H, J = 7.2 Hz, CH_2), 2.5 (s, 3H, CH_3), 1.4 (t, 3H, J = 7.2Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 193.75, 151.1, 129.9, 106.4, 47.5, 26.4, 15.5; ms (EI, 70Ev): *m/z* (%) 138 (33, M^+), 123 (100, M^+-CH_3), 95 (87, M^+-CH_3CO), 43(78.5, CH_3CO^+); Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H,7.30; N, 20.28. Found: C, 60.77; H, 7.63; N, 21.03.

Table 1

Synthesis of 1-(1-alkyl-1*H*-pyrazolyl) ethanones.

Entry	R_1	R_2 position in pyrazol ring 3	4	5	Yield of **4** (%)
4a	Me	$COCH_3$	H	H	67
4b	Et	$COCH_3$	H	H	75
4c	Et	$COCH_3$	Br	H	82
4d	*i*-Pr	$COCH_3$	H	H	77
4e	Me	H	$COCH_3$	H	71
4f	Me	H	H	$COCH_3$	73
4g	Et	H	H	$COCH_3$	81
4h	Me	CF_3	H	$COCH_3$	53
4i	Me	H	NO_2	$COCH_3$	48

Overall isolated yield calculated for three steps, 300 mmol scale.

1-(4-Bromo-1-ethyl-1H-pyrazol-3-yl)ethanone (4c). Colorless crystals (ether), mp 60–61°C; ^{1}H NMR ($CDCl_3$): δ 7.5 (s, 1H, CH), 4.15 (q, 2H, *J* = 7.2 Hz, CH_2), 2.5 (s, 3H, CO-CH_3), 1.45 (t, 3H, *J* = 7.2Hz, CH_3); ^{13}C NMR ($CDCl_3$):δ 192.7, 145.8, 131.4, 93.8, 48.2, 27.0, 14.9; ms (EI, 70Ev): *m/z* (%) 218 (29.5, $^{81}BrM^+$), 216 (30,$^{79}BrM^+$), 203 (74), 201(79), 175 (34), 173 (36), 43(100, CH_3CO^+); Anal. Calcd. for $C_7H_9BrN_2O$: C, 38.73; H, 4.18; N, 12.91. Found: C, 38.99; H, 3.71; N, 13.54.

1-(1-Isopropyl-1H-pyrazol-3-yl)ethanone (4d). Light yellow oil, bp101–102°C/12 Torr; ^{1}H NMR ($CDCl_3$): δ 7.4 (s, 1H, CH), 6.7 (s, 1H, CH), 4.53 (sept, 1H, *J* = 6.6Hz, CH), 2.6 (s, 3H, CO-CH_3), 1.51 (d, 6H, *J* = 6.6Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 194.1, 150.7, 127.9, 106.1, 54.5, 26.3, 22.7; ms (EI, 70Ev): *m/z* (%) 152 (27.5 M^+), 137 (40, M^+-CH_3), 95 (100), 43 (36.5, CH_3CO^+); Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.29; H, 8.17; N, 18.75.

1-(1-Methyl-1H-pyrazol-4-yl)ethanone (4e). Light brown crystals, bp 96–98°C/2 Torr, mp 39–40°C; ^{1}H NMR ($CDCl_3$): δ 7.90(s, 1H, CH), 7.81(s, 1H, CH), 3.9 (s, 3H, N—CH_3), 2.45 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 192.0, 140.1, 132.4, 124.1, 39.0, 27.6; ms (EI, 70Ev): *m/z* (%) 124 (24.5, M^+), 109(100, M^+-CH_3), 53 (16.7), 43 (31.4, CH_3CO^+), 42 (31.6); Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.34; H, 6.67; N, 22.61.

1-(1-Methyl-1H-pyrazol-5-yl)ethanone (4f). Colorless oil, bp 84–85°C/18 Torr; ^{1}H NMR ($CDCl_3$): δ 7.4 (s, 1H, CH), 6.8 (s, 1H, CH), 4.1 (s, 3H, N—CH_3), 2.4 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 188.7, 138.4, 137,4, 111.8, 40.0, 28.1; ms (EI, 70Ev): *m/z* (%) 124 (50, M^+), 109 (100, M^+-CH_3), 81 (14), 54 (36.4), 43 (58, CH_3CO^+); Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.19; H, 6.81; N, 22.73.

1-(1-Ethyl-1H-pyrazol-5-yl)ethanone (4g). Colorless oil, bp 89–90°C/20 Torr; ^{1}H NMR ($CDCl_3$): δ 7.4 (s, 1H, CH), 6.8 (s, 1H, CH), 4.5 (q, 2H, *J* = 7.2 Hz, CH_2), 2.5 (s, 3H, CH_3), 1.3 (t, 3H, *J* = 7.2Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 188.5, 137.5, 112.1, 47.4, 28.4, 15.4; ms (EI, 70Ev): *m/z* (%) 138 (52, M^+), 123 (100, M^+-CH_3), 95 (65, M^+ -$COCH_3$), 43 (17.5, CH_3CO^+); Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 61.11; H, 7.79; N, 20.09.

1-[1- Methyl -3-(trifluoromethyl)-1H-pyrazol-5-yl]ethanone (4h). Colorless oil, bp 55–56°C/3 Torr; ^{1}H NMR ($CDCl_3$): δ 7.1 (s, 1H, CH), 4.2 (s, 3H, N—CH_3), 2.5 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 188.2, 140.8 (q, *J* = 38.7 Hz), 139.5, 122.5, 118.9, 109.7, 40.9, 28.3; ms (EI, 70Ev): *m/z* (%) 192 (36, M^+), 177 (100, M^+-CH_3), 80 (17), 44 (53.5), 43 (72, CH_3CO^+); Anal. Calcd. for $C_7H_7F_3N_2O$: C, 43.76; H, 3.67 N, 14.58. Found: C, 43.19; H, 4.03; N, 14.17.

1-(1-Methyl-4-nitro-1H-pyrazol-5-yl)ethanone (4i). White needles, mp (ethylacetate-ether) 63–64°C; bp 103–105°C/3 Torr; ^{1}H NMR ($CDCl_3$): δ 8.0 (s,1H, CH), 3.9 (s, 3H, N—CH_3), 2.65 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 191.9, 137.6, 135.0, 39.4, 30.9; ms (EI, 70Ev): *m/z* (%) 169 (26, M^+), 152 (56, M^+ —OH), 83 (55), 43 (100, CH_3CO^+); Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.61; H,4.17; N, 24.84. Found: C, 43.06; H, 4.51; N, 24.99.

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