The Preparation of 1,1′-Carbonyl- and 1,1′-Sulfinyl-dipyrazoles and their Reactions with Carbonyl Compounds

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The compounds 1,1′-carbonylbis(3-methylpyrazole) (**1**), 1,1′-carbonylbis(3,5-dimethylpyrazole) (**2**), and 1,1′-sulfinyldipyrazole (**3**) have been prepared. They react with aldehydes and ketones in the presence of metal ion catalysts to form 1,1′-alkylidenedipyrazoles together with carbon dioxide, from **1** and **2**, or sulfur dioxide, from **3**. Tetrapyrazol-1-ylmethane results from the pyrolysis at 200° of 1,1′-carbonyldipyrazole in the presence of cobalt(II) chloride.

La préparation du carbonyl-1,1′ bis (méthyl-3 pyrazole) (**1**), carbonyl-1,1′ bis (diméthyl-3,5 pyrazole) (**2**) et sulfinyl-1,1′ dipyrazole (**3**) a été rapportée. Ces composés réagissent sur les aldéhydes et cétones en présence de catalyseurs ion métallique pour conduire aux alkylidène-1,1 dipyrazoles et gaz carbonique pour le **1** et **2** et anhydride sulfureux pour **3**. Le tétrapyrozyl-1 méthane résulte de la pyrolyse à 200° du carbonyl-1,1′ dipyrazole en présence de chlorure de cobalt(II). [Traduit par le journal]

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As previously reported (1, 2), 1,1′-carbonyldipyrazole reacts with various carbonyl compounds in the presence of metal salt catalysts, liberating carbon dioxide to form 1,1′-alkylidenedipyrazoles. We have now prepared the related compounds 1,1′-carbonylbis(3-methylpyrazole), 1,1′-carbonylbis(3,5-dimethylpyrazole), and 1,1′-sulfinyldipyrazole in order to study steric and electronic substituent effects.

Experimental

Elemental analyses were performed by the departmental analyst. Melting points are uncorrected. The n.m.r. spectra[1] were recorded on a Varian A 56/60 using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were determined with a double-focusing RMU-6E Hitachi Perkin–Elmer instrument, and for all compounds reported below (**1–13**), the mass corresponding to the observed parent peak was in agreement with the calculated molecular weight.[2]

Preparation of 1,1′-Carbonylbis(3-methylpyrazole) (1)

3-Methylpyrazole (0.10 mol) in dry ether (50 ml) was added slowly, under a nitrogen atmosphere, to a stirred ethereal (200 ml) suspension of sodium amide (0.10 mol); the mixture was stirred for 16 h at 25° and then heated at reflux temperature for 4 h. With the reaction vessel attached to the vacuum system, phosgene (0.05 mol) was condensed onto the mixture, which was initially held at −78° for 1 h, then heated under reflux for several hours, again under a nitrogen atmosphere. The sodium chloride precipitate (0.10 mol) was filtered off and the solvent was distilled under N_2 to give a yellow solid which was purified by zone fractionation under vacuum to yield pure **1**, m.p. 68–69°, in 80% yield.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.8; N, 29.4; H, 5.3. Found: C, 56.5; N, 29.6; H, 5.2.

N.m.r.: τ 7.63 (s, 3H, CH_3), 3.68 (d, 1H, 4-H, J = 3.0 Hz), 1.37 (d, 1H, 5-H, J = 3.0 Hz).

Preparation of 1,1′-Carbonylbis(3,5-dimethylpyrazole) (2)

Compound **2** was prepared from 3,5-dimethylpyrazole according to the method used for compound **1**; m.p. 85–86° (lit. (3) 89–90°); yield, 70%.

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.6; N, 25.7; H, 6.4. Found: C, 60.8; N, 25.8; H, 6.5.

N.m.r.: τ 7.75 (s, 3H, 3-CH_3), 7.52 (d, 3H, 5-CH_3, J = 1.0 Hz), and 3.95 (m, 1H, 4-H).

Preparation of 1,1′-Sulfinyldipyrazole (3)

Compound **3** was prepared in the same way as 1,1′-carbonyldipyrazole (2), using thionyl chloride in place of phosgene; yield, 55%; m.p. 73–74°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.5; N, 30.8; H, 3.2. Found: C, 39.6; N, 31.1; H, 3.4.

