

## EFFECT OF CROWN ETHER ON THE FORMATION OF FLAVANONES

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The condensation of 2-hydroxyacetophenone with benzaldehydes was catalysed with crown ether and directly gave flavanones in fair yield.

Flavanones are most often obtained by cyclization of 2'-hydroxychalcones which are produced by condensation of 2-hydroxyacetophenones with benzaldehyde derivatives. 2-Hydroxyacetophenone is also known to react with benzaldehyde in borate-sodium hydroxide buffer solution (pH 10.9) to form flavanone directly<sup>1)</sup>. Recently, an attempt was made to use dicyclohexyl 18-crown-6 in the synthesis of 2'-hydroxychalcone in ethanol-water solution, but chalcone did not form<sup>2)</sup>.

In this communication, we report an alternative and preferable direct synthesis of flavanones catalyzed by 18-crown-6 in nonaqueous solution.

The reactions were carried out in a stirred mixture of 2-hydroxyacetophenone, benzaldehyde, sodium hydride and 18-crown-6 in benzene solution at 37°C for 3 days then the products were determined by gas chromatography. Large amount of by-product, probably consisting of benzylidenediacetophenone, was formed but this difficulty could be overcome by addition of an organic base (imidazole was especially effective), which seemed to control the reactivity of the carbonyl group of benzaldehyde.

As the amount of by-product increased when the reaction temperature was high (50°), and the reaction was extremely slow at low temperatures, 37°C appeared to be a suitable temperature, at which 3 days were required for the condensation and cyclization.

The molar ratio of sodium hydride to 2-hydroxyacetophenone was varied from 1.0 to 0.1, whereupon the yield of chalcone decreased gradually, while the yield of flavanone showed the maximum value at a molar ratio in the range of 0.3 to 0.5 (Table I). The molar ratio of 2-hydroxyacetophenone, benzaldehyde, 18-crown-6 and imidazole, given in Table I, was 1:1.5:1:2.

The amount of crown ether could be reduced to one-third of its portion, while the proportion of imidazole could not be reduced, as this led to an increase in the amount of by-product.

When hexamethyldisilazane was used to form a silyl ether of 2-hydroxyacetophenone, the best

Table I Effect of the molar ratio of sodium hydride to 2-hydroxyacetophenone on the formation of flavanone

| Molar ratio of NaH | Product yield (%) |          |
|--------------------|-------------------|----------|
|                    | Flavanone         | Chalcone |
| 1.0                | 20.7              | 26.5     |
| 0.5                | 29.3              | 7.1      |
| 0.3                | 31.3              | 5.1      |
| 0.1                | 14.3              | 2.0      |

result was obtained.

Based on our findings the optimum condition, the best molar ratio of each reagent and the suggested procedure is as follows. A mixture of 2-hydroxyacetophenone (0.5 mM) and hexamethyldisilazane (0.1 ml) was heated at 90°C for 1 h, cooled, then added to a suspension of sodium hydride (0.15 mM) in dry benzene (6 ml), after which a tetrahydrofuran (1 ml) solution containing 18-crown-6 (0.15 mM), benzaldehyde (0.75 mM) and imidazole (1 mM) was added. This mixture was stirred at 37°C for 3 days. Next, 20 mg of n-hexacosane was added as an internal standard, followed by addition of 10% hydrochloric acid under cooling. The organic layer which separated was washed with water, dried and evaporated. The residue was dissolved in 10 ml benzene, then a portion of this solution was analyzed quantitatively by gas chromatography.

Under these conditions, flavanone was formed in 42.4% yield with a small amount of chalcone (6.4 %), whereas, when the mixture suggested by Reichel et al. of 2-hydroxyacetophenone, benzaldehyde, ethanol and borate-sodium hydroxide (pH 10.9)<sup>1)</sup> was kept at 37°C for 7 days only 13.8% of flavanone and 4.6% of chalcone were obtained. When some derivatives of benzaldehyde were used for this reaction, the predominant products were also flavanones (Table II).

Table II Yields of flavanones

|                            | Flavanone (%) | Chalcone (%) |
|----------------------------|---------------|--------------|
| Benzaldehyde               | 42.4          | 6.4          |
| 4-Methoxybenzaldehyde*     | 44.0          | 3.3          |
| 3,4-Dimethoxybenzaldehyde* | 29.3          | 11.5         |

\* Reaction was carried out with refluxing for 20 h without hexamethyldisilazane

#### References

- 1) L. Reichel and W. Burkart, *Ber.*, 1941, **74**, 1802.
- 2) N. S. Poonia, K. Chhabra, C. Kumer and V. W. Bhagwat, *J. Org. Chem.*, 1977, **42**, 3311.

Received, 28th August, 1980