A Reliable Synthesis of 1,1-Dimethylpyrazolium 5-Oxides

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Reliable syntheses of compounds having the novel 1,1-dimethylpyrazolium 5-oxide ring system are reported. The method involves treating the dimethylhydrazone of a β-ketoester with a small amount of concentrated sulfuric acid or other catalyst and heating under reduced pressure for 1-24 hours. In this manner two new members of the series have been prepared and characterized.

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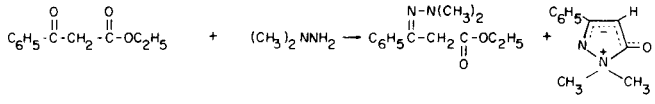
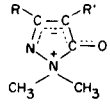
The synthesis and crystal structure of 1,1-dimethyl-3-phenylpyrazolium-5-oxide (**4**) were reported in 1970 (1,2). This compound was the first reported member of this kind of heterocyclic betaine, and to date no other members have appeared in the literature. Furthermore, no studies of the original member have been reported. The absence of these compounds from the literature is probably due to the lack of a reliable method of synthesis.



1 **2** **3** **4**

In the original work (1) the betaine **4** was isolated in 3% yield from the reaction of ethyl benzoylacetate (**1**) with 1,1-dimethylhydrazine (**2**) to form the dimethylhydrazone **3**. A better yield (58%) of **4** was obtained (1) from the reaction of **3** with methyl *p*-toluenesulfonate; however, subsequent attempts to produce **4** by this method led only to the formation of 1,1,1-trimethylhydrazinium *p*-toluenesulfonate.

Here we report a reproducible method in which **4** is obtained in high yield. Further, we report the synthesis of two new examples, **5** and **6**, of this type of betaine. All three betaines are white crystalline compounds with only **6** being slightly unstable in air.



	R	R'
4	C_6H_5-	H-
5	C_6H_5-	CH_3-
6	CH_3-	CH_3-

In our attempts to prepare **4** in high yield, it was first observed that cyclization of the hydrazone **3** to **4** could be easily induced by heating **3** just below its boiling point under reduced pressure (0.8 torr) for 6 hours. It was further noted that the success of this method appeared to depend on the origin of the ethyl benzoylacetate. When **3** was prepared from **1** which had been synthesized as described in the literature (3), conversion to **4** occurred consistently. However, when **3** was made from **1** which had been obtained from commercial sources, repeated attempts at cyclization were unsuccessful. These results were obtained even when the commercial and noncommercial ethyl benzoylacetate were purified by identical distillations. Likewise, identical distillations of the hydrazone **3** did not alter the results. Spectroscopic comparisons of samples of **1** and **3** revealed no differences in purity between those that did lead to **4** and those that did not.

A scheme for synthesizing **4** in high yield that does not depend on the origin of the starting ketoester involves addition of several drops of concentrated sulfuric acid to **3** followed by heating of this mixture under reduced pressure. This method also has been used to prepare the new betaines **5** and **6** from the corresponding dimethylhydrazones. Good yields can be obtained even without isolation of the intermediate hydrazone.

It is quite interesting that substituting Linde 4A molecular sieves for concentrated sulfuric acid provides an alternate route to **4** and **3**. Since both sulfuric acid and molecular sieves are capable of effectively removing ethanol from a reaction mixture, it is possible that the role of each is to drive the following equilibrium to the right:

Alternatively, either the acid or sieves may provide acid catalysis for the cyclization (4).

Although the crystal structure of **4** reveals near coplanarity of the phenyl and pyrazole rings, it also suggests that conjugation between the double bond systems of the two rings is insignificant (2). The synthesis of **6** establishes with full certainty that the phenyl ring is not required for the stabilization of the pyrazole ring.

EXPERIMENAL

Infrared spectra were recorded on a Perkin-Elmer 337 spectrometer. Nuclear magnetic resonance spectra were taken on a Varian T-60 instrument with deuteriochloroform as solvent and tetramethylsilane as internal reference. Mass spectra were obtained from a Dupont 21-490 spectrometer. The uv spectra were recorded on a Beckman ACTA spectrometer. Melting points were taken from a Fisher-Johns apparatus and are reported uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Samples of ethyl benzoylacetate were prepared as previously described (3) or obtained from Aldrich or Eastman chemical companies. Ethyl 2-methylacetoacetate was obtained from Aldrich and 1,1-dimethylhydrazine was obtained from Eastman. The dimethylhydrazones were prepared according to standard procedures described elsewhere (1,5).