N.m.r.: τ 2.23 (q, 1H, 3-H, J_{34} = 1.6, J_{35} = 0.5 Hz), 3.53 (q, 1H, 4-H, J_{45} = 2.7, J_{34} = 1.6 Hz), and 2.00 (q, 1H, 5-H, J_{45} = 2.7, J_{35} = 0.5 Hz).

Reactions of 1 with Carbonyl Compounds

(*a*) With acetone: The following procedure is typical of all reactions in this section. A mixture of **1** (0.90 mmol), dry acetone (~5 ml), and cobalt(II) chloride (~4 mg) was heated in a sealed tube at 90–95° for 16 h to liberate CO_2 quantitatively (only traces of CO_2 were detected at 25°). The solid product was purified by zone fractionation under vacuum to yield 2,2-bis(3-methylpyrazol-1-yl)-propane (**4**); yield, 70%; m.p. 101–102°.

[1]N.m.r. spectra and bands showing unresolved fine structure are signified by an asterisk.

[2]The mass spectra of compounds **1–13** exhibited strong parent peaks in all cases. Major fragments corresponding to loss of pyrazolyl or methylpyrazolyl moieties were observed. Compounds **1**, **2**, and 1,1′-carbonyldipyrazole gave rise to di(methylpyrazolyl), and dipyrazolyl recombination species, respectively.

Anal. Calcd. for $C_{11}H_{16}N_4$: C, 64.7; N, 27.5; H, 7.8. Found: C, 65.2; N, 27.6; H, 8.0.

N.m.r.: τ 7.80 (s, 6H, $C(CH_3)_2$, 7.72 (m, 6H, 3-CH_3), 3.98 (d*, 2H, 4-H, J = 2.3 Hz) and 2.78 (d*, 2H, 5-H, J = 2.3 Hz).

(*b*) Acetone-d_6 gave 2,2-bis(3-methylpyrazol-1-yl)-hexadeuteropropane (**5**); yield, 85%; m.p. 102–103°.

N.m.r.: τ 7.73 (s*, 3, CH_3), 4.00 (d*, 1H, 4-H, J = 2.4 Hz), 2.83 (d*, 1H, 5-H, J = 2.4 Hz).

(*c*) Acetaldehyde gave 1,1-bis(3-methylpyrazol-1-yl)-ethane (**6**); yield, 65%.

Anal. Calcd. for $C_{10}H_{14}N_4$: C, 63.2; N, 29.5; H, 7.4. Found: C, 63.2; N, 28.6; H, 7.6.

N.m.r.: τ 7.78 (s*, 6H, ring-CH_3), 4.00 (d*, 2H, 4-H, J = 2.3 Hz), 2.55 (m*, 2H, 5-H), 3.60 (9, 1H, >CH—CH_3, J = 6.7 Hz), and 7.83 (m*, 3H, >CH—CH_3).

(*d*) Cyclobutanone gave 1,1-bis(3-methylpyrazol-1-yl)-cyclobutane (7); yield, 75%; m.p. 43.5–45°.

Anal. Calcd. for $C_{12}H_{16}N_4$: C, 66.7; N, 25.9; H, 7.4. Found: C, 66.6; N, 25.6; H, 7.6.

N.m.r.*: 7.73 (s, 6H, CH_3), 3.98 (d, 2H, 4-H, J = 2.4 Hz), 2.77 (d, 2H, 5-H, J = 2.4 Hz), 7.93 and 6.83 (m, 6H, —$(CH_2)_3$—).

(*e*) Cyclopentanone gave 1,1-bis(3-methylpyrazol-1-yl)-cyclopentane (**8**); yield, 30%; m.p. 121–122°.

Anal. Calcd. for $C_{13}H_{18}N_4$: C, 67.8; N, 24.4; H, 7.8. Found: C, 67.7; N, 24.3; H, 7.9.

N.m.r.*: τ 7.75 (s, 6H, CH_3), 4.00 (d, 2H, 4-H, J = 2.4 Hz), 2.68 (d, 2H, 5-H, J = 2.4 Hz), 8.17 and 7.13 (m, 8H, —$(CH_2)_4$—).

