Notes

Heterocyclic Studies. 32. Some Reactions of 3-Diazoacetyl-4-phenylpyrazoline. A Correction on 1-Diazoacetyl-4-phenyl-3-buten-2-one[1]

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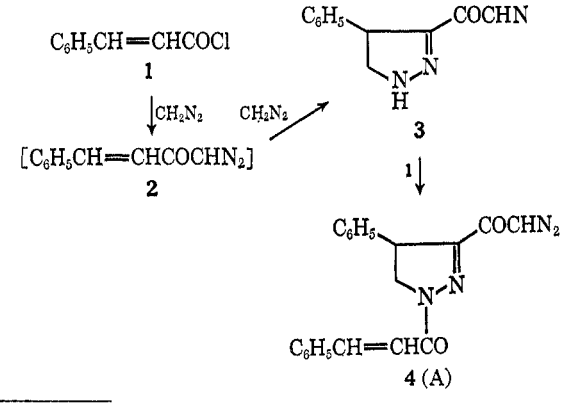
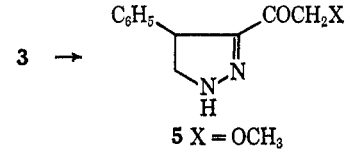
In the course of work on the cyclization of diazoacetylpyrazolines, the unsaturated diazo ketone **2** was of interest as a possible source of 5(3)-diazoacetyl-3(5)-pyrazolinecarboxylic ester, which would arise by addition of diazoacetic ester. The preparation of **2**, mp 172°, has been reported by the reaction of *trans*-cinnamoyl chloride and a limited amount of diazomethane at low temperature.[2] The diazoacetylpyrazoline **3** or the unstable Δ^1 isomer are obtained under the usual conditions with excess diazomethane.[2,3]

We have repeated the procedure for the preparation of the diazo ketone **2** and isolated a product (A) with melting point and ir spectrum corresponding to those reported.[2] However, the nmr spectrum immediately ruled out the proposed structure **2**, and the chloro ketone derived from A differed widely in melting point from that reported for 1-chloro-4-phenyl-3-buten-2-one.[4] The nmr spectra of A and the chloro ketone were also inconsistent with the 5-cinnamoylpyrazoline which might arise by addition of the diazomethyl group of one molecule of **2** to the unsaturated carbonyl group of another molecule. The spectra were compatible, however, with a 1-cinnamoylpyrazoline unit, and structure **4** for A was confirmed by acylation of **3** with cinnamoyl chloride.[5] The formation of **4** reveals that the rate of 1,3-dipolar addition of diazomethane to the unsaturated chloride or diazo ketone **2**, in contrast to the α-methyl derivative,[3] is comparable with the rate of acylation of diazomethane, permitting the pyrazoline **3** to compete successfully with diazomethane for acid chloride. This situation places an unfortunate restriction on the availability of α,β-unsaturated diazo ketones such as **2**.



In connection with the attempted preparation of **2**, several substituted pyrazolines were obtained from **3**. Reaction with methanolic hydrochloric acid, under conditions which generally give chloromethyl ketones,[3] gave a mixture of methoxyacetyl- and chloroacetylpyrazolines from which the former was isolated; the chloroacetyl compound was best prepared in aqueous tetrahydrofuran containing hydrochloric acid and lithium chloride. The chloro ketone was quite sensitive, and darkened rapidly on heating in solution with the formation of tarry polymeric material. Efforts to characterize products arising from cyclization to a 1,2-diazabicyclo[3.2.0]heptene derivative were unsuccessful. Attempts were also made to convert pyrazolines **3**, **4**, and **6** into the respective 3-acetylpyrazoles by oxidation with manganese dioxide or lead tetraacetate; no products could be isolated.



5 X = OCH_3
6 X = Cl
7 X = OH

Experimental Section

1-Cinnamoyl-3-diazoacetyl-4-phenyl-2-pyrazoline (4). A.—To a solution of 0.12 mol of diazomethane in ether at 0°, a solution of 9.3 g (0.056 mol) of cinnamoyl chloride in 50 ml of ether was added dropwise. After standing at 0° overnight, pale yellow crystals separated. These were collected and dried to give 2.5 g (26%) of **4**: mp 180° dec (recrystallization from methanol–tetrahydrofuran did not change the melting point); λ_{max}^{EtOH} 302 mμ (ϵ 31,000), 333 (25,000); ν_{KBr} 2080, 1665, 1625 cm^{-1}; δ ($CDCl_3$) 4.0–4.8 (m, 3, H-4 and H-5), 6.1 (s, 1, CHN_2), 7–8 (m, 12, aromatic and vinyl).

B.—Ether solutions of 3-diazoacetyl-4-phenylpyrazoline (**3**), 214 mg (1 mmol), and 84 mg (0.5 mmol) of cinnamoyl chloride were combined and allowed to stand. Evaporation gave 124 mg (72%) of the cinnamoylpyrazoline **4**, mp 180° dec, ir same as that from A.

