temperature for 4 h, poured into 50 g chipped ice, and extracted with four 20-ml ether portions. The extracts were washed with two 15-ml water portions and dried over $MgSO_4$. The solvent was distilled off in vacuum. The residue was washed with boiling hexane until (V) was completely removed as indicated by thin-layer chromatography. Hexane was distilled off in vacuum. Recrystallization from hexane gave 0.33 g (15%) (V), mp 90°C, R_f 0.70 ($CHCl_3$). IR spectrum (ν, cm^{-1}): 680, 705, 1120, 1260, 1650, 1680. ^{13}C NMR spectrum in $CDCl_3$: 91.03 (CBr), 173.38 (CO). ^{14}N NMR spectrum in $CDCl_3$: −52.75 (NO). Mass spectrum, m/z (relative intensity, %): 274 M^+ (15), 272 M^+ (25), 270 M^+ (15), 193(24), 191(24), 151(95), 149(100), 123(36), 121(40), 112(75), 93(25), 91(25). Found: C, 13.30; Br, 59.03; N, 10.19%. Calculated for $C_3Br_2N_2O_3$: C, 13.25; Br, 58.78; N, 10.30%.

LITERATURE CITED

1. R. H. Wiley and B. J. Wakefield, J. Org. Chem., 25, 546 (1960).
2. E. Robson, J. M. Tedder, and D. J. Woodcock, J. Chem. Soc., C, No. 12, 1324 (1968).
3. C. Grundmann and H. D. Frommel, Liebigs Ann. Chem., 367, 52 (1909).
4. H. Wieland, Chem. Ber., 40, 1667 (1907).
5. M. D. Coburn, J. Heterocycl. Chem., 5, 83 (1968).
6. J. H. Bateman, US Patent No. 3,717,678 (1973).
7. K. Kanungo, M. D. Rathakar, and P. B. Chakravarty, Vijnana Parishad Anusandhan Patrica, 24, 321 (1981).
8. A. P. Kurtz and D. J. Themistocles D'Silva, J. Pharm. Sci., 76, 599 (1987).
9. B. Unterhalt and U. Pindur, Arch. Pharm., 309, 781 (1976).
10. G. Longo, Gazz. Chim. Ital., 66, 815 (1936).
11. R. Behrend and H. Tryller, Liebigs Ann. Chem., 283, 209 (1894).
12. M. Z. Iowitschitsch, Chem. Ber., 39, 784 (1906).
13. J. Watanabe and H. Okabe, Shionogi Kendyusho Nempo, 22, 72 (1972).

SYNTHESIS OF 2-SUBSTITUTED INDOLES

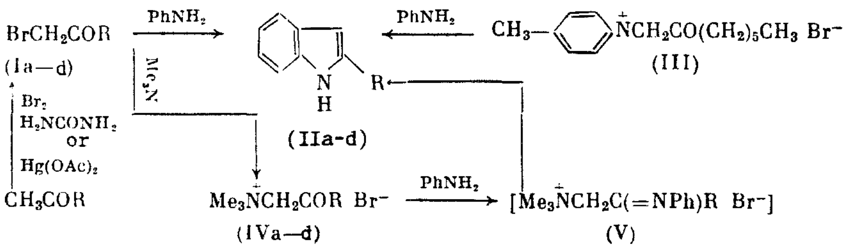
S. I. Zav'yalov, A. G. Zavozin,
O. V. Dorofeeva, and E. E. Rumyantseva

UDC 542.91:547.753

2-Substituted indoles are obtained upon the cyclocondensation of (2-R-2-oxoethyl)trimethylammonium bromides.

The cyclocondensation of α-bromoketones with aromatic amines, which is known as the Bischler reaction, is considered one of the basic methods for the synthesis of substituted indoles [1,2].

However, we have found that this reaction is unsuitable for obtaining 2-substituted indoles (IIa)-(IIc) from aniline and 1-bromo-2-alkanones (Ia)-(Ic) due to the formation of contaminated products in yields less than 30%.



$R = CH_2CHMe_2$ (a), $(CH_2)_4CH_3$ (b), $(CH_2)_5CH_3$ (c), Ph (d).

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 509-511, February, 1991. Original article submitted April 2, 1990.

0568-5230/91/4002-0441$12.50

The Bischler reaction between aniline and ω-bromoacetophenone (Id) or between aniline and (2-oxooctyl)-4-picolinium bromide (III) according to the method of Blades and Wilds [3] also does not give a single product.

