

SHORT  
COMMUNICATIONS

## Regioselectivity in Azoles Alkylation. Benzoylation of Indazole under Conditions of the Phase-transfer Catalysis

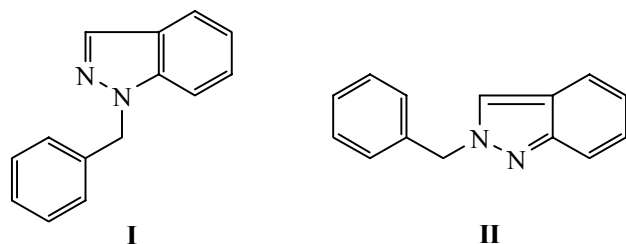
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Received August 23, 2005

DOI: 10.1134/S1070428002120266

The alkylation of indazole and other nitrogen-containing heterocycles under the conditions of the phase-transfer catalysis may be regarded as a convenient procedure for preparation of various heterocyclic and other compounds [1, 2]. In these syntheses a problem exists of isomers formation depending on the direction of the alkyl attack



on one or another of the nitrogen atoms [3]. Two isomers form at the indazole benzoylation.

The ratio of isomers **I** and **II** depends essentially on the mode of performing reaction under the phase-transfer conditions. The phase-transfer catalysis was carried out in systems liquid–solid and liquid–liquid. The data obtained for indazole benzoylation are given in the table. As seen, the isomer ratio is considerably affected by the reaction temperature: At lower temperature increased the fraction of isomer **II** (cf. runs nos. 1–3). At the same time the isomer ratio at a constant temperature is sensitive to the nature of the solvent (cf. runs nos. 3 and 5). The most significantly the isomer ratio is affected by the nature of

Benzoylation of indazole under the conditions of the phase-transfer catalysis

| Run no. | Organic solvent                        | Catalyst                              | Reaction temperature, °C | Reaction time, h | Yield of target product, % | Isomer ratio <b>I</b> : <b>II</b> , % |
|---------|--|---------------------------------------|--------------------------|------------------|----------------------------|---------------------------------------|
| 1       | <i>o</i> -Dichlorobenzene <sup>a</sup> | Tetrabutylammonium chloride           | 180                      | 16               | 85                         | 72.2 : 27.8                           |
| 2       | Xylene <sup>a</sup>                    | Tetrabutylammonium chloride           | 160                      | 16               | 86                         | 60.5 : 39.5                           |
| 3       | Acetonitrile <sup>a</sup>              | Tetrabutylammonium chloride           | 80                       | 16               | 87                         | 59.2 : 40.8                           |
| 4       | Toluene <sup>a</sup>                   | Tetrabutylammonium chloride           | 110                      | 16               | 84                         | 55.3 : 44.7                           |
| 5       | Benzene <sup>a</sup>                   | Tetrabutylammonium chloride           | 80                       | 16               | 79                         | 53.6 : 46.4                           |
| 6       | Toluene <sup>a</sup>                   | Polyethylene glycol 600               | 110                      | 16               | 83                         | 41.5 : 58.5                           |
| 7       | Toluene <sup>a</sup>                   | 18-Crown-6                            | 110                      | 16               | 86                         | 49.9 : 58.1                           |
| 8       | Toluene <sup>a</sup>                   | Triethylnonylammonium bromide         | 110                      | 16               | 81                         | 59.1 : 40.9                           |
| 9       | Toluene <sup>a</sup>                   | Tetramethylammonium bromide           | 110                      | 16               | 79                         | 63.8 : 36.2                           |
| 10      | Toluene <sup>a</sup>                   | Dimethylphenylbenzylammonium chloride | 110                      | 16               | 88                         | 66.8 : 33.2                           |
| 11      | Benzene <sup>b</sup>                   | Tetrabutylammonium chloride           | 25                       | 6                | 78                         | 49.9 : 50.1                           |
| 12      | Carbon tetrachloride <sup>b</sup>      | Tetrabutylammonium chloride           | 25                       | 6                | 77                         | 40.9 : 59.1                           |
| 13      | Carbon tetrachloride <sup>b</sup>      | 18-Crown-6                            | 25                       | 6                | 72                         | 38.7 : 61.3                           |

<sup>a</sup>System liquid–solid. <sup>b</sup>System liquid–liquid.

the catalyst. For instance, at growing hydrophobicity of the catalyst in going from poly(ethylene glycol) to ammonium salts an inversion of isomer ratio was observed (cf. runs nos. 6 and 8). The reaction under the phase-transfer conditions in the system liquid–liquid provided virtually equal amounts of both isomers when the organic phase was benzene. Yet at the use of carbon tetrachloride the replacement of the ammonium salt catalyst by a crown ether resulted in decrease in the content of isomer **I** in the mixture of isomeric N-benzylindazoles (cf. runs nos. 12 and 13). Thus the use of the phase-transfer catalysis makes it possible to carry out regioselective alkylation of azoles furnishing the target products in high yield.

**General procedure of indazole alkylation.** *a. In a system liquid–solid.* A mixture of 3 mmol of indazole, 3 mmol of potassium carbonate, 3 mmol of powdered potassium hydroxide, 0.015 mmol of catalyst, and 3 mmol of benzyl chloride in 20 ml of solvent were boiled for 16 h, then the precipitate was filtered off and washed with hot solvent, and the solution was dried with sodium sulfate. On removing the solvent the residue was distilled.

*b. In a system liquid–liquid.* To a mixture of 3 mmol of indazole, 3 mmol of benzyl chloride, and 0.015 mmol of catalyst in 20 ml of solvent was added 20 ml of 50% water solution of potassium hydroxide. The emulsion was vigorously stirred with a magnetic stirrer for 6 h at room temperature, the organic layer was separated, washed with water till neutral washings, and dried with sodium sulfate. Further workup was as described above.

The isomer composition was estimated by  $^1\text{H}$  NMR spectroscopy. The  $^1\text{H}$  NMR spectra were registered from solutions in deuteriochloroform on a spectrometer Varian-300 (operating frequency 300 MHz) using TMS as internal reference.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm., isomer **I**: 8.03 s (3H), 7.08–7.32 d (7H); isomer **II**: 7.81 s (3H), 7.59–7.64 d (7H).

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