A CONVENIENT SYNTHESIS OF 2-PYRAZOLINES AND PYRAZOLES FROM ALDEHYDE HYDRAZONES AND ETHYL PROPIOLATE

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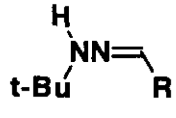
Abstract - Aldehyde methylhydrazones (**3**) reacted with ethyl propiolate in the presence of acetic acid affording 4-ethoxycarbonyl-1-methyl-2-pyrazolines (**4**) in 13 - 44% yields. Easily **4** was dehydrated to the corresponding pyrazoles (**6**) by treatment with H_2O_2 in the presence of $FeCl_2$.

Recently we reported a new convenient synthetic method of 4-trifluoroacetylpyrazole (**2a**) from aldehyde tert-butylhydrazones (**1**) and ethyl β-trifluoroacetylvinyl ether in the presence of AcOH.[1] Similarly **1** and ethyl propiolate afforded the corresponding 4-ethoxycarbonylpyrazole (**2b**). In these reactions 4-pyrazoline (**2a'**) and (**2b'**) were initially formed and subsequent air oxidation gave **2a** and **2b**, respectively. In contrast, behavior of aldehyde methylhydrazones (**3**) *in the same reaction conditions was quite different. For example,* **3** *and ethyl β-*trifluoroacetylvinyl ether gave adduct (**5a**),[2] which was treated with trifluoroacetic acid affording 1- methyl-3-trifluoromethylpyrazole as a main product.[3] In addition, the reaction of 3 with ethyl propiolate in the presence of



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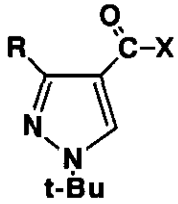
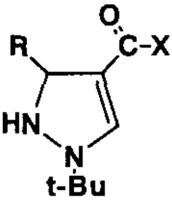
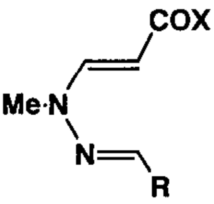


X

CF_3 **2a**
OEt **2b**



2a'
2b'



5a
5b

AcOH was found to give unexpected 4-ethoxycarbonyl-1-methyl-2-pyrazoline (**4**). Now we wish to communicate definitely the latter interesting 2-pyrazoline formation reaction.

p-Tolualdehyde methylhydrazone (**3 b**) reacted with ethyl propiolate in MeCN to afford adduct **5 b** (**R**=*p*-Tol)[4] in 96 % yield. However our attempts to cyclize **5 b** (**R**=*p*-Tol) to pyrazole ring system resulted in failure. Surprisingly, the presence of AcOH in the reaction of **3 b** with ethyl propiolate coursed a drastic change for a product. Main product of this reaction was 4-ethoxycarbonyl-1-methyl-5-(*p*-tolyl)-2-pyrazoline (**4 b**). Experimental procedure are as follows. To a mixture of **3 b** (1 mmol) and AcOH (15 mmol) in MeCN (1 ml) was added ethyl propiolate (1.2 mmol), and the mixture was stirred for 24 h at ambient temperature. The mixture was diluted with CH_2Cl_2 (50 ml), and the whole was washed with aq. 10% Na_2CO_3 and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel column (benzene/AcOEt = 9/1) to afford **4 b** in 38% yield. Similarly aldehyde hydrazones (**3 a-g**) were successfully converted to the corresponding 2-pyrazolines (**4 a-g**) in 13-44% yields. In the cases of **4 a**, **4 d**, **4 e**, and **4 g**, dehydrogenated pyrazoles (**6 a**, **6 d**, **6 e**, and **6 g**), respectively, were also obtained together with **4**.[5] The results are summarized in Table 1. In ^{1}H nmr spectra, pyrazoline ring methine protons of **4 b** appear at 3.60 (d of d), 4.12 (d, J = 14 Hz), 6.39 (d, J = 2 Hz). These coupling constants suggest **4 b** is a cis isomer. In ^{13}C nmr spectra, pyrazoline ring carbons of **4 b** appear at 136.9 (C3, $^1J_{CH}$= 195.8 Hz), 62.0 (C4, $^1J_{CH}$= 132.2 Hz), 73.7 (C5, $^1J_{CH}$= 134.0 Hz).