We are the first to show that replacing bromoketones (Ia)-(Id) and bromide (III) by (2-R-2-oxoethyl)trimethylammonium bromides (IVa)-(IVd) in the reaction with aniline facilitates indolization and gives 2-substituted indoles (IIa)-(IId) in 60-90% yields.

The cyclocondensation of (IVa)-(IVd) with aniline probably proceeds through the intermediate formation of anils (V) and their cyclization.

Starting quaternary ammonium salts (IVa)-(IVc) were synthesized according to our procedure [4] from trimethylamine and 1-bromo-2-alkanones (Ia)-(Ic), which are obtained, in turn, by the bromination of 2-alkanones in methanol in the presence of urea [5] or $Hg(OAc)_2$.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-467 spectrometer at 60 MHz. The mass spectra were taken on a Varian MAT CH-6 spectrometer with direct sample inlet into the ion source. Thin-layer chromatography was carried out on Silufol UV-254. The spots were developed with UV light or iodine vapor.

2-Isobutylindole (IIa). A sample of 10 ml 20% ethanolic Me_3N was added to 3 g crude 1-bromo-4-methyl-2-pentanone (Ia) [6], maintained for 24 h at ~20°C, and evaporated in vacuum. The residue was treated with ether. The precipitate was filtered off, washed with ether, and dried in the air to give 2.8 g (70%) (4-methyl-2-oxopentyl)trimethylammonium bromide (IVa), mp 133-135°C. PMR spectrum in CF_3CO_2H (δ, ppm, J, Hz): 1.03 m ($2CH_3$, CH), 2.08 d (CH_2, J = 6), 3.28 s ($3CH_3$), 4.10 s (CH_2).

Salt (IVa) was used in the next step without further purification.

A mixture of 2.8 g salt (IVa) and 5 ml aniline was heated at reflux for 2 h, cooled, diluted with water, and extracted with ether. The extract was dried over K_2CO_3 and evaporated. The residue was distilled in vacuum to give 1.2 g (59%) (IIa), bp 162-165°C (15 mm), R_f 0.87 (1:1 benzene—ethyl acetate). PMR spectrum in CCl_4 (δ, ppm, J, Hz): 1.15 d ($2CH_3$, J = 7), 2.05 m (CH), 2.65 d (CH_2, J = 7), 6.32 br.s (H at C^3), 7.20 m and 7.65 m (aromatic protons). M^+ 173. Molecular mass 173.

The same indices were found for an authentic sample of (IIa) [7].

2-Pentylindole (IIb) was obtained from aniline and (2-oxoheptyl)trimethylammonium bromide (IVb) [4] by analogy to (IIa) in 60% yield, bp 167-170°C (15 mm), mp 41-43°C [7], R_f 0.75 (2.5:1 benzene—hexane). PMR spectrum in CCl_4 (δ, ppm, J, Hz): 1.05 t (CH_3, J = 3), 1.43 m ($-(CH_2)_3-$), 2.53 m (CH_2), 6.35 br.s (H at C^3), 7.23 m and 7.65 m (aromatic protons). M^+ 187. Molecular mass 187.

2-Hexylindole (IIc) was obtained from aniline and (2-oxooctyl)trimethylammonium bromide (IVc) [4] by analogy to (IIa) in 64% yield, bp 172-175°C (15 mm), mp 38-41°C [7, 8], R_f 0.79 (2.5:1 benzene-hexane). PMR spectrum in CCl_4 (δ, ppm, J, Hz): 1.05 t (CH_3, J = 3), 1.42 m ($-(CH_2)_4-$), 2.65 m (CH_2), 6.22 br. s, (H at C^3), 7.15 m and 7.55 m (aromatic protons). M^+ 201. Molecular mass 201.

A mixture of 1.4 g 1-bromo-2-octanone (Ic) [9] and 2.5 ml 4-picoline was maintained for 24 h at ~20°C and diluted with ether. The oily, viscous precipitate was washed with ether by decantation to give 1.8 g (86%) N-(2-oxoethyl)(4-picolininium) bromide (III). PMR spectrum in CF_3CO_2H (δ, ppm, J, Hz): 0.85 t (CH_3, J = 3), 1.30 m ($-(CH_2)_3-$), 1.60 m (CH_2), 2.50 m (CH_2), 2.68 s (CH_3), 5.60 s (CH_2), 7.70 d and 8.35 d (4-picolinium ring protons, J = 2.5). Bromide (III) was used in the next step without further purification. A mixture of 3.2 g (III) and 6 ml aniline was heated at reflux for 2 h. After treatment as described above, 0.6 (28%) crude (IIc) was obtained.