(*f*) 4-Methylcyclohexanone gave 1,1-bis(3-methylpyrazol-1-yl)-4-methylcyclohexane (**9**); yield, 60%; m.p. 77.5–78.5°.

Anal. Calcd. for $C_{15}H_{22}N_4$: C, 70.1; N, 21.8; H, 8.2. Found: C, 69.9; N, 21.6; H, 8.5.

N.m.r.: τ 9.13 (m, 3H, —CH_2—CH(—CH_3)—), 7.72 and 7.75 (2s, 6H, —N=C(—CH_3)—), 4.13 and 3.92 (2d*, 2H, 4-H, J = 2.3 Hz), 3.13 and 2.43 (2d*, 2H, 5-H, J = 2.3 Hz), and 7–9 (complex band, 9H, cyclohexane ring).

Reactions of 2 with Ketones

The procedure was essentially the same as that used with compound **1** above, except that temperatures of 150–170° were required to facilitate reaction.

(*a*) Acetone gave 2,2-bis(3,5-dimethylpyrazol-1-yl)propane (**10**); yield, 65%; m.p. 80–81.5°.

Anal. Calcd. for $C_{13}H_{20}N_4$: C, 67.3; N, 24.1; H, 8.6. Found: C, 67.5; N, 24.1; H, 6.6.

N.m.r.: τ 7.77 (s, 6H, 3-CH_3), 4.17 (broad band, 2H, 4-H), 8.32 (d, 6H, 5-CH_3, J = 0.8 Hz), and 7.87 (s, 6H, >$C(CH_3)_2$).

(*b*) Cyclobutanone gave 1,1-bis(3,5-dimethylpyrazol-1-yl)-cyclobutane (**11**); yield, 50%; m.p., 72–73°.

Anal. Calcd. for $C_{14}H_{20}N_4$: C, 68.8; N, 22.9; H, 8.2. Found: C, 68.9; N, 22.6; H, 8.3.

N.m.r.: τ 7.78 (s, 6H, 3-CH_3), 4.22 (m*, 2H, 4-H), 8.13 (d, 6H, 5-CH_3, J = 0.8 Hz), 8.00 and 6.73 (complex bands, 6H, —$(CH_2)_3$—).

(*c*) With methyl ethyl ketone, CO_2 was evolved quantitatively, together with a difficult-to-purify oil and 3,5-dimethylpyrazole. The latter was identified by i.r., n.m.r., and mass spectra. The expected compound 2,2-bis(3,5-dimethylpyrazol-1-yl)-butane was not detected.

(*d*) With cyclohexanone, CO_2 was evolved quantitatively together with an impure oil and 3,5-dimethylpyrazole. The expected compound 1,1-bis(3,5-dimethylpyrazol-1-yl)-cyclohexane was not detected.

Reactions of 3 with Ketones

(*a*) With acetone: A typical procedure was as follows: Dry acetone (~5 ml), 1,1′-sulfinyldipyrazole (2.05 mmol), and a catalytic amount of dry $CoCl_2$ were sealed under vacuum into a reaction vessel and cooled in liquid nitrogen. On warming from −196° to room temperature, a blue solution, gradually turning yellow, was observed. After 16 h, the products were SO_2 (quantitatively), identified by its i.r. spectrum and vapor phase molecular weight (M(calcd.), 64.06; M(obsd.), 63.8), and a residue of solids which was purified by zone fractionation to yield 2,2-dipyrazol-1-ylpropane (75% yield), identified by its m.p. and i.r., mass, and n.m.r. spectra (2, 4).

(*b*) Cyclobutanone gave 1,1-dipyrazol-1-ylcyclobutane (80% yield) by its m.p. and i.r., mass, and n.m.r. spectra (2).

(*c*) Cyclopentanone, a reaction temperature of 120–130° was required; the product was identified as 1,1-dipyrazol-1-ylcyclopentane (35% yield) by its m.p. and i.r., mass, and n.m.r. spectra (2, 4).

(*d*) 4-Methylcyclohexanone gave 1,1-(dipyrazol-1-yl)-4-methylcyclohexane at room temperature, in 60% yield, and identified by its m.p. and i.r., mass, and n.m.r. spectra (2).

