Novel Synthesis of Pyrazole and Pyrazoline Derivatives

Noboru Matsumura*, Akira Kunugihara and Shigeo Yoneda*

Department of Applied Chemistry, College of Engineering,
University of Osaka Prefecture, Sakai, Osaka 591, Japan

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The 1,4-dianion of acetophenone *N*-ethoxycarbonylhydrazone reacts with carbonyl compounds such as esters, acyl chlorides, amides and α-haloketones such as phenacyl chloride, 1-chloroacetone, 1,3-dichloroacetone, to produce pyrazole and pyrazoline derivatives in good yields, respectively.

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The 1,4-dianion of monosubstituted hydrazone is important as a versatile intermediate in synthetic chemistry [1]. We have recently investigated the reactivity of the 1,4-dianion **2** of acetophenone *N*-ethoxycarbonylhydrazone (**1**) and briefly reported in the preceding communications [2, 3]. In this study on the reaction behavior of **2**, we have found that **2** reacts with carbonyl compounds such as esters, acyl chlorides, amides, and α-chloroketones such as phenacyl chloride, 1-chloroacetone, 1,3-dichloroacetone, to give pyrazole and pyrazoline derivatives in good yields, respectively. Although synthetic methods to pyrazole and pyrazoline derivatives have been extensively reported [4], the reaction in this paper provides a convenient new synthetic method to 2-pyrazoles and 2-pyrazolines having various functional groups at the 5 position.

Our initial experiments involved the synthesis of pyrazole by the reaction of substrate attached to a leaving group with **2**. *N*-Ethoxycarbonylhydrazone of acetophenone was treated with two molar equivalents of *n*-butyllithium in tetrahydrofuran (THF) at −78° under argon. The resulting dianion **2** was then reacted with a molar equivalent of methyl benzoate to afford **A** followed by cyclization giving the intermediate **B**. The final acid treatment of **B** would give 1-ethoxycarbonyl-3,5-diphenylpyrazole (**3a**). The results obtained by the use of various carbonyl compounds are summarized in Table 1. Analytical and spectral data of products are presented in Tables 2 and 3.

Scheme I

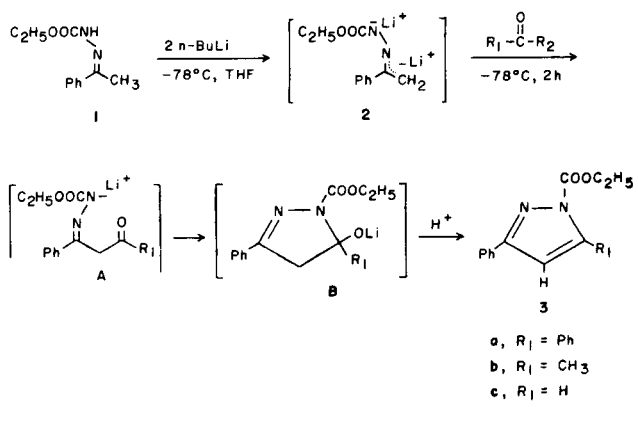


Table 1

Reaction of Ester, Amide, Acid Anhydride, and Acyl Chloride with **2** [a]

Entry	Carbonyl Compound R_1	Carbonyl Compound R_2	Yield, % [b] **3**
a	C_6H_5	CH_3O	74
b	CH_3	n-C_4H_9O	36
c	H	n-C_4H_9O	77
d	CH_3	$(CH_3)_2N$	37
e	H	$(CH_3)_2N$	38
f	C_6H_5	C_6H_5COO	43
g	CH_3	CH_3COO	25
h	C_6H_5	Cl	49
i	CH_3	Cl	32

[a] The reactions were carried out at −78° in tetrahydrofuran for 2 hours. [b] Isolated yields by column chromatography and/or preparative tlc

Table 2

The Melting Points and Analyses of 1-Ethoxycarbonyl-3-phenyl-5-substituted Pyrazole Derivatives **3**

