The Direct Carboxylation of Pyrazoles

C. I. Chiriac

"Petru Poni" Institute of Macromolecular Chemistry
Aleea Gr. Ghica-Vodă 41 A, Jassy – Romania

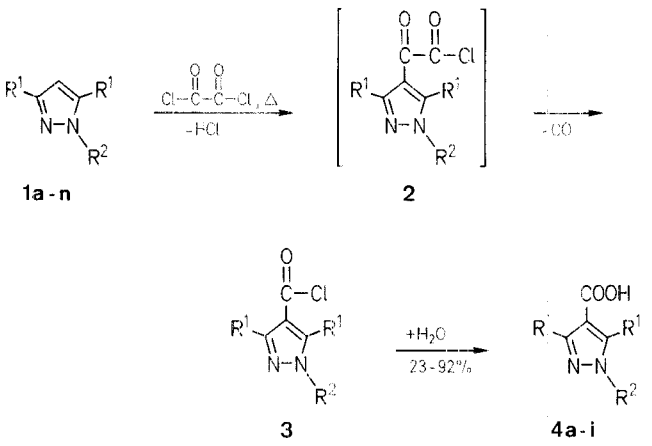
Various pyrazole-4-carboxylic acids **4** were obtained by a direct carboxylation reaction of pyrazoles **1** with excess, oxalyl chloride.

The electrophilic substitution reactions have limited applications in pyrazole chemistry due to the fact that the intermediate cation formed in the presence of acid catalyst is more resistent to electrophilic attack than pyrazole itself[1]. For this reason the acylation of pyrazoles requires a very large excess of the acylating reagent and aluminium chloride[2]. Other electrophilic substitutions also occur with

difficulty[3]. An interesting reaction is the phosphorylation of pyrazoles in the 4-position with phosphorus oxychloride at 230–250 °C without catalyst[4], which probably involves electrophilic substitution[4].

On the other hand, oxalyl chloride or oxalyl bromide reacts, also without catalyst, with reactive aromatic compounds such as, antracene[5], acenaphtene, pyrene[6], indole[7], etc. We have now investigated this reaction is possible for pyrazoles. We have found that this reaction takes place, also without any catalyst (similar to phosphorous oxychloride), at lower temperature. This shows that oxalyl chloride is more reactive than phosphorus oxychloride in this type of reaction. The reaction is carried out either by refluxing a solution of e.g. 3,5-dimethyl-1-1-phenylpyrazole (**1a**) in a large excess of oxalyl chloride, which serves as reagent and solvent for keeping the mixture at room temperature for 24 h. The reaction occurs with loss of hydrochloric acid and carbon monoxide. The excess of oxalyl chloride was removed by heating and the residue remained in the flask was hydrolysed, to give 3,5-dimethyl-1-phenylpyrazole-4-carboxylic acid (**4a**) in high yield.

The direct carboxylation of pyrazolic cycle with oxalyl chloride is an unknown reaction in the chemistry of pyrazoles. Till now, the carboxylic acids of pyrazoles were prepared by indirect synthese. e.g. by oxidation of formylated pyrazoles[8], etc.



t	R^1	R^2
a	CH_3	C_6H_5
b[9]	CH_3	4-$CH_3C_6H_4$
c[10]	CH_3	2-$NO_2C_6H_4$
d[9]	CH_3	2,4-di$NO_2C_6H_3$
e[11]	CH_3	CH_3
f[11]	CH_3	C_2H_5
g[12]	CH_3	$C_6H_5CH_2$
h[13]	H	C_6H_5
i[14]	C_6H_5	C_6H_5
j[15]	CH_3	H
k[9]	CH_3	2,4,6-tri$NO_2C_6H_2$
l[16]	CH_3	$COCH_3$
m[17]	CH_3	COC_6H_5
n[18]	COOH	C_6H_5

We suppose that the first stage of this reaction involves an electrophilic attack of ClOC—$\overset{+}{C}$=O cation in the 4-position of pyrazoles **1**, similar to other cases[6]. The pyrazolyl oxylic acid chlorides **2**, which result as intermediary products, lose carbon monoxide under the conditions of the reaction, resulting in pyrazole carboxylic acid chlorides **3**. These are stable compounds and as an example we have characterized 3,5-dimethyl-1-phenylpyrazole-4-carboxylic acid chloride (**3a**) (see experimental). The acid chlorides **3** were hydrolysed to the corresponding acids **4** (Table).

We have carried out this reaction with a serie of pyrazoles containing electron-releasing and electron-withdrawing substituents (R^1 and R^2). The pyrazoles **1a–i** was carboxylated in the 4-position with oxalyl chloride. The direct carboxylation reaction was unsuccessful in the cases of *N*-acylated pyrazoles **1l, m**, *N*-unsubstituted **1j** or with electron-withdrawing substituents **1n**. For the carboxylation of the pyrazoles **1b–d** with electron-releasing substituents R^1 and electron-withdrawing substituents R^2, it is necessary to heat 5–6 h at reflux. The yield decreases when the number of nitro groups in R^2 increases. Thus, the pyrazole **1d** gives a lower yield and the pyrazole **1k** does not react. The pyrazoles with R^1 and R^2 = alkyl (**1e–g**) were easy to carboxylate with oxalyl chloride in high yields (24 h at room temperature). The low yield obtained in the case of pyrazole **1i**, can be explained by a steric hindrance owing to the phenyl groups at positions 3 and 5.