2-Pyrazolines (**4**) were stable under atmosphere, but readily dehydrated to aromatic pyrazole (**6**)[6] by treatment with H_2O_2 in the presence of $FeCl_2$. A tentative procedure is illustrative for **4 b**. To a solution of **4 b** (1 mmol) in MeOH (1 ml) was added $FeCl_2$ (0.22 mmol) and 30% H_2O_2 (2 mmol), and the mixture was stirred for one day at ambient temperature. The reaction mixture was poured into sufficient amounts of aq. 20% $NaHSO_3$ solution and **6 b** was extracted with CH_2Cl_2 (50 ml X 2). The extracts were combined and dried over Na_2SO_4 and the solvent was removed to afford **6 b** in 82% yield. Quite similarly, **4 a**, **4 c-e** and **4 g** were converted to the

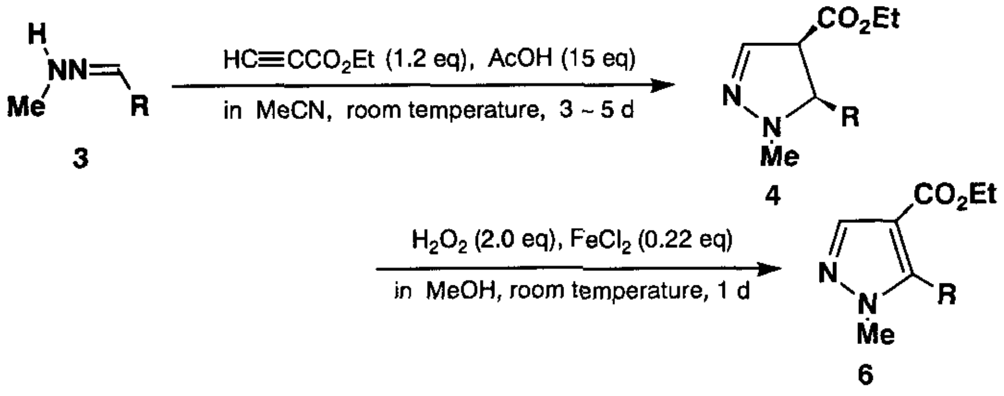


Table 1. 4-Ethoxycarbonyl-1-methyl-2-pyrazoline (**4**).

