# Synthesis of pyrazol-4-ols

M. J. NYE[1] AND W. P. TANG
*Department of Chemistry, University of Guelph, Guelph, Ontario*

Received July 6, 1970

3,5-Diphenylpyrazol-4-ol (**4**) has been prepared by four convenient routes starting with the following compounds: diphenylpropanetrione (**1**), 2-acetoxyl-1,3-diphenyl-1,3-propanedione (**5**), chalcone oxide (**7**), and 1,3-diphenyl-2-propanone (**10**).

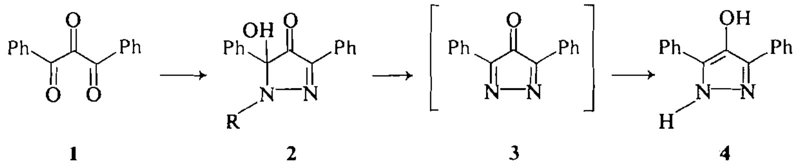
Canadian Journal of Chemistry, 48, 3563 (1970)

Pyrazoles bearing an oxygen atom in the 4-position have not been extensively studied, in contrast to the 3- and 5-oxygenated compounds. Two review articles have regarded such compounds as "relatively few" (1) and "relatively inaccessible" (2). We report here the experimental details of four synthetic routes to the previously unknown (3) 3,5-diphenylpyrazol-4-ol (**4**).

In route 1 treatment of diphenylpropanetrione (**1**) (4) (or its hydrate) with excess hydrazine (or its hydrate) gives an 88% yield of **4**. The mechanism involves the intermediacy of first **2***a* and then **3** (5), since either will produce **4** under the conditions of the reaction, and **2***a*[2] can be isolated as a by-product. Further support for the mechanism is given by the observation that if methylhydrazine is used instead of hydrazine, a good yield of **2***b* is produced and none of **12***a* (N-1 in formula **2** must bear a hydrogen for the reaction to proceed further). This route is based on the method for the preparation of **12***b* of Sachs and Röhmer (6).

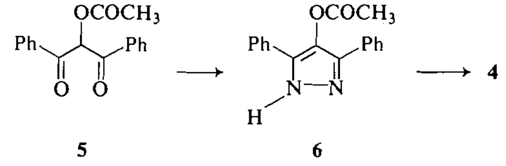
Route 2 gives a 97% yield of **4** by treatment of 2-acetoxyl-1,3-diphenyl-1,3-propanedione (**5**) (7) with hydrazine hydrate. An intermediate (**6**)

[1]

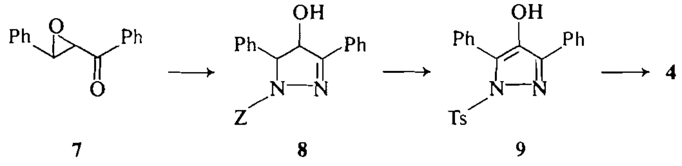


*a* R = H
*b* R = $CH_3$

[2]



[3]



*a* Z = *p*-Toluenesulfonyl (Ts)
*b* Z = H

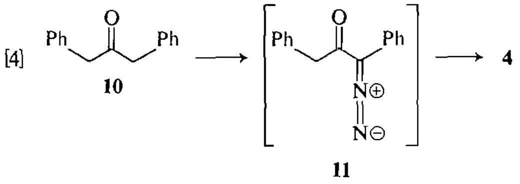
---

[1] To whom correspondence should be addressed.

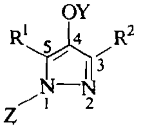
[2] Structural identification of this compound and other related hydrazones will be reported in a later paper.

is formed by a double condensation, and it can be isolated as a by-product if the temperature is kept low. This method has no close precedents in the literature.

Route 3 involves treatment of chalcone oxide (**7**) with *p*-toluenesulfonylhydrazide to give **8***a* which is oxidized by chromium trioxide to **9**, and then hydrolyzed by acid to **4** in a 20% overall yield. The first step of this synthesis is taken from the work of Padwa (8).

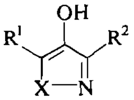


In route 4, 1,3-diphenyl-2-propanone is treated with *p*-toluenesulfonylazide and sodium ethoxide to give a 45% yield of **4**. This route is analogous to Regitz's preparation of **12***e* (9).



**12**

| | $R^1$ | $R^2$ | Y | Z |
|---|---|---|---|---|
| *a* | phenyl | phenyl | H | $CH_3$ |
| *b* | methyl | phenyl | H | H |
| *c* | phenyl | phenyl | $COCH_3$ | H |
| *d* | phenyl | phenyl | $COCH_3$ | $CH_3$ |
| *e* | benzoyl | benzoyl | H | H |



**13**

*a* X = O
*b* X = NH

## Discussion

Probably the most versatile of the four routes is route 2, since on initial inspection it appears that by slightly modifying the reactants, compounds of general formula **12** can be prepared with different substituents at N-1, C-3, C-5, and O. In this laboratory we have only prepared compounds **4**, **12***a*, **12***c*, and **12***d* by this method, but in each case yields were excellent. Routes 1 and 4 on the other hand have variation of substituents limited to C-3 and C-5, and route 3 allows substituent variation at N-1, C-3, and C-5. However, on the last route, if N-1 carries a hydrogen atom, the chromium trioxide oxidation is not successful, probably because under the conditions used, which were similar to those used in the oxidation of **8***a*, **8***b* is more completely oxidized to **3** which would react further to give complex products (5).

