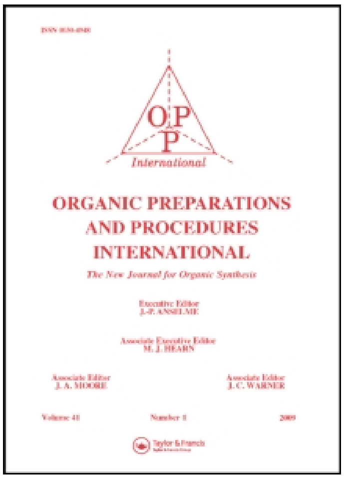

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# REDUCTION OF 1,3,5-TRISUBSTITUTED 2-ALKYLPYRAZOLIUM SALTS WITH COMPLEX METAL HYDRIDES. SYNTHESIS OF 3-PYRAZOLINES

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# REDUCTION OF 1,3,5-TRISUBSTITUTED 2-ALKYLPYRAZOLIUM SALTS WITH COMPLEX METAL HYDRIDES. SYNTHESIS OF 3-PYRAZOLINES

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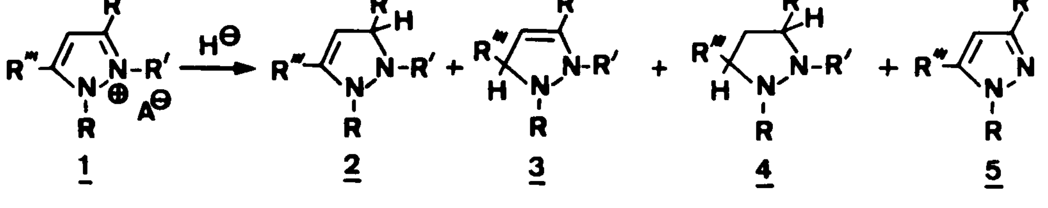
Although it has been reported that complex metal hydrides do not affect the azole ring,[1] we reported in previous papers that the reduction of activated isoxazole compounds by complex metal hydrides provides a good method for the regioselective synthesis of 2-, 3- and 4-isoxazolines.[2] The isoxazoline obtained depends on the kind of activation of the isoxazole nucleus. Thus, 3,5-dialkylisoxazoles with electron-withdrawing groups at C-4 are reduced to 2-isoxazolines regioselectively, whereas isoxazolium salts react with the same hydrides to give 4-isoxazolines.

This paper extends the scope of the process to pyrazoles and we now report a highly selective method for the synthesis of 3-pyrazolines (2, 3) by reduction of 1,3,5- trisubstituted 2-alkylpyrazolium salts (1) with either lithium aluminium hydride, sodium borohydride, or lithium tri-t-butoxy aluminium hydride. Some of these procedures also afforded pyrazolidines (4) and pyrazoles (5), the latter resulting from the hydrogenolysis of the N-R' bond. The results obtained in all these reactions are summarized in Table 1.



The results indicate that the reduction of 1 with lithium aluminium hydride or lithium tri-t-butoxyaluminium hydride is a highly efficient method for the synthesis of 3-pyrazolines; sodium borohydride is less satisfactory as reducing agent, leading mainly to pyrazoles resulting from the dequaternization of the N-R' bond. The structure of the resulting pyrazoline depends on where the initial attack of the hydride ion occurs (i.e., C-3 or C-5). On the other hand, the attack at C-3 or C-5 is related to the steric hindrance of these positions. Thus, when R and R''' are less bulky than R' and R'', the hydride attack occurs at C-5 regiospecifically. In contrast, hydride addition occurs at C-3 if the total steric hindrance of R and R''' is higher than that expected for R' and R''. Physical constants and spectral and analytical data for 3-pyrazolines (2 and 3) and pyrazolidines (4) are given in Table 2 and Table 3.

## EXPERIMENTAL SECTION

Melting points were determined on a Buchi apparatus and are uncorrected as are the boiling points. IR spectra were recorded using a Pye-Unicam Sp-1100 spectrometer and the $^1$H-NMR spectra were performed on a Varian T-60 A instrument; chemical shifts are expressed in ppm relative to TMS as internal standard.