Compound	R_1	Mp, °C	Molecular Formula	Analysis % Calcd./Found C	H	N
3a	C_6H_5	105.5-106.5	$C_{18}H_{16}N_2O_2$	73.95	5.52	9.58
				74.04	5.46	9.86
3b	CH_3	73.5-74.0	$C_{13}H_{14}N_2O_2$	67.81	6.31	12.17
				67.79	6.25	12.36
3c	H	Liquid	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95
				66.61	5.58	13.20
4	$CH_2COC_6H_5$	151-152	$C_{20}H_{18}N_2O_3$	71.84	5.43	8.38
				71.99	5.30	8.44

On the other hand, in the reaction of the substrate attached to two leaving groups such as diethyl carbonate with **2**, 1-ethoxycarbonyl-3-phenyl-5-phenacylpyrazole (**4**) having a $PhCOCH_2$- group at the 5 position was obtained in 22% yield. The mechanistic interpretation is outlined in Scheme 2. The reaction would be initiated by the C-C bond formation to give intermediate **C**. The intermediate **C** would furthermore undergo nucleophilic attack by **2** to afford intermediate **D**. Subsequent ring closure would give intermediate **E** and the product **4** was obtained by hydrolysis and dehydration of **E**. In the reaction of methyl

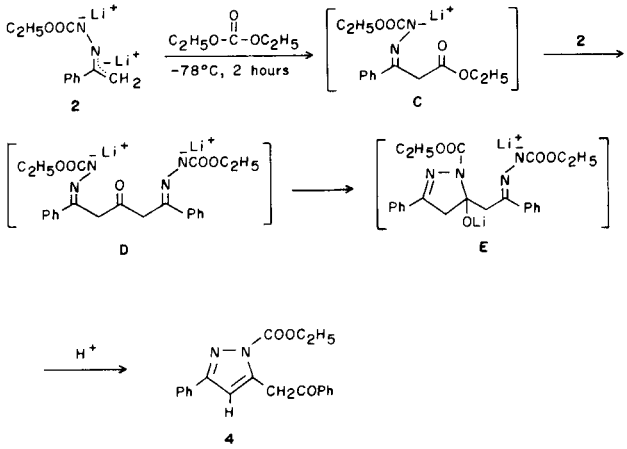
Table 3

Spectral Data of Pyrazole Derivatives **3**

Compound	R_1	IR (cm^{-1}) (potassium bromide)	^{1}H-NMR (δ, ppm) (deuteriochloroform)	MS, m/e	UV λ max, nm (log ϵ) (acetonitrile)
3a	C_6H_5	1770 (C=O)	1.29 (t, 3H, J = 7.0 Hz, CH_2CH_3), 4.33 (q, 2H, J = 7.0 Hz, CH_2CH_3), 6.63 (s, 1H, $C(C_6H_5)$=CH-), 7.07-7.56 (m, 8H, aromatic), 7.67-8.06 (m, 2H, aromatic)	292 (M^+), 248, 247, 233, 220, 191, 165, 130, 104, 77	248.5 (4.48), 261 (4.46), 266 (sh) (4.45), 280 (sh) (4.14), 288 (sh) (3.90)
3b	CH_3	1760 (C=O)	1.46 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.57 (s, 3H, N-$C(CH_3)$=), 4.45 (q, 2H, J = 7.0 Hz, CH_2CH_3), 6.40 (brs, 1H, N-$C(CH_3)$=CH-), 7.15-7.56 (m, 3H, aromatic), 7.60-8.05 (m, 2H, aromatic)	230 (M^+), 171, 159, 158, 157, 130, 128, 77, 51, 29	226 (sh) (4.00), 261.5 (4.41), 272.5 (sh) (4.17), 280.5 (sh) (3.91), 288 (sh) (3.59)
3c	H	1770 (sh) 1750 (C=O)/film	1.45 (t, 3H, J = 7.0 Hz, CH_2CH_3), 4.45 (q, 2H, J = 7.0 Hz, CH_2CH_3), 6.60 (d, 1H, J = 3.0 Hz, N-CH=CH-), 7.09-7.42 (m, 3H, aromatic), 7.55-7.92 (m, 2H, aromatic), 8.03 (d, 1H, J = 3.0 Hz, N-CH=CH-)	216 (M^+), 157, 144, 117, 115, 90, 89, 77, 51, 29	223 (sh) (3.94), 263 (4.39), 281 (sh) (3.95), 288.5 (sh) (3.68)
4	$CH_2COC_6H_5$	1740, 1680 (C=O)	1.35 (t, 3H, J = 7.0 Hz, CH_2CH_3), 4.35 (q, 2H, J = 7.0 Hz, CH_2CH_3), 4.64 (s, 2H, CH_2CO), 6.56 (s, 1H, N-C=CH-), 7.04-8.30 (m, 10H, aromatic)	288 (M^+-C_2H_6O), 262, 215, 186, 105, 78, 46, 45, 44	253 (4.45), 261, (sh) (4.44), 281 (sh) (4.02), 289 (sh) (3.74)