1,1-Dimethyl-3-phenylpyrazolium-5-oxide (**4**).

Method A.

A sample of ethyl benzoylacetate, prepared as described in reference (3), was converted to ethyl benzoylacetate dimethylhydrazone (1). The hydrazone (9.4 g, 0.040 mole) was heated at 120-130°C (0.8 torr) for 6 hours. Solidification of the reaction mixture occurred upon cooling it in an ice bath. Recrystallization from cyclohexane gave the product as white needles (86%). Identification was by mp, nmr and ir as previously described. The same procedure, when carried out with hydrazone prepared from ethyl benzoylacetate obtained from Eastman or Aldrich, failed to produce the desired product even with heating for 35 hours.

Method B.

To 9.4 g (0.040 mole) of ethyl benzoylacetate dimethylhydrazone was added 3 drops of concentrated sulfuric acid. The mixture was heated as in Method A for 50 minutes. The solid obtained upon cooling, gave a 93% yield of product.

Method C.

To 9.6 g (0.041 mole) of ethyl benzoylacetate dimethylhydrazone was added 10 g of Linde 4A molecular sieves which had been activated at 300° for 3 hours. The mixture was heated as in Method A for 6 hours and the product was obtained as described above in 75% yield.

Methods B and C apply to hydrazone **3** prepared from synthesized or commercial ethyl benzoylacetate.

Ethyl 2-methylacetoacetate dimethylhydrazone (**7**) (5 g). A solution of ethyl 2-methylacetoacetate (28.8 g, 0.200 mole, 26.0 ml) and dimethylhydrazine (24.0 g, 0.400 mole, 31.0 ml) in 40 ml of methanol was refluxed under a nitrogen atmosphere for 24 hours. Excess hydrazine and methanol were removed under reduced pressure and the crude hydrazone was distilled to give 31.8 g (85%) of a colorless oil, bp 55-56° (0.5 torr); nmr: δ 1.20 (t, 3H, J = 7.0 Hz), 1.23 (d, C*H*-CH$_3$ of the imine, J = 7.0 Hz), 1.83 (s, imine + enamine CH$_3$), 2.31 (s, 6H), 3.23 (q, CH-CH$_3$ of the imine, J = 7.0 Hz), 4.10 (q, 2H, J = 7.0 Hz), 9.6 (s, enamine H); ir (liquid film): 1733 (s) 1650 (s), 1595 (s), 1385 (m), 1190 (s) cm^{-1}; ms: m/e 186 (M$^+$), 140, 113, 97, 70, 56, 48, 44, 43 (base peak) 42.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 57.76; H, 9.83; N, 15.06.

1,1,3,4-Tetramethylpyrazolium 5-Oxide (**6**).

To 3.50 g of **7** was added 3 drops of concentrated sulfuric acid. The mixture was heated under reflux at 110° for 24 hours at reduced pressure (water aspirator). The flask was fitted with a distillation apparatus and the product was distilled to give 1.45 g (55%) of a nearly colorless oil which solidified upon cooling, bp 88° (0.2 torr), mp 45-46°; nmr δ 1.63 (s, 3H), 2.03 (s, 3H), 2.88 (s, 6H); ir (carbon tetrachloride): 1740 (s), 1620 (w), 1520 (w) cm^{-1}; uv (cyclohexane): λ max 303 (ϵ = 6,000); ms: m/e 140 (M$^+$, base peak) 125, 98, 68, 56, 44, 43.

On a 0.10 mole scale, the crude hydrazone **7** obtained as above was diluted with ether and dried with magnesium sulfate. Filtration and removal of ether gave 15.8 g (85%) of crude hydrazone. It was then treated with 10 drops of concentrated sulfuric acid and subjected to the conditions for the preparation of **6** above. Distillation gave 9.62 g (69% overall yield from the ketoester) of **6** which quickly solidified.

Anal. Calcd. for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.91; H, 8.53; N, 20.04.