Pyrazoles 5a, 5c, 5e-g, have been previously described: 5a, mp. 37° (lit.[3] mp. 37-38°); 5c, mp. 22°, bp. 120°/4.5 mm (lit.[4] mp. 22°, bp. 146°/12 mm); 5e, mp. 36°, (lit.[4] 35-36° bp. 162°/12 mm); 5f, mp. 58° (lit.[5] mp. 59-60°); 5g, mp. 138° (lit.[6] mp. 137-138°).

1-Ethyl-5-methyl-2,3-diphenyl-3-pyrazoline (2d). Typical Procedure.- 2-Ethyl-3-methyl-1,5-diphenylpyrazolium tetrafluoroborate[7] (1d; 1.5 g, 4.2 mmol) in ether (20 ml) was added to a suspension of lithium aluminium hydride (0.32 g, 8.4 mmol) in ether (15 ml). The mixture was stirred at room temperature for 4 hrs and then hydrolyzed with a saturated solution of ammonium chloride (20 ml). The etheral layer was separated and dried over magnesium sulfate. Evaporation of the solvent left a solid, which was chromatographed on silica gel with dichloromethane to give 0.91 g (81%) of 2d, mp. 62-63° (hexane).

2-Ethyl-1,5-dimethyl-3-phenyl-3-pyrazoline (3e). Typical Procedure.- 2-Ethyl- 1,5-dimethyl-3-phenylpyrazolium tetrafluoroborate[7] (1e; 2 g, 6.9 mmol) in tetrahydrofuran (25 ml) was added to a suspension of lithium tri-t-butoxy-aluminium hydride (3.5 g, 13.8 mmol) in tetrahydrofuran (25 ml). The mixture was stirred at room temperature for 5 hrs and acidified with a saturated solution of ammonium chloride (25 ml). The organic layer was separated and chromatographed on silica gel with dichloromethane as eluent. The following products were obtained:

2-Ethyl-1,5-dimethyl-3-phenyl-3-pyrazoline (3e) from the first fraction; yield 0.85 g (61%), mp. 27-28° (hexane).

1,5-Dimethyl-3-phenylpyrazole (5e) from the second fraction; yield: 0.12 g (10%), mp. 36°.[4]

TABLE 1. Reduction of 1,3,5-Trisubstituted 2-Alkylpyrazolium Salts 1 with Complex Metals Hydrides.[a]

| Substrate No. | R | R' | R" | R'" | $A^-$ | Hydride[b] | Time (hr) | Products and Yields(%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1a | Me | Et | Me | Me | $BF_4$ | A | 6 | 4a(25) and 5a(50) |
| | | | | | | B | 6 | 5a(70) |
| | | | | | | C | 6 | 5a(75) |
| 1b | Ph | Et | Me | Me | $BF_4$ | A | 6 | 2b(61) |
| | | | | | | C | 6 | 4b(43) |
| 1c | Me | Et | Me | Ph | $BF_4$ | A | 5 | 2c(82) |
| | | | | | | B | 5 | 2c(72) and 5c(5) |
| | | | | | | C | 5 | 5c(52) |
| 1d | Ph | Et | Me | Ph | $BF_4$ | A | 4 | 2d(81) |
| | | | | | | B | 4 | 2d(63) |
| | | | | | | C | 4 | 2d(56) |
| 1e | Me | Et | Ph | Me | $BF_4$ | A | 5 | 3e(65) |
| | | | | | | B | 5 | 3e(61) and 5e(10) |
| | | | | | | C | 5 | 5e(23) |
| 1f | Me | Et | Ph | Ph | $BF_4$ | A | 6 | 3f(53) |
| | | | | | | B | 6 | 3f(34) |
| | | | | | | C | 6 | 5f(59) |
| 1g | Ph | Me | Ph | Ph | $BF_4$ | A | 4 | 2g(84) |
| | | | | | | B | 4 | 2g(65) |
| | | | | | | C | 4 | 5g(32) |

a) Reactions were carried out at R.T. b) A = $LiAlH_4$ in $Et_2O$; B = $LiAlH(O-{}^tBu)_3$ in THF; C = $NaBH_4$ in EtOH; molar ratio 1:hydride = 1:2. c) Yields refer to isolated pure products.