From the point of view of yields and availability of starting materials, route 4 is probably the most attractive since 1,3-diphenyl-2-propanone is available from suppliers and is inexpensive, and the whole synthesis is carried out in one step. Routes 1 and 2 however are also attractive since the starting materials can be prepared from the available 1,3-diphenyl-1,3-propanedione in yields of 84 and 71% respectively.

In view of these four simple routes to pyrazol-4-ols, we point out that this area of chemistry need no longer be neglected. Indeed this group of compounds together with the isoxazoles (**13***a*) invites a much more thorough investigation since they are the main representatives of the heterocyclic system of general formula **13** (where X is a heteroatom) which has chemistry quite distinct from the isomeric 3- and 5-hydroxy analogues.

## Experimental

Melting points were determined on a Meltemp apparatus and are uncorrected. Microanalyses were carried out by A. B. Gygli, Microanalysis Laboratories Limited, Toronto, Ontario. The reported i.r. spectra give only the principal sharply defined peaks. The n.m.r. spectra are reported in p.p.m. relative to internal tetramethylsilane.

### *Route 1*

(*A*) A solution of 1.28 g (0.005 mole) of diphenylpropanetrione hydrate (4) in 15 ml 95% ethanol was treated with 0.51 g (0.01 mole) of 99–100% hydrazine hydrate in 1.5 ml ethanol. The reaction mixture became yellow and was refluxed on a water-bath for 30 min. On cooling, bright colorless prisms were formed, filtered, and washed with cold diluted ethanol. Yield: 1.033 g (87.5%), m.p. 231–233°. One recrystallization from ethanol gave 3,5-diphenylpyrazol-4-ol (**4**), m.p. 235–237°.

(*B*) A solution of 1.19 g (0.005 mole) of diphenylpropanetrione (4) in 25 ml absolute ethanol was treated with 0.51 g (0.01 mole) of 99–100% hydrazine hydrate in 1.5 ml ethanol. The color of triketone solution intensified on addition of hydrazine solution. The reaction mixture was worked-up as above, giving colorless prisms. Yield: 1.057 (89.6%), m.p. 231–233°. This substance was identical with the one prepared by method *A* by mixture m.p. and i.r. spectrum.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.26; H, 5.12; N, 11.86. Found: C, 76.04; H, 5.28; N, 11.62.

The i.r. (KBr): 3222, 2520, 1591, 1263, 1150 $cm^{-1}$. The u.v. (95% EtOH, 25°): $\lambda_{max}$ mμ (ε): 252 (22 700); 276 (shoulder, 17 100), 295 (shoulder, 10 040). The n.m.r.: (dimethyl sulfoxide-$d_6$): 7.45 (7H, multiplet: 6H aromatic, 1H hydroxyl exchangeable with $D_2O$); 8.02 (4H, multiplet, aromatic); 8.40 (1H, broad, NH).

(*C*) Into a stirred, cooled (ice-bath) solution of 1.025 g (0.004 mole) of diphenylpropanetrione (4) in 12 ml of methanol was dropped fairly rapidly a solution of 0.44 g (0.0088 mole) of 99–100% hydrazine hydrate in 2 ml of methanol. During addition of hydrazine solution, some precipitates formed which soon dissolved to give a yellow solution. After stirring for 30 min, 70 ml of water was added resulting in heavy precipitation. The mixture was well chilled and the bright yellow prisms of 3,5-diphenyl-5-hydroxyl-4-pyrazolone were collected on a filter and washed with cold, diluted methanol, m.p. 120–122° (dec.). Further recrystallization from cold, diluted methanol gave the same m.p. (dec.). Yield: 89% (from 1,3-diphenylpropanetrione hydrate); 95.8% (from 1,3-diphenylpropanetrione). Recrystallization from hot solvents rendered a complete change of this substance (see below).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.44; H, 4.80; N, 11.11. Found: C, 71.48; H, 5.08; N, 10.89.

The i.r. (KBr): 3368, 1747, 1714, 1306, 1197, 1018 cm$^{-1}$. The u.v. (95% EtOH, 25°): $\lambda_{max}$ mμ (ε): 254 (19 100); 356 (3210). The n.m.r. (acetone-$d_6$): 6.32 (1H, broad, OH); 7.45 (8H, multiplet, aromatic), 8.08 (2H, multiplet, aromatic); 9.50 (1H, broad, NH).

Conversion of 3,5-diphenyl-5-hydroxyl-4-pyrazolone to the desired 3,5-diphenylpyrazol-4-ol (4) was effected by: (*a*) recrystallization in boiling ethanol, (*b*) heating at its melting temperature, or (*c*) treating with strong acids with dehydrating properties. Under conditions (*a*) and (*b*), orange–brown dirty substances were formed as side products. Under condition (*c*), a purple solution containing **3** formed initially and then gradually turned light brown. Crystallization from ethanol gave **4**. The yields ranged from 40–70%.