chloroformate with **2**, **4** was obtained in 42% yield. The analytical and spectral data of **4** are listed in Tables 2 and 3.

Scheme 2



Next, we have investigated the reactivity of α-haloketones having two reaction sites with **2**. In this case, we have found that the reaction is quite different from that of ester with **2**. In the reaction of α-chloroketones such as phenacyl chloride, 1-chloroacetone, 3-chloro-2-butanone, and 1,3-dichloroacetone with **2**, pyrazoline derivatives **5** were obtained in good yields. Scheme 3 shows a possible pathway for the reaction. The regiospecific attack of the anion at

Table 4

Reaction of α-Chloroketone with **2** [a]

Entry	α-Chloroketone R_3	α-Chloroketone R_4	Yield, % [b] **5**
a	C_6H_5	H	61
b	CH_3	H	39
c	CH_3	CH_3	62
d	$ClCH_2$	H	43

[a] The reactions were carried out at −78° in tetrahydrofuran for 2 hours. [b] Isolated yields by column chromatography and/or preparative tlc

Table 5

The Melting Points and Analyses of 1-Ethoxycarbonyl-3-phenyl-5-substituted Pyrazoline Derivatives **5**

Compound	R_3	R_4	Mp, °C	Molecular Formula	Analysis % Calcd./Found C	H	N
5a	C_6H_5	H	150-151	$C_{19}H_{20}N_2O_3$	70.35	6.21	8.64
					70.65	6.53	8.37
5b	CH_3	H	121-122	$C_{14}H_{18}N_2O_3$	64.11	6.92	10.68
					63.96	7.17	10.85
5c	CH_3	CH_3	160-164	$C_{15}H_{20}N_2O_3$	65.20	7.29	10.14
					65.29	7.60	9.79
5d	$ClCH_2$	H	142-144	$C_{14}H_{17}ClN_2O_3$	56.67	5.77	9.44
					56.69	6.00	9.17