TABLE 2. Elemental Analyses Data

| Product No. | Molecular Formula | | Elemental Analysis | | | |
|---|---|---|---|---|---|---|
| 2b | $C_{13}H_{18}N_2$ | (202.3) | Calcd. | C 77.18 | H 8.96 | N 13.84 |
| | | | Found | C 76.96 | H 8.81 | N 13.88 |
| 2c | $C_{13}H_{18}N_2$ | (202.3) | Calcd. | C 77.18 | H 8.96 | N 13.84 |
| | | | Found | C 77.25 | H 9.06 | N 13.96 |
| 2d | $C_{18}H_{20}N_2$ | (264.4) | Calcd. | C 81.76 | H 7.62 | N 10.59 |
| | | | Found | C 81.83 | H 7.48 | N 10.62 |
| 2g | $C_{22}H_{20}N_2$ | (336.1) | Calcd. | C 78.57 | H 5.95 | N 8.33 |
| | | | Found | C 79.02 | H 5.48 | N 8.16 |
| 3e | $C_{13}H_{18}N_2$ | (202.3) | Calcd. | C 77.18 | H 8.96 | N 13.84 |
| | | | Found | C 77.05 | H 8.84 | N 13.95 |
| 3f | $C_{18}H_{20}N_2$ | (264.4) | Calcd. | C 81.76 | H 7.62 | N 10.59 |
| | | | Found | C 81.87 | H 7.75 | N 10.47 |
| 4a | $C_8H_{18}N_2$ | (142.2) | Calcd. | C 67.57 | H 12.75 | N 19.69 |
| | | | Found | C 67.71 | H 12.88 | N 19.78 |
| 4b | $C_{13}H_{20}N_2$ | (204.3) | Calcd. | C 76.43 | H 9.86 | N 13.71 |
| | | | Found | C 76.31 | H 9.98 | N 13.67 |

TABLE 3. 3-Pyrazolines 3 and 3 and Pyrazolidines 4

| Product[a,b] | mp or bp(ºC)/Torr[c] | $^1$H-NMR | (CDCl$_3$/TMS) | | δ ppm[d] | J[Hz] |
|---|---|---|---|---|---|---|
| | | R'' | R''' | 3-H | 4-H | 5-H |
| 2b | 70-72/1 | 1.20<br>(d,3H,J=6) | 1.70<br>(s,3H) | ----- | 4.30<br>(d,1H,J=2) | 3.50<br>(dq,1H,J=2,J=6) |
| 2c | 28-30[e] | 1.25<br>(d,2H,J=7) | 7.20<br>(m,5H) | ----- | 5.25<br>(d,1H,J=4) | 3.85<br>(dq,1H,J=4,J=7) |
| 2d | 62-63[e] | 1.40<br>(d,3H,J=7) | 7.30<br>(m,5H) | ----- | 5.80<br>(d,1H,J=4) | 3.60<br>(dq,1H,J=4,J=7) |
| 2g | 107-108[e] | 7.20<br>(m,5H) | 7.40<br>(m,5H) | ----- | 4.50<br>(d,1H,J=3) | 5.60<br>(d,1H,J=3) |
| 3e | 27-28[e] | 7.40<br>(m,5H) | 1.20<br>(d,3H,J=7) | ----- | 5.15<br>(d,1H,J=3) | 3.50<br>(dq,1H,J=3) |
| 3f | 60-61[e] | 7.30<br>(m,5H) | 7.30<br>(m,5H) | ----- | 5.10<br>(d,1H,J=3) | 4.50<br>(d,1H,J=3) |
| 4a | oil[f] | 1.20<br>(d,3H,J=7) | 1.15<br>(d,3H,J=7) | 3.20<br>(m,1H) | 1.80<br>(m,1H) | 3.10<br>(m,1H) |
| 4b | oil[f] | 1.20<br>(d,3H,J=7) | 1.40<br>(d,3H,J=7) | 3.10<br>(m,1H) | 2.00<br>(m,2H) | 3.60<br>(m,1H) |

a) Yields of isolated products are listed in Table 1. b) The C=C stretch for compounds 2b-2d,2g,3e and 3f are found at about 1630-1660 cm$^{-1}$. c) Uncorrected. d) N-R are found at about δ 2.6(s) for R=CH$_3$; δ[C$_6$H$_5$]=6.8-7.1(m) for R=C$_6$H$_5$. N-R' are found at about δ 2.9(s) for R'=CH$_3$; δ [C$_2$H$_5$] are found at about 1.1(t) and 2.7(q) for R'=C$_2$H$_5$. e) Recrystallized from hexane. f) Unstable oily compound.

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