A solution of **4** in methanol containing sodium methoxide was allowed to stand overnight, and the pyrazoline **3** was isolated.

1-Cinnamoyl-3-chloroacetyl-4-phenyl-2-pyrazoline.—A solution of 200 mg of the cinnamoylpyrazoline **4** in 3 ml of tetrahydrofuran was treated with 2 ml of concentrated hydrochloric acid. After gas evolution subsided, the solution was warmed briefly and then diluted with water. The resulting solid was collected and recrystallized from methanol to give colorless prisms of the title compound: mp 180°; ν_{KBr} 1700, 1660, 1620; δ ($CDCl_3$) 4.0–4.7 (m, 3), 4.7 (s, 2), 7–8 (m, 12).

Anal. Calcd for $C_{20}H_{17}ClN_2O_2$: C, 68.09; H, 4.86; N, 7.94. Found: C, 68.36; H, 4.88; N, 7.82.

Treatment of this 1-cinnamoyl-3-chloroacetylpyrazoline with 1 equiv of bromine in chloroform solution gave, after the usual

(1) Supported by Grant G.P. 5219 from the National Science Foundation.

(2) J. H. Wotiz and S. N. Buco, *J. Org. Chem.*, **20**, 210 (1955).

(3) J. A. Moore, *ibid.*, **20**, 1607 (1955).

(4) A. N. Nesmajanov, M. I. Kybinskaya and N. K. Kochetkov, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 1197 (1956); *Chem. Abstr.*, **51**, 5727 (1957).

(5) NOTE ADDED IN PROOF.—In a paper which became available to us after this note was submitted, M. Itoh and A. Sugihara, *Chem. Pharm. Bull.*, **17**, 2105 (1969), report a similar conclusion about **4**. Our findings agree in all respects with those of Itoh and Sugihara.

isolation procedure, 440 mg (85%) of **1-(2,3-dibromo-3-phenylpropionyl)-3-chloroacetyl-4-phenyl-2-pyrazoline**: mp 183–185° (recrystallized from methanol); δ ($CDCl_3$) 4.1–4.7 (m, 3), 4.7 (s, 2), 5.63, 5.88 (dd, 2, AB, $|J_{AB}| = 11.5$ Hz), 7.2–7.5 (m, 10).

Anal. Calcd. for $C_{20}H_{17}Br_2ClN_2O_2$: C, 46.86; H, 3.34. Found: C, 46.92; H, 3.49.

3-Methoxyacetyl-4-phenyl-2-pyrazoline (**5**).—A solution of 1.07 g of **3** in 20 ml of methanol was treated with 2 ml of 1 *N* methanolic hydrochloric acid. After gas evolution ceased, the solution (two spots on tlc) was diluted with water. After extraction, etc., evaporation of the ether gave 260 mg of colorless crystals, mp 115–118°. Two recrystallizations from ether–petroleum ether gave needles of **5**: mp 120–122°; ν_{KBr} 1650 cm^{-1}; δ ($CDCl_3$) 3.4 (s, 3), 3.4–4.5 (m, 3), 4.5 (apparent doublet, 2-Hz separation, probably center of AB dd), 6.8 (s, 1, NH), 7.2 (s, 5).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.59; N, 12.84. Found: C, 65.84; H, 6.25; N, 12.94.

3-Chloroacetyl-4-phenyl-2-pyrazoline (**6**).—To a solution of 1.07 g of **3** and 2.1 g of LiCl in 10 ml of THF and 5 ml of water was added 4.5 ml of 1 *N* hydrochloric acid. The two-phase mixture was stirred for 2 hr and then extracted, etc. Evaporation gave 0.8 g of white solid still containing an ir peak at 2080 cm^{-1}. Crystallization from ether–pentane gave crystals of **6**: mp 97° (darkening at 60°); one spot tlc (corresponding to faster moving spot in tlc of reaction mixture from **5**); δ ($CDCl_3$) 3.3–4.5 (m, 3), 4.5 (apparent doublet), 6.75 (s, 1, NH), 7.2 (s, 5). Analytically pure material was not obtained since prolonged drying caused decomposition.

Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.82; 4.92; N, 12.12.

The hydroxyacetylpyrazoline **7** was prepared from **3** in aqueous THF plus 1 *N* sulfuric acid. A viscous oil was obtained. After purification on a 20 × 20 cm, 2-mm-thick silica gel plate ($CHCl_3$–MeOH 23:2), the product remained an oil. Treatment with phenyl isocyanate gave the **N-phenylcarbamate ester of 1-N-phenylcarbamoyl-3-hydroxyacetyl-4-phenylpyrazoline**: mp 257°; ν_{KBr} 3100, 1720, 1660 cm^{-1}.