Ethyl α-benzoylpropionate Dimethylhydrazone (**8**).

A mixture of ethyl α-benzoylpropionante (6) (3.0 g, 15 mmole) and 1,1-dimethylhydrazine (1.8 g, 30 mmoles) in 10 ml of absolute ethanol was refluxed under nitrogen for 24 hours. The yellow oil (70%) was obtained by distillation, bp 108-112° (1 torr); nmr: δ 1.17 (t, 3H, J = 7.0 Hz), 1.50 (d, CH-C*H*$_3$ of the imine, J = 7.0 Hz), 1.87 (s, imine + enamine CH$_3$), 3.08 (s, 6H), 4.13 (q, 2H, J = 7.0 Hz), 4.38 (q, C*H*-CH$_3$ of the imine, J = 7.0 Hz), 7.62 (m, 5H), 10.60 (s, enamine H); ir (liquid film): 1725 (s), 1690 (s), 1595 (m), 1370 (m), 1180 (w) cm^{-1}.

1,1,4-Trimethyl-3-phenylpyrazolium 5-Oxide (**5**).

To 3.2 g (0.013 mole) of **8** was added 3 drops of concentrated sulfuric acid. The solution was heated under reflux for 4 hours at reduced pressure (water aspirator). The solid, obtained upon cooling, was recrystallized from cyclohexane to give white needles (81%), mp 122.5°; nmr: δ 2.03 (s, 3H), 3.20 (s, 6H), 7.67 (m, 5H); ir (potassium bromide): 1720 (s), 1575 (s), 1490 (s), 1450 (s) cm^{-1}; uv (cyclohexane): λ max 234 (ϵ = 17,000), 338 (ϵ = 7,500); ms: m/e 202 (M$^+$, base peak), 186, 158, 129, 114, 86, 77, 58, 43.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 17.25; H, 6.98; N, 13.85. Found: C, 17.59; H, 7.19; N, 13.87.

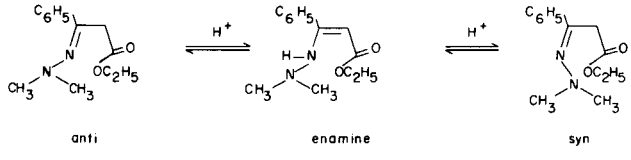
REFERENCES AND NOTES

(1) K. R. Henery-Logan and E. A. Keiter, *J. Heterocyclic chem.* **7**, 923 (1970).

(2) W. H. DeCamp and J. M. Stewart, *ibid.*, **7**, 895 (1970).

(3) *Org. Synth.*, Coll. Vol. **3**, 379 (1955).

(4) As suggested by a referee, the reaction may depend upon the relative amounts of *syn* and *anti* forms of the hydrazone. It is possible that the commercial ketoester produces hydrazones in which the *anti* form predominates. This material would be less easily cyclized and would respond to acid catalysis.



(5) For examples of the preparation of a large number of dimethylhydrazones see: (a) S. I. Yakimovich, I. V. Zerova and N. A. Starygina, *Zh. Org. Khim.*, **13**, 1168 (1977); (b) S. I. Yakimovich, I. V. Zerova and N. N. Garrilova, *ibid.*, **13**, 263 (1977); (c) S. I. Yakimovich and V. A. Khrustalev, *ibid.*, **11**, 1386 (1975); (d) S. I. Yakimovich, V. A. Khrustalev and L. A. Kayukova, *ibid.*, **10**, 2527 (1974); (e) S. I. Yakimovich, V. A. Khrustalev and T. A. Favorskaya, *ibid.*, **10**, 191 (1974); (f) S. I. Yakimovich, T. A. Favorskaya and V. A. Khrustalev, *ibid.*, **8**, 2250 (1972); (g) S. I. Yakimovich, N. Yu. Baron, T. A. Favorskaya and V. A. Khrustalev, *ibid.*, **6**, 2628 (1970). See also E. J. Corey and Dieter Enders, *Tetrahedron Letters*, 3 (1976).

(6) V. H. Wallingford and A. H. Homeyer, U. S. Patent 2,407,942 (1946); *Chem. Abstr.*, **41**, 1699f (1947).