Table. Pyrazole-4-carboxylic Acids **4** Obtained by Direct Carboxylation with Oxalyl Chloride

Product No.	Yield[a] [%]	IR (KBr) $\nu_{C=O}$ [cm^{-1}]	m.p. [°C][c]	Molecular Formula[b] or Lit. m.p. [°C]
4a	92	1690	196–198	197–198[8]
4b	81	1700	198–200	$C_{12}H_{11}N_3O_4$ (261.2)
4c	77	1705	195–197	$C_{12}H_{11}N_3O_4$ (261.2)
4d	58	1700	209–211	$C_{12}H_{10}N_4O_6$ (306.2)
4e	85	1690	215–217	217
4f	87	1685	144–146	$C_8H_{12}N_2O_2$ (168.2)
4g	90	1690	152–154	$C_{13}H_{14}N_2O_2$ (230.3)
4h	71	1690	216–218	217–219[13]
4i	23	1695	241–243	242–243[19]

[a] Yields calculated on pyrazole **1** used. The reaction mixture refluxed for 5–6 h in the cases of **4b–d**.

[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.30, H ±0.20, N ±0.25.

[c] After recrystallisation, ethanol for **4b–d**, **4g–i** and ethanol/water for **4e–g**.

3-5-Dimethyl-1-phenylpyrazole-4-carboxylic Acid (4a); Typical Procedure:

3,5-Dimethyl-1-phenylpyrazole-4-carboxylic Acid Chloride (**3a**):
A solution of 3,5-dimethyl-1-phenylpyrazole (**1a**; 5.16 g, 0.03 mole) in oxalyl chloride (10 ml, 0.12 mole) is refluxed for 2–3 h or kept 24 h at room temperature. The excess of oxalyl chloride is removed by distillation to give the acid chloride **3a**; yield 96%, 6.75 g; m.p. 65–67 °C (Petroleum ether, 90–100 °C).

$C_{12}H_{11}ClN_2O$ (234.7) calc. C 61.41 H 4.72 N 11.93 Cl 15.10
found 61.34 4.75 11.98 15.07

IR (KBr): ν = 1740 cm^{-1} (C=O).

Hydrolysis of **3a** *to* **4a**:
To the crude acid chloride **3a** obtained as above is added ice (15–20 g) and water (20–30 ml) and the mixture is stirred for 4–5 h. The precipitated product is collected by suction filtration and washed with water (10–15 ml). The product is dissolved in 10% aqueous sodium hydroxide solution (20–30 ml) till pH = 9–10. The solution is stirred with active charcoal (1–2 g) for 30 min and filtered. The filtrate is acidified with 0.1 mmol normal hydrochloric acid to pH = 1–2 with stirring, the precipitated carboxylic acid is filtered, washed with water till neutral and dried in vacuum at 70–80°C; yield: 5.9 g (92%); m.p. 197–199°C (ethanol).

$C_{12}H_{12}N_2O_2$	calc.	C 66.65	H 5.59	N 12.95
(216.2)	found	66.47	5.41	12.14

Received: July 10, 1985
(Revised form: October 25, 1985)

[1] Rojahn, C.A. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 737.
Rojahn, C.A. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 291.
[2] Grandberg, I.I., Vasina, L.G. *Zh. Obshch. Khim.* **1961**, *31*, 1887; *C.A.* **1963**, *58*, 9049.
[3] Katritzky, A.R. *Adv. Heterocycl. Chem.* **1966**, *6*, 390.
[4] Grandberg, I.I., Kost, A.N. *Zh. Obshch. Khim.* **1961**, *31*, 129; *C.A.* **1961**, *55*, 16517.
[5] Latham, Jr. H.G., Mosetting, E. *J. Am. Chem. Soc.* **1948**, *70*, 1079.
[6] Treibs, W., Orttmann, H. *Chem. Ber.* **1960**, *93*, 545.
[7] Specter, M.F. *U.S. Patent* 2825734 (1958); *C.A.* **1958**, *52*, 12923.
[8] Finar, I.L. *J. Chem. Soc.* **1957**, 3314. Finar, I.L. *J. Chem. Soc.* **1961**, 2736.
[9] Chiriac, C.I., Zugrăvescu, I. *Rev. Roumaine Chim.* **1970**, *15*, 789.
[10] Elguero, J. *Bull. Soc. Chim. Fr.* **1970**, 1348.
[11] Grandberg, I.I. *Zh. Obshch. Khim.* **1962**, *32*, 1556; *C.A.* **1963**, *58*, 3290.
[12] Auwers, K., Broche, h. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 3910.
[13] Finar, I.L. *J. Chem. Soc.* **1954**, 2295.
[14] Chiriac, C.I., Stoicescu-Crivetz, L., Zugrăvescu, I. *Rev. Roumaine Chim.* **1969**, *14*, 1263.
[15] Wiley, R.H., Hexner, P.E. *Org. Synth. Coll. Vol. IV* **1962**, 351.
[16] Hüttel, R. *Chem. Ber.* **1959**, *92*, 2019.
[17] Ried, W., Königstein, F.J. *Justus Liebigs Ann. Chem.* **1959**, *622*, 40.
[18] Balbiano, L. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1449.
[19] Sandstrom, J. *Acta Chem. Scand.* **1962**, *16*, 2395.