SYNTHESIS OF SOME 2-SUBSTITUTED 1-PHENYLIMIDAZOLES

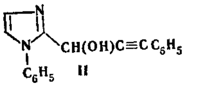
L. M. Sitkina and A. M. Simonov

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 3, pp. 410–411, 1970

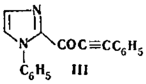
UDC 547.782.783'785.1.07

Products of the reaction of 2-formyl-1-phenylimidazole with compounds containing labile hydrogen atoms and with phenylethynylmagnesium bromide have been described.

2-Formyl-1-arylimidazoles |1|, which are readily obtained by the oxidation of the 2-hydroxymethyl derivatives with selenium dioxide, take part in various reactions with the formation of potential biologically active compounds. The reaction of 1-phenylimidazole-2-carbaldehyde (I) with nitromethane leads to a nitroalcohol which is readily converted into a β-nitrovinyl derivative (see |2|). The latter is also formed by heating I with nitromethane in acetic anhydride. This compound inhibits the growth of pathogenic microorganisms in vitro. In contrast to 2-formyl-1-methylbenzimidazole, I reacts with malonic acid forming β-(1-phenylimidazol-2-yl)acrylic acid, whose structure is similar to that of the biologically important urocanic acid |3|. In an alkaline medium, I smoothly condenses with 1 mole or (under more severe conditions) 2 moles of acetophenone. By reaction with phenylethynylmagnesium bromide |4|, I can be converted into the carbinol II which, by oxidation with selenium dioxide, gives the ketone III.



II



III

EXPERIMENTAL

1-Arylimidazole-2-carbaldehydes. These were obtained by oxidizing the corresponding hydroxymethyl derivatives (0.01 mole) with selenium dioxide (5 mM)* in absolute dioxane (10 ml) at the boil.

2-(β-Nitrovinyl)-1-phenylimidazole. In drops, 1 ml of a 10% aqueous solution of caustic soda was added to a solution of 0.06 g (1 mM) of nitromethane in 1 ml of ethanol cooled to 0° C, and this was followed by an ethanolic solution of 0.17 g (1 mM) of I. The mixture was kept in an ice bath for 30 min and then neutralized with 10% HCl. The precipitate was filtered off, washed with water and ethanol, and dried over phosphorus pentoxide. This gave 0.15 g of an almost colorless compound with mp 117–118.5° C. The nitroalcohol obtained was dissolved in the minimum amount of acetic anhydride with heating on a water bath until dissolution was complete (1–2 min), and then 3–5 ml of water was added. The precipitate was filtered off and washed with water. Yellow needles with mp 147° C (from ethanol). Yield 0.07 g (36%). Found, %: N 19.6. Calculated for $C_{11}H_9N_3O_2$, %: N 19.5.

β-(1-Phenylimidazol-2-yl)acrylic acid. A mixture of 0.17 g (1 mM) of I, 0.1 g (1 mM) of malonic acid, and 1.5 ml of dry pyridine was heated in a boiling water bath for 1 hr in the presence of catalytic amounts of piperidine. The precipitate that separated out at first redissolved with the evolution of a gas. After cooling, the crystals which formed were separated off and washed with ether. Yield 0.11 g (52%). Colorless crystals with mp 218–219° C (from water), insoluble in ethanol and benzene. Found, %: N 12.7. Calculated for $C_{13}H_{10}N_2O_2$, %: N 13.1. **Picrate.** Yellow needles with mp 225–227° C (from ethanol). Found, %: N 15.9. Calculated for $C_{12}H_{10}N_2O_2 \cdot C_5H_3N_3O_3$, %: N 15.8.

2-(β-Benzoylvinyl)-1-phenylimidazole. With stirring, 0.25 ml of 2% caustic potash solution was added dropwise to a solution of 0.17 g (1 mM) of I and 0.12 g (1 mM) of acetophenone in 1 ml of ethanol cooled to 0° C. The precipitate was filtered off and washed with water. Yield 0.24 g (89%). Light-yellow needles with mp 109–110° C (from petroleum ether). Found, %: C 79.0; H 5.4; N 10.7. Calculated for $C_{18}H_{14}N_2O$, %: C 78.8; H 5.1; N 10.2.

2-Bisphenacylmethyl-1-phenylimidazole. A solution of 0.17 g (1 mM) of I and 0.24 g (2 mM) of acetophenone in 1 ml of ethanol was heated in a boiling water bath with 0.2 ml of 20% KOH. The precipitate that deposited after 3 days was filtered off and washed with ethanol and ether. Yield 0.28 g (72%). Snow-white crystals with mp 133–134° C.

---

*There is a printing error in |1|: 0.05 mole.

Found, %: C 79.5; H 5.6; N 7.4. Calculated for $C_{26}H_{22}N_2O_2$, %: C 79.2; H 5.6; N 7.1.

Phenylethynyl(1-phenylimidazol-2-yl)methanol (II). With vigorous stirring, a solution of 4.3 g (0.025 mole) of I in 80 ml of absolute ether was added dropwise at 15–20° C to an emulsion of phenylethynylmagnesium bromide |4| obtained from 0.96 g (0.04 g-at.) of magnesium, 5.45 g (0.05 mole) of ethyl bromide, and 5.1 g (0.05 mole) of phenylacetylene in 50 ml of absolute ether. The mixture was boiled for 3–4 hr, after which 150 ml of saturated ammonium chloride solution was added. The ethereal layer was separated off and the aqueous solution was extracted with ether (3 × 50 ml). The extracts were combined and dried with Na_2SO_4, and the ether was distilled off. The residue was kept in a vacuum desiccator over P_2O_5 for 2–3 days. Yield 3.3 g (42%). Colorless crystals with mp 121–122° C (from hexane), readily soluble in organic solvents. Found, %: C 78.6; H 5.2. Calculated for $C_{18}H_{14}N_2O$, %: C 78.8; H 5.1.

Phenylethynyl 1-phenylimidazol-2-yl ketone (III). With stirring, 0.3 g (2.5 mM) of freshly sublimed selenium dioxide was added to a boiling solution of 1.37 g (5 mM) of II in 20 ml of anhydrous dioxane, and the mixture was heated to the boil for another 30 min. The precipitate of selenium was separated off, the dioxane was evaporated, and the reaction product was extracted from the residue with ether. The ether was driven off and the substance was dissolved in benzene and chromatographed on a column of alumina. The second fraction was collected (the first contained resinous impurities), a check being carried out by thin-layer chromatography (the spots being revealed in iodine vapor). Yield 0.54 g (40%). Colorless crystals with mp 123–124.5° C (from hexane), soluble in ethanol, benzene, and acetone. Found, %: C 79.5; H 4.7; N 10.6. Calculated for $C_{18}H_{12}N_2O$, %: C 79.4; H 4.4; N 10.3. **2,4-Dinitrophenylhydrazone.** Orange crystals with mp 155–157° C (from ethanol). Found, %: C 63.4; H 3.3; N 18.9. Calculated for $C_{24}H_{16}N_6O_4$, %: C 63.7; H 3.6; N 18.6.

REFERENCES

1. A. M. Simonov and L. M. Sitkina, KhGS [Chemistry of Heterocyclic Compounds], collection 1, 116, 1967.
2. A. M. Simonov and D. D. Dalgatov, ZhOKh, 34, 3052, 1964.
3. F. Ghiretti, Angew. Chem., 76, 982, 1964.
4. L. D. Bergel'son, collection: Reactions and Methods of Investigating Organic Compounds [in Russian], vol. 4, 62, 1956.

15 October 1968

Rostov-on-Don State University