The Reaction of 1,1′-Carbonyldipyrazole with Benzophenone

A preliminary experiment indicated that no reaction occurs between 1,1′-carbonyldipyrazole and benzophenone in the presence of a catalytic amount of cobalt(II) chloride in refluxing THF (2). However, when equimolar quantities (1.75 mmol) of these two reagents and a trace of dry $CoCl_2$ were heated in a sealed tube at 190–200° for 16 h, carbon dioxide (1.16 mmol) and a mixture of brown solid and liquid products was formed. The solid was purified by zone fractionation and recrystallization from methanol, yielding white crystals of diphenyldipyrazol-1-ylmethane (**12**); yield, 25%; m.p. 153–154°.

Anal. Calcd. for $C_{19}H_{16}N_4$: C, 76.0; N, 18.7; H, 5.3. Found: C, 75.6; N, 18.8; H, 5.3.

N.m.r.: τ 3.83 (q, 2H, 4-H, J_{45} = 2.5, J_{34} = 1.8 Hz), 2.53 (m, 4H, 3-H and 5-H), 3.07 and 2.72 (m, 10H, C_6H_5).

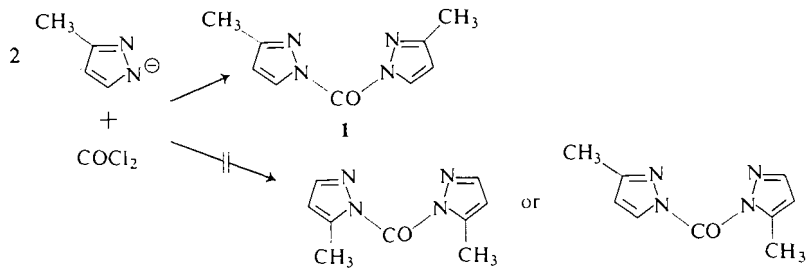
The Pyrolysis of 1,1′-Carbonyldipyrazole

Pure 1,1′-carbonyldipyrazole was found to be stable up to 180°; however, a sample (2.34 mmol) heated at 190° for 16 h, in the presence of a catalytic amount of dry $COCl_2$, yielded CO_2 (0.97 mmol) and a brown residue. Tetrapyrazol-1-ylmethane (**13**) was separated from the residue by zone fractionation; yield, 50%; m.p., 146–147° (lit. (4), 146–147°).

N.m.r.: τ 2.07 (q, 3-H, J_{34} = 1.8, J_{35} = 0.7 Hz), 3.45 (q, 4-H, J_{45} = 2.9, J_{34} = 1.8 Hz), and 2.23 (q, 5-H, J_{45} = 2.9, J_{35} = 0.7 Hz).

Discussion

1,1′-Carbonylbis(3,5-dimethylpyrazole) (**2**) and the new compounds 1,1′-carbonyl-bis(3-methylpyrazole) (**1**) and 1,1′-sulfinyldipyrazole (**3**) are obtained in high yield by the reaction of

[1] 

14

the appropriate sodium pyrazolide salt with either phosgene or thionyl chloride, in a manner analogous to the procedures reported in the literature for the synthesis of 1,1′-sulfinyldiimidazole (5) and various derivatives of 1,1′-carbonyldipyrazole (1, 3, 6–8) and 1,1′-carbonyldiimidazole (9). Compound **1** is obtained as a single substance, there being no evidence for the formation of the isomeric 1,1′-carbonylbis-(5-methylpyrazole) or the mixed isomer **14** (eq. 1).

Thus N-1, though more remote than N-2 from the electron-releasing methyl group, is clearly the more nucleophilic center in the methylpyrazolide anion. Compounds **1**–**3** are sensitive to moisture, being hydrolyzed to free base and carbon dioxide or sulfur dioxide. They are readily characterized on the basis of m.p., elemental analysis, and i.r., mass, and p.m.r. spectral measurements; the assignment of the lowest-field resonance to H-5 of **1** and **3** is related to the electron-withdrawing effect of the C=O or S=O group attached at N-1. The resonances of the 3- and 5-methyl groups in compound **2** can be distinguished on the basis of similar arguments (10).