R	Products[a] **4** : **6**	Yield,%[b] **4**	Yield,%[b] **6**	Oven Temp.[c] of **4**, °C/torr	^{1}H nmr[d] δ
3a Ph	2 : 1	25	11	160/4	1.26 (t, J = 7 Hz, 3H, $CH_2\underline{Me}$), 2.76 (s, 3H, NMe), 3.80 (d of d, J = 14 Hz and 2 Hz, 1H, $\underline{H}C4$), 4.18 (q, J = 7 Hz, 2H, $C\underline{H}_2Me$), 4.27 (d, J = 14 Hz, 1H, $\underline{H}C5$), 6.62 (d, J = 2 Hz, 1H, $\underline{H}C3$), 7.18-7.64 (m, 5H, ArH)
3b p-MeC_6H_4	1 : 0	38	0	165/5	1.25 (t, J = 7 Hz, 3H, $CH_2\underline{Me}$), 2.32 (s, 3H, Me), 2.70 (s, 3H,NMe), 3.60 (d of d, J = 14 Hz and 2Hz, 1H,$\underline{H}C4$), 4.11and 4.12 (q, and d, respectively, J = 7 Hz and 14 Hz, 3H, $C\underline{H}_2Me$ and $\underline{H}C5$), 6.39 (d, J = 2 Hz, 1H, $\underline{H}C3$), 6.98, 7.22 (2d, J = 8 Hz, 4H, ArH)
3c o-MeC_6H_4	1 : 0	18	0	140/4	1.23 (t, J = 7 Hz, 3H, $CH_2\underline{Me}$), 2.33 (s, 3H, Me), 2.70 (s, 3H, NMe), 3.71 (d of d, J = 14 Hz and 2 Hz, 1H, $\underline{H}C4$), 4.07 (q, J = 7 Hz, 2H, $C\underline{H}_2Me$), 4.45 (d, J = 14 Hz, 1H, $\underline{H}C5$), 6.38 (d, J = 2 Hz, 1H, $\underline{H}C3$), 6.90-7.69 (m, 4H, ArH)
3d p-$MeOC_6H_4$	5 : 8	44	9	190/4	1.23 (t, J = 7 Hz, 3H, $CH_2\underline{Me}$), 2.63 (s, 3H, NMe), 3.53 (d of d, J = 14 Hz and 2 Hz, 1H, $\underline{H}C4$), 3,67 (s, 3H, OMe), 4.06 (q and d, J = 7 Hz and 14 Hz, 3H, $C\underline{H}_2Me$ and $\underline{H}C5$), 6.34 (d, J = 2 Hz, $\underline{H}C3$), 6.69, 7.17 (2d, 4H, J = 8 Hz, ArH)
3e p-ClC_6H_4	4 : 1	13	2	170/7	1.27 (t, J = 7 Hz, 3H, $CH_2\underline{Me}$), 2.70 (s, 3H, NMe), 3.60 (d of d, J = 14 Hz and 2Hz, 1H, $\underline{H}C4$), 4.16 and 4.18 (q and d, respectively, J = 7 Hz and 14 Hz, 3H, $C\underline{H}_2Me$ and $\underline{H}C5$), 6.45 (d, J = 2 Hz, 1H, $\underline{H}C3$), 7.11-7.50 (q, J = 9 Hz, 4H, ArH)
3f[e] p-$O_2NC_6H_4$	1 : 0	32	(26)[f]	155/4	1.30 (t, J = 7 Hz, 3H, $CH_2\underline{Me}$), 2.77 (s, 3H, NMe), 3.77 (d of d, J = 14 Hz and 2 Hz, 1H, $\underline{H}C4$), 4.33 and 4.37 (q and d, respectivery, J = 7 Hz and 14Hz, 3H, $C\underline{H}_2Me$ and $\underline{H}C5$), 6.62 (d, J = 2 Hz, 1H, $\underline{H}C3$), 7.38, 8.11 (2d, J = 9 Hz, 4H, ArH)
3g i-Pr	3 : 1	36	13	90/3	0.86, 0.87 (2d, J = 7 Hz, 6H, $CH\underline{Me}$) 1.26 (t, J = 7.2 Hz, 3H, $CH_2\underline{Me}$), 1.62-3.22 (m, 1H, $C\underline{H}Me$), 3.72 (s, 3H, NMe), 2.92-3.25 (m, 1H, $\underline{H}C5$), 3.44 (d of d, J = 12 Hz and 2 Hz, 1H, $\underline{H}C4$), 4.08 (q, J = 7.2 Hz, 2H, $C\underline{H}_2Me$), 6.18 (d, J = 2 Hz, $\underline{H}C3$)

a) Products ratio of crude materials. b) Yield refer to pure isolated compounds. c) Oven temperature of Kugelrohr distillation. d) Recorded at 60 MHz on a JEOL PMX60SI. For **4 b-d** and **4 g**, CCl_4 was used as a solvent. For the others $CDCl_3$ was used as a solvent. e) Instead of MeCN, CH_2Cl_2 was used as solvent for the reaction. f) Instead of **6 f**, **5 b** (R= $O_2NC_6H_4$) was obtained in this case. Its yield is listed in parenthesis.

Table 2. 4-Ethoxycarbonyl-1-methylpyrazoles (**6**).