2-Phenylindole (IId). A mixture of 0.7 g trimethylphenacylammonium bromide (IVd) [10] and 1.5 ml aniline was heated at reflux for 2 h, cooled to ~20°C, and treated with a mixture obtained from one part concentrated hydrochloric acid and four parts water. The residue was filtered off, washed with water, and dried in the air to give 0.45 g (92%) (IId), mp 187-189°C (from ethanol), R_f 0.63 (2.5:1 benzene—hexane). PMR spectrum in $CDCl_3$ (δ, ppm): 6.91 br.s (H at C^3), 7.26 m (aromatic protons). The same indices were found for authentic (IId). The reaction of aniline with bromoketone (Id) under these conditions led to contaminated (IId) with mp 110-145°C.

1-Bromo-2-octanone (Ic). A sample of 1.1 ml (3.45 g, 21.6 mmoles) Br_2 was added with stirring over 5 min to a mixture of 3.2 ml (2.62 g, 20.5 mmoles) 2-octanone and 3 g (9.4 mmoles) $Hg(OAc)_2$ in 10 ml methanol. The mixture was stirred for about 1 h until bromine disappeared, diluted with water, left for 1 h at ~20°C, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated. The residue was distilled in vacuum to give 3.4 g (80%) (Ic) with 14% isomeric 3-bromo-2-octanone as indicated by gas-liquid chromatography and PMR spectroscopy [5], bp 119-124°C (20 mm), n_D^{20} 1.4658.

LITERATURE CITED

1. The Chemistry of Heterocycles. Indoles. Part 1, John Wiley and Sons, New York (1972), p. 317.
2. General Organic Chemistry [Russian translation], Vol. 8, Khimiya, Moscow (1985), p. 550.
3. C. E. Blades and A. L. Wilds, J. Org. Chem., 21, 1013 (1956).
4. S. I. Zav'yalov, O. V. Dorofeeva, and O. K. Taganova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2145 (1986).
5. S. I. Zav'yalov and N. E. Kravchenko, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 454 (1984).
6. S. I. Zav'yalov, I. V. Sitkareva, and G. I. Ezhova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 140 (1989).
7. F. Piozzi and M. R. Langella, Gazz. Chim. Ital., 39, No. 11, 1382 (1963).
8. A. R. Katritsky and K. Akutagawa, J. Am. Chem. Soc., 108, 6808 (1986).
9. S. I. Zav'yalov and I. V. Sitkareva, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2408 (1985).
10. H. Böhme, E. Mundlos, W. Lehners, and O. E. Herbot, Chem. Ber., 90, 2008 (1957).

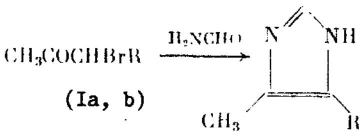
SYNTHESIS OF IMIDAZOLES

S. I. Zav'yalov, G. I. Ezhova,
and I. V. Sitkareva

UDC 542.91:547.781.2

Silica gel was found to facilitate the conversion of 3-bromo-2-alkanones to imidazoles by the action of formamide. The selective 3-bromination of 2-alkanones was carried out in ethyl acetate.

The cyclocondensation of α-haloketones with formamide known as the Bredereck reaction [1] is a convenient method for the synthesis of 4- and 4,5-substituted imidazoles. In previous work [2], we extended this reaction to 3-bromo-2-heptanone (Ia) and 3-bromo-2-octanone (Ib), which give the corresponding imidazoles (IIa) and (IIb) [2].



(Ia, b)

(IIa, b)

$R = (CH_2)_3CH_3$ (a); $(CH_2)_4CH_3$ (b).

However, the cyclocondensation of bromoketones (Ia) and (Ib) with formamide is accompanied by significant tar formation and the yields of (IIa) and (IIb) are not constant. We are the first to establish that the addition of silica gel to the reaction mixture suppresses the tar formation and provides for high and constant yields of desired products (IIa) and (IIb).

Silica gel also facilitates the formation of 4-pentylimidazole (III) from 2-phenyl-4-hexanoyl-5-oxazolinone (IV) and formamide. This unique reaction probably proceeds through the hydrolytic cleavage of the azlactone ring of (IV) and subsequent cyclocondensation of intermediate benzamidoketone (V) with formamide.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 511-513, February, 1991. Original article submitted April 3, 1990.

0568-5230/91/4002-0443$12.50