Like 1,1′-carbonyldipyrazole, compounds **1**, **2**, and **3** react with aldehydes and ketones, in the presence of catalytic amounts of cobalt(II) chloride, to yield dipyrazol-1-ylmethanes and CO_2 and SO_2 (eq. 2). However, whereas most

[2] $$(py)_2XO + R_2CO \rightarrow R_2C(py)_2 + XO_2$$

X = C or S
py = pyrazol-1-yl, 3-methylpyrazol-1-yl, or 3,5-dimethylpyrazol-1-yl

of the reactions of 1,1′-carbonyldipyrazole occur at room temperature, more vigorous conditions *viz.* 100–110° and 160–180°, are required with compounds **1** and **2**, respectively. Although the sulfinyl compound **3** reacts readily at room temperature, it is less reactive than the corresponding carbonyl compound as shown by the exclusive formation of carbon dioxide when acetone was allowed to compete for both reagents. It is noteworthy that Staab and Wendel (5) have reported the opposite reactivity order for the corresponding imidazole derivatives. The reactivity decrease in the series 1,1′-carbonyldipyrazole > **1** > **2** clearly indicates that both the 3- and the 5-methyl substituent are sterically active during the course of the reaction; unfortunately, one cannot deduce, from this evidence alone, the relative significance of steric effects on individual steps of the detailed reaction mechanism.

Bulky groups also influence the reactivity of the ketones. Thus, the catalytic reaction of 1,1′-carbonyldipyrazole with benzophenone only occurs at 190–200° to give diphenyldipyrazol-1-ylmethane (**12**); and 1,1′-carbonyldipyrazole condenses with itself at 190–200°, in the presence of cobalt(II) chloride, to yield tetrapyrazol-1-ylmethane (**13**) (eqs. 3 and 4). Neither reaction

[3] $$(py)_2CO + (C_6H_5)_2CO \xrightarrow[190\text{–}200^\circ]{CoCl_2} (py)_2C(C_6H_5)_2 + CO_2$$

[4] $$2(py)_2CO \xrightarrow[190\text{–}200^\circ]{CoCl_2} (py)_4C + CO_2$$

is observed in the absence of catalyst. Interestingly, 1,1′-carbonyldipyrazole reacts preferentially with benzophenone (eq. 3) rather than with itself (eq. 4) which is consistent with the general rule that resonance interactions of the type

$$>N-\overset{|}{C}=O \leftrightarrow >\overset{\oplus}{N}=\overset{|}{C}-\overset{\ominus}{O}$$

make the carbonyl carbon of an amide less electropositive, *i.e.*, less susceptible to nucleophilic attack than that of a ketone. In view of this fact, it is surprising indeed that 1,1′-carbonyldipyrazole reacts *at all* according to eq. 4; one may

attribute the enhanced reactivity of its carbonyl group, relative to simple amide systems, to a preferred delocalization of the nitrogen lone pair of electrons over the aromatic pyrazole ring, rather than over the three atoms forming the amide group. I.r. spectroscopic measurements (2) provide further support for this interpretation.

Our studies with 1,1′-carbonylbis(3,5-dimethylpyrazole) (**2**) indicate a dramatic limitation to the number of stable derivatives which may be obtained with ketones. Thus, acetone and cyclobutanone react at 160° in the established typical fashion, yielding 2,2-bis(3,5-dimethylpyrazol-1-yl)propane (**10**) and 1,1-bis(3,5-dimethylpyrazol-1-yl)cyclobutane (**11**), respectively. The comparable reactions with methyl ethyl ketone and with cyclohexanone, on the other hand, produce carbon dioxide, 3,5-dimethylpyrazole and unidentified oils which are presumably decomposition products of the desired 1,1′-alkylidene(3,5-dimethylpyrazoles). A study of models suggests several favorable conformations for **10** and **11**, respectively. However, models of the unknown 2,2-bis(3,5-dimethylpyrazol-1-yl)butane and 1,1-bis(3,5-dimethylpyrazol-1-yl)cyclohexane are sterically congested, locked structures; considerable interaction between the N-2 lone electron pair and the C-3 proton of the hydrocarbon moiety could lead to facile decomposition.

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