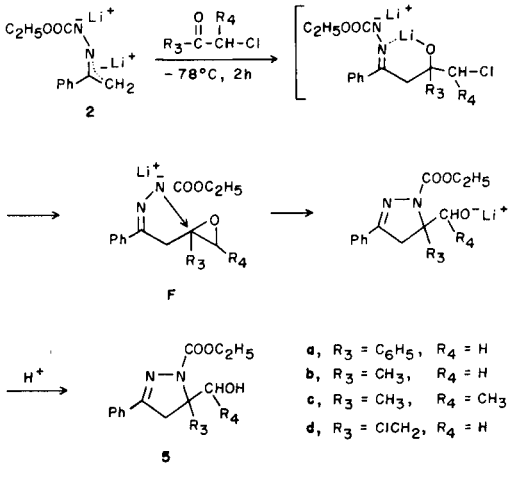
Table 6

Spectral Data of Pyrazoline Derivatives **5**

Compound	R_3	R_4	IR (cm^{-1}) (potassium bromide)	^{1}H-NMR (δ, ppm) (deuteriochloroform)	MS, m/e	UV λ max, nm (log ε) (acetonitrile)
5a	C_6H_5	H	3400 (OH) 1700 (C=O)	1.37 (t, 3H, CH_2CH_3), 3.05-4.80 (m, 7H, CH_2CH_3, CH_2OH, C-CH_2-C), 6.75-7.75 (m, 10H, aromatic)	324 (M^+), 323, 293, 278, 249, 233, 221, 191, 115, 103, 91, 78, 77	286 (4.28), 295 (4.28), 307 (sh) (4.10)
5b	CH_3	H	3400 (OH) 1685 (C=O)	1.10-1.60 (m, 6H, CH_2CH_3, N-C-(CH_3)-CH_2OH), 2.70-4.45 (m, 7H, CH_2CH_3, CH_2OH, N=C(C_6H_5)-CH_2-), 7.06-7.82 (m, 5H, aromatic)	262 (M^+), 231, 216, 187, 159, 129, 118, 104, 103, 91, 78, 77	221 (4.17), 288 (4.35), 294 (4.35), 309 (sh) (4.10)
5c	CH_3	CH_3	3430 (OH) 1690 (C=O)	0.94-1.80 (m, 9H, CH_2CH_3, CHOH-CH_3, N-C(CH_3), 2.65-4.55 (m, 6H, CH_2CH_3, CH_2-CHOH-CH_3), 6.70-8.35 (m, 5H, aromatic)		221 (4.10) 288 (4.28), 295 (4.28), 307 (sh) (4.08)
5d	$ClCH_2$	H	3450 (OH) 1665 (C=O)	1.38 (t, 3H, CH_2CH_3), 2.95-4.57 (m, 9H, CH_2CH_3, CH_2OH, CH_2Cl, C-CH_2-C), 7.18-7.94 (m, 5H, aromatic)		221 (4.23), 225 (sh) (4.16), 286 (4.35), 292 (4.34), 306 (sh) (4.10)

nitrogen atom on the epoxy-ring carbon in the intermediate **F** should be a key step in formation of pyrazoline derivatives **5**. The yields are shown in Table 4. Tables 5 and 6 present the analytical and spectral data for all pyrazoline derivatives **5** prepared.

Scheme 3



EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and were uncorrected. Proton magnetic resonance (^{1}H-nmr) spectra were obtained using a Hitachi Perkin-Elmer R-24 spectrometer (60 MHz). Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. The ir spectra were determined on a Hitachi 215 Grating infrared spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E instrument equipped with a solid sample injector; the ionizing voltage was 80 eV.

General Procedure for the Preparation of Pyrazole and Pyrazoline Derivatives.

To a cooled THF solution (−78°) of acetophenone *N*-ethoxycarbonylhydrazone (**1**, 2.42 mmoles) was added a hexane solution of *n*-butyllithium (5.32 mmoles) with stirring at −78° under argon. To the resulting yellowish brown colored solution was added dropwise a THF solution of substrate (2.18 mmoles). After complete fading of the color, the reaction mixture was stirred for additional 2 hours at −78°, and THF was removed *in vacuo*. To the residual mixture was added water, concentrated hydrochloric acid, acetic acid, and methanol (10 ml each), and stirred for 2 hours at room temperature. After methanol was evaporated, the residue was extracted with ether. The extract was washed with water, dried over anhydrous magnesium sulfate, and condensed under reduced pressure. The residue was chromatographed on a silica gel column or preparative tlc to give pyrazole **3** and pyrazoline **5** derivatives. The yields, the melting points, the ^{1}H-nmr and elemental analyses of pyrazole **3** and pyrazoline **5** derivatives are listed in Tables 1-6.

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