*Route 2*

A solution of 0.15 g of 99–100% hydrazine hydrate in 1 ml of 95% ethanol was added to a warm solution of 0.564 g 2-acetoxyl-1,3-diphenyl-1,3-propanedione (7) in 7 ml of 95% ethanol. The mixture was refluxed for 20 min and allowed to cool to room temperature. It was then poured into 20 ml of ice-water under slight agitation to give colorless prisms, m.p. 235–237°. The yield of **4** was 97%.

*Route 3*

Into a stirred, cooled (10–15°) solution of 0.784 g (0.002 mole) of 3,5-diphenyl-4-hydroxy-1-*p*-toluenesulfonyl pyrazoline (**8***a*) (8) in 100 ml acetone was added dropwise a standard chromic acid reagent[3] (*ca.* 1.5 ml) until a permanent brown color persisted. After 10 min, 500 ml of water were added and the mixture was stirred in an ice-bath for an additional hour. During this time, the initially waxy mass turned into yellow crystals which were filtered and washed with water; m.p. 150–155°. Recrystallization from ethanol afforded 3,5-diphenyl-1-*p*-toluenesulfonyl-pyrazol-4-ol (**9**) as slightly yellow plates, m.p. 161–163°, 0.465 g (59.6%). Another crystallization raised the m.p. to 165–167°.

Anal. Calcd. for $C_{22}H_{18}N_2O_3S$: C, 67.66; H, 4.65; N, 7.18. Found: C, 67.74; H, 4.81; N, 7.13.

The i.r. (KBr): 3357, 3301, 1452, 1384, 1226, 1190, 1175 cm$^{-1}$. The u.v. (95% EtOH, 25°): $\lambda_{max}$ mμ (ε): 224 (25 100), 275 (13 000), 289 (12 100), 370 (814). The n.m.r. (acetone-$d_6$): 2.38 (3H, singlet, $CH_3$); 7.48 (13H, multiplet, aromatic, including OH exchangeable with $D_2O$); 8.08 (2H, multiplet, aromatic).

Hydrolysis of this product to (**4**) was achieved by refluxing it in a mixture of concentrated HCl and acetic acid for 10 h. Recrystallization of the crude, colorless solids gave the desired product; colorless prisms, m.p. 233–235°; yield, *ca.* 70%.

*Route 4*

Into a well-stirred and well-cooled (ice-bath) solution of 1.05 g (0.005 mole) of 1,3-diphenyl-2-propanone in 15 ml of absolute ethanol was added a solution of 0.01 mole of sodium ethoxide in 10 ml absolute ethanol, followed immediately by rapid addition of a solution of 1 g of *p*-toluenesulfonyl azide (10) in 5 ml ethanol. The reaction mixture was then stirred for 1 h at ice-bath temperature. Dry ether (100 ml) was added to precipitate sodium salts of *p*-toluenesulfonamide which were filtered and well-washed with dry ether. The ethereal filtrate was extracted with 80 ml of water and the ethereal layer dried with sodium sulfate. Evaporation of ether at reduced pressure to a quarter of its initial volume afforded the almost colorless product as prisms, m.p. 232–236°. Further concentration of the filtrate gave two crops of the same material, m.p. 232–236°. The combined yield was 47%.

We thank the National Research Council of Canada for their financial support.

1. R. H. WILEY and P. WILEY. Pyrazolones, pyrazolidones and derivatives. John Wiley and Sons, New York, 1964. p. 111.
2. A. N. KOST and I. I. GRANDBERG. Advances in heterocyclic chemistry. Vol. 6. Academic Press, New York, 1966. p. 372.
3. M. J. NYE and W. P. TANG. 1st International Congress of Heterocyclic Chemistry, Albuquerque, New Mexico, June 1967, Abstracts No. 80; J. P. FREEMAN, J. J. GANNON, and D. L. SURBEY. J. Org. Chem. **34**, 187 (1969).
4. L. A. BIGELOW and R. S. HANSLICK. Org. Syn. Col. Vol. **2**, 244 (1943).
5. P. J. FAGAN, M. J. NYE, and W. P. TANG. 2nd International Congress of Heterocyclic Chemistry, Montpelier, France, July 1969, Abstracts No. A15.
6. F. SACHS and A. RÖHMER. Ber. **35**, 3307 (1902).
7. R. DE NEUFVILLE and H. v. PECHMANN. Ber. **23**, 3375 (1890).
8. A. PADWA. J. Org. Chem. **30**, 1274 (1965).
9. M. REGITZ and H. J. GEELHAAR. Ber. **101**, 1473 (1968).
10. W. v. E. DOERING and C. H. DEPUY. J. Amer. Chem. Soc. **75**, 5955 (1953). M. REGITZ, J. HOCKER, and A. LIEDHEGENER. Org. Syn. **48**, 36 (1968).

---

[3] Prepared by dissolving 2.67 g chromium trioxide in 2.3 ml concentrated sulfuric acid diluted to a volume of 10 ml.