Substrate	Yield, %[a] of **6**	Oven,°C/torr[b] temp.	^{1}H nmr[c] δ
4a	99	170/6	1.12 (t, *J* = 7 Hz, 3H, CH$_2$Me), 3.60 (s, 3H, NMe), 4.00 (q, *J* = 7 Hz, 2H, CH$_2$Me), 7.25 (s, 5H, ArH), 7.67 (s, 1H, CH)
4b	82	165/5	1.15 (t, *J* = 7 Hz, 3H, CH$_2$Me), 2.37 (s, 3H, Me), 3.65 (s, 3H, NMe), 4.16 (q, *J* = 7 Hz, 2H, CH$_2$Me), 7.17 (s, 4H, ArH), 7.89 (s, 1H, CH)
4c	83	155/4	1.08 (t, *J* = 7 Hz, 3H, CH$_2$Me), 2.03 (s, 3H, Me), 3.47 (s, 3H, NMe), 3.96 (q, *J* = 7 Hz, 2H, CH$_2$Me), 6.87-7.33 (m, 4H, ArH), 7.98 (s, 1H, CH)
4d	71	190/4	1.17 (t, *J* = 7 Hz, 3H, CH$_2$Me), 3.68 (s, 3H, NMe), 3.80 (s, 3H, OMe), 4.12 (q, *J* = 7 Hz, 2H, CH$_2$Me), 6.77, 7.10 (2d, *J* = 8.2 Hz, 4H, ArH), 7.88 (s, 1H, CH)
4e	98	165/7	1.17 (t, *J* = 7 Hz, 3H, CH$_2$Me), 3.65 (s, 3H, NMe), 4.07 (q, *J* = 7 Hz, 2H, CH$_2$Me), 7.13-7.45 (q, *J* = 8.6 Hz, 4H, ArH), 7.73 (s, 1H, CH)
4g	47	90/4	1.33 (t, *J* = 7Hz, 3H, CH$_2$Me), 1.38 (d, *J* = 6.6 Hz, 6H, CHMe), 3.71 (hept, *J* = 6.6 Hz, 1H, CHMe), 3.85 (s, 3H, NMe), 4.24 (q, *J* = 7 Hz, 2H, CH$_2$Me), 7.75 (s, 1H, CH)

a) Yield refer to pure isolated compounds. b) Oven temperature of Kugelrohr distillation. c) Recorded at 60 MHz on a JEOL PMX60SI. For **6a**, **6c** and **6e**, CCl$_4$ was used as a solvent. For the other cases CDCl$_3$ was used as a solvent.

corresponding **6a**, **6c-e** and **6g** in high yields. However we were failed to obtain **6 f** from **4 f**. These are shown in Table 2. In ^{13}C nmr spectra, pyrazoline ring carbons of **6 b** appear at 141.1 (C3, $^1J_{CH}$= 189.8), 112.6 (C4), 146.2 (C5).

We could present a convenient method accessing 2-pyrazoline and pyrazole ring systems. Key step of the method is an interesting cyclization reaction of aldehyde methylhydrazones (**3**) and ethyl propiolate. Elucidation about mechanism of this cyclization reaction is now in progress.

REFERENCES AND NOTES

1. Y. Kamitori, M. Hojo, R. Masuda, M. Fujisiro, I. Nakamura, and K. Yamamoto, *J. Heterocycl. Chem.*, **1993**, *30*, 389.
2. **5a** (R=*p*-Tol): Yield, 98%; ^{1}H nmr (CDCl$_3$ / 60 MHz) 2.37 (s, 3H, Me), 3.37 (br s, 3H, NMe), 5.57 (br d, *J*= 14 Hz, 1H, CHCO), 7.03-7.68 (q, *J*= 8 Hz, 4H, ArH), 7.72 (s, 1H, N=CH), 8.39 (br d, *J*= 14 Hz, 1H, N-CH=).
3. E. Okada, R. Masuda, and M. Hojo, *Heterocycles*, **1992**, *34*, 791. 1-Methyl-3-trifluoromethylpyrazole: Yield, 88%; ^{1}H nmr (CDCl$_3$ / 60 MHz) 3.92 (s, 3H, Me), 6.42 (d, *J*= 2 Hz, 1H, NCH), 7.25-7.40 (br, 1H, CH).