Anal. Calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 67.86; H, 5.01; N, 12.66. Found: C, 67.65; H, 5.16; N, 12.44.

Registry No.—**2**, 24265-71-2; **3**, 24265-72-3; **4**, 24265-73-4; **5**, 24265-74-5; **6**, 24265-75-6; 1-cinnamoyl-3-chloroacetyl-4-phenyl-2-pyrazoline, 24265-76-7; 1-(2,3-dibromo-3-phenylpropionyl)-3-chloroacetyl-4-phenyl-2-pyrazoline, 24265-77-8; N-phenylcarbamate ester of 1-N-phenylcarbamoyl-3-hydroxyacetyl-4-phenylpyrazoline, 24265-78-9.

Reaction of 6,6-Dihalobicyclo[3.1.0]hexanes with Morpholine[1]

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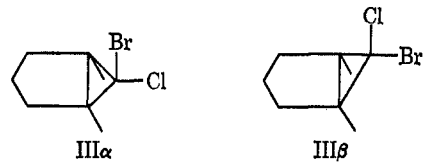
No reports appear in the literature covering the reaction of *gem*-dihalobicyclo[3.1.0]hexanes with amines to give N-substituted derivatives. This report describes the reactions of morpholine with the 6,6-dibromo- (I), 6,6-dichloro- (II), and 6-bromo-6-chlorobicyclo[3.1.0]hexanes (III) at 128°.

Compound I readily reacted with morpholine at 128° in 5 min to give a heavy precipitate of morpholine hydrobromide and 2-bromo-3-morpholinocyclohexene (IV). Compound II had to be heated for 24 hr before reacting entirely to give 2-chloro-3-morpholinocyclohexene (V).

Compound III exists in two isomeric forms, α and β.



IIIα IIIβ

In an earlier brief report[2] it was indicated that the α and β isomers react stereospecifically with aqueous silver nitrate to give from one isomer only silver chloride and 2-bromo-3-hydroxycyclohexene and from the other isomer only silver bromide and 2-chloro-3-hydroxycyclohexene.

It was now of interest to determine whether these isomers again would exhibit the same stereospecificity in their reaction with morpholine and to determine the products of this reaction.

Compound III was prepared by adding dibromochloromethane to a mixture of cyclopentene and potassium *t*-butoxide at 0°. Crude III was purified by vacuum distillation at temperatures low enough to avoid thermal rearrangement[3,4] to the bromochlorocyclohexenes. The ir spectrum and bromine unsaturation tests indicated the absence of unsaturation.

Reaction of III with refluxing morpholine (118°) for 5 min gave an exothermic reaction and the precipitation of morpholinehydrobromide. Quenching of the reaction with water and neutralizing with hydrochloric acid afforded 46% V and 32% the less reactive isomer IIIβ. The rapid reaction of the reactive isomer of III with morpholine was similar to the reactivity of I under identical conditions.

The unreactive isomer was obtained by fractional distillation and its purity was ascertained by the vpc and ir and nmr spectra. The ir spectrum of the unreactive isomer lacked the following peaks present in the mixture of isomers: 10.52, 10.87, 11.77, 12.75, and 13.33 μ. Further spectral details are described in Table I. The nmr of the unreactive isomer also lacked a peak at δ 2.05 which was present in the nmr of the mixture of IIIα and IIIβ. Reaction of this isomer with morpholine at 128° gave no immediate reaction as determined by vpc analysis. After 24 hr the reaction was complete and afforded 62% IV. The reactivity of this isomer was similar to the reactivity of II with morpholine.

In the study of the epimeric 7-chlorobicyclo[4.1.0]-heptanes, cristol and coworkers[5] suggested that the loss of the halide ion *trans* to the hydrogen atoms at C-2 and C-4 is preferred by a large factor. Schleyer[6] has observed a similar order of reactivity in the solvolysis of the epimeric monotosylbicyclo[4.1.0]heptanes. Cristol further reasoned that, on the basis of the rates of solvolysis (carried out at 124.6° in glacial acetic acid–sodium acetate), the same halogen leaves in 7,7-bicyclo[4.1.0]heptane.

(1) For the previous paper on the reaction of *gem*-dibromocyclopropanes with morpholine, see S. R. Sandler, *J. Org. Chem.*, **33**, 4537 (1968).

(2) P. S. Skell and S. R. Sandler, *J. Amer. Chem. Soc.*, **80**, 2024 (1958).

(3) S. R. Sandler, *Chem. Ind.* (London), 1481 (1968).

(4) S. Winstein and J. Sonnenberg, *J. Org. Chem.*, **27**, 748 (1962).

(5) S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *J. Amer. Chem. Soc.*, **87**, 4007 (1965).

(6) P. von R. Schleyer, G. W. Van Dine, U. Schollkopf, and J. Paust, *ibid.*, **88**, 2868 (1966).