4. **5b** (R=*p*-Tol): mp 134°C (c-hexane); ^{1}H nmr ($CDCl_3$ / 60 MHz) 1.27 (t, J = 7 Hz, 3H, $CH_2\underline{Me}$), 2.33 (s, 3H,Me), 3.18 (s, 3H, NMe), 4.13 (q, J = 7 Hz, 2H, $C\underline{H}_2Me$), 5.13 (d, J = 13 Hz, 1H, $C\underline{H}CO$), 6.97-7.53, 7.40 (q and s, J = 8 Hz, 5H, ArH and $N{=}C\underline{H}$), 7.78 (d, J= 13 Hz, 1H, $N\text{-}C\underline{H}{=}$).
5. **4a**: Ir (KBr) 2930 (m), 1720 (s), 1431 (m), 1348 (m), 1264 (m), 1238 (m), 1194 (m), 1190 (s), 1160 (m), 1065 (m), 965 (m), 864 (m), 755 (s), 700 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found C, 67.36; H, 6.96. **4b**: Ir (KBr) 2800-2990 (m, br), 1740 (s), 1574 (m), 1517(m), 1451 (m), 1371 (m), 1286 (m), 1185 (s), 1070 (m), 960 (m), 864 (m), 810 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found C, 68.38; H, 7.27; N, 11.56. **4c**: Ir (KBr) 2975 (m), 1725 (s), 1546 (m), 1491 (m), 1370 (m), 1291 (m), 1194 (m), 1100 (m), 1046 (m), 865 (m), 755 (m) cm^{-1}. **4d**: Ir (KBr) 2950 (m), 1730 (s), 1608 (m), 1510 (m), 1452 (m), 1295 (s), 1250 (s), 1180 (s), 1028 (s), 964 (m), 870 (s), 828 (s) cm^{-1}. **4e**: Ir (KBr) 2950 (m), 1725 (s), 1484 (m), 1441 (m), 1366 (m), 1275 (m), 1200 (s), 1185 (s), 1090 (s), 1009 (m), 966 (m), 870 (m), 790 (s) cm^{-1}. **4f**: Ir (KBr) 2960 (m), 1727 (s), 1523 (s), 1341 (s), 1282 (m), 1190 (s), 1098 (m), 1060 (m), 845 (s), 743 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45. Found C, 56.02; H, 5.36. **4g**: Ir (KBr) 2957 (m), 1710 (s), 1541 (m), 1240 (m), 1183 (m), 1116 (m), 1064 (m), 1030 (m), 780 (m) cm^{-1}.
6. **6a**: Ir (KBr) 2975 (m), 1700 (s), 1542 (m), 1493 (m), 1384 (m), 1291 (m), 1243 (m), 1200 (m), 1150 (s), 1039 (m), 834 (m), 770 (s), 701 (s) cm^{-1}. **6b**: Ir (KBr) 2890-3000 (m), 1700 (s), 1504 (m), 1471 (m), 1386 (m), 1291 (m), 1246 (m), 1195 (s), 1140 (s), 1101 (m), 1044 (m), 1021 (m) cm^{-1}. **6c**: Ir (KBr) 2975 (m), 1715 (s), 1500 (m), 1250 (m), 1210 (s), 1157 (m), 1152 (m), 1145 (m), 777 (m), 760 (m) cm^{-1}. Anal Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27;H, 7.37. Found C, 68.29; H, 7.48. **6d**: Ir (KBr) 2950 (m), 1700 (s), 1604 (m), 1597 (m), 1467 (m), 1291 (m), 1245 (s), 1200 (s), 1170 (m), 1151 (m), 1054 (m), 1037 (m), 836 (s), 780 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20. Found C, 64.31; H, 6.50. **6e**: Ir (KBr) 2950 (m), 1705 (s), 1539 (m), 1492 (m), 1281 (m), 1247(m), 1200 (s), 1194 (m), 1150 (m), 1090 (s), 1054 (m), 1031 (m), 840 (s), 780 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_2O_2Cl$: C, 58.99; H, 4.95. Found C,58.93; H, 5.12. **6g**: Ir (KBr) 2950 (m), 1705 (s), 1541 (m), 1278 (m), 1241 (m), 1114 (m), 1064 (m), 1031 (m), 964 (m), 780 (m) cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22. Found C, 61.80; H, 8.31.

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