Chemistry of Heterocyclic Compounds, Vol. 38, No. 6, 2002

SYNTHESIS OF N- AND S-VINYL DERIVATIVES OF HETEROAROMATIC COMPOUNDS USING PHASE-TRANSFER CATALYSIS

E. Abele, O. Dzenitis, K. Rubina, and E. Lukevics

A method has been developed for the synthesis of N- and S-vinyl derivatives of heteroaromatic compounds from NH heterocycles or their thiols in the phase-transfer catalytic system $ClCH_2CH_2Br$–KOH (s)–18-crown-6–toluene. It is shown that it is possible to prepare N,S-divinyl derivatives of 3-mercaptoindole and 2-mercaptobenzimidazole.

Keywords: N- and S-vinyl derivatives, heteroaromatic compounds, phase-transfer catalysis.

Vinyl derivatives of heterocyclic compounds are widely used in the synthesis of polymeric [1] and photoactive materials [2, 3]. Moreover they are intermediates in the synthesis of biologically active compounds and in some cases possess biological activity. For example 2-vinylthiobenzothiazole possesses fungicidal activity [4].

N- and S-Vinyl derivatives of heteroaromatic compounds are obtained by vinylation of N-heterocycles or thiols with acetylene in the presence of KOH–dioxane [5] or metal salts (Cu, Cd) [6]. Derivatives of 1-vinylindole were prepared by the reaction of 1-lithioindole with olefins in the presence of palladium complexes [7] or by catalytic dehydrogenation of 1-ethylindole [8]. However in most cases these reactions have poor selectivity. Vinylpyrroles and vinylindoles can be obtained by the reaction of ketoximes with acetylene in the presence of KOH and DMSO. Moreover, it is known that 6-substituted purines in the phase-transfer catalytic system 1-bromo-2-chloroethane–50% aqueous NaOH–R_4NBr (R = alkyl)–benzene gave 1-vinylpurines as by products [10].

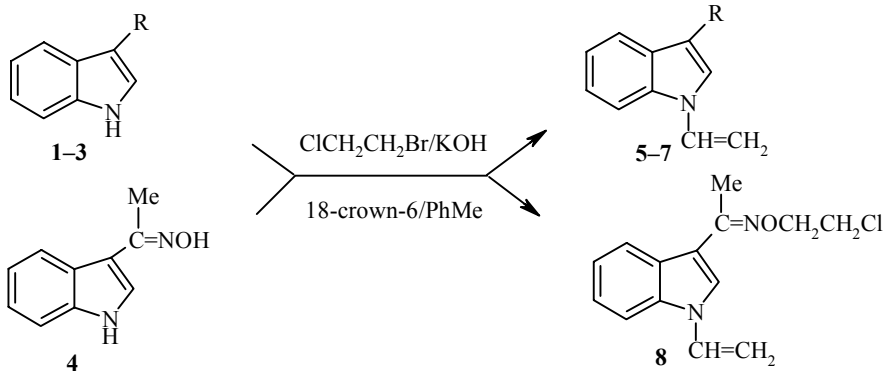
We have developed a new phase-transfer catalytic method for the synthesis of N- and S-vinyl derivatives of heteroaromatic compounds from N-heterocycles or their thiols. It was established that the phase-transfer catalytic liquid-solid system of $BrCH_2CH_2Cl$–KOH (s)–18-crown-6–toluene is most active in the synthesis of N-vinyl derivatives of indole **5-7** from the corresponding indoles **1-3**. The vinylating agent is used in 1.5-2 fold excess which is connected with its partial resinification during the reaction. For successful completion of the second stage of the reaction - elimination of HCl - a two-fold excess of potassium hydroxide was used. This elimination is the limiting step and does not go to completion otherwise because of deactivation of the base.

1-Vinylindoles were isolated in 42-68% yields. In most cases the N-vinylation occurs selectively. Only in the case of vinylation of indole was complete conversion of the starting material not achieved: at the end of the process the reaction mixture contained ~30% of indole **1**. Formation of the vinyl derivatives occurs *via*

Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: abele@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, 776-779, June 2002. Original article submitted May 8, 2001.

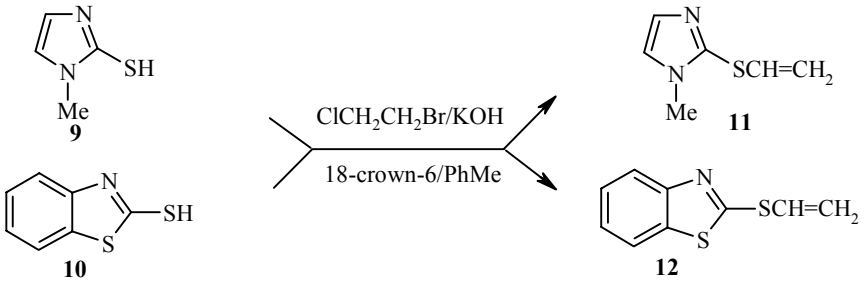
 0009-3122/02/3806-0682$27.00©2002 Plenum Publishing Corporation

formation of the 2-chloroethyl derivatives as shown by GLC-MS. For example, in the vinylation of indole the intermediate 1-(2-chloroethyl)indole was detected, 179 (M^+, 42), while for the oxime of 3-acetylindole **4** the chloro derivative **8** was the final product. N- and S-(2-Chloroethyl) derivatives of heteroaromatic compounds usually give the corresponding vinyl derivatives readily in the presence of alkali. However, as noted above, the preparation of the O-vinyl oxime from the oxime of 3-acetylindole **4** in the $BrCH_2CH_2Cl$–KOH (s)–18-crown-6–toluene system was not successful. The major product in this case was the O-(2-chloroethyl)oxime of 1-vinyl-3-acetylindole (**8**).

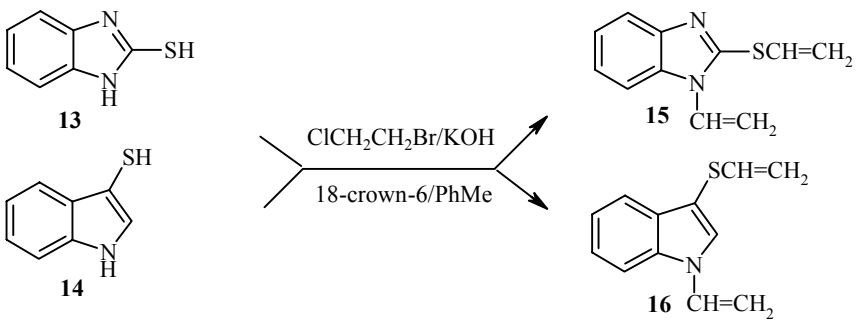


1, 5 R = H; **2, 6** R = CHO; **3, 7** R = COMe

Thiols of 1-methylimidazole **9** and benzothiazole **10** were also selectively converted to the corresponding vinylthio derivatives **11** and **12** in the $BrCH_2CH_2Cl$–KOH (s)–18-crown-6–toluene system. The low yield of 2-vinylthiobenzothiazole **12** is connected to the large extent of polymerization of the product during distillation.



It has also been shown that N,S-divinyl compounds can be obtained. For example, reaction of 2-mercaptobenzimidazole (**13**) or 3-mercaptoindole (**14**) were converted into the corresponding N,S-divinyl derivatives **15** and **16** in 43-56% yield with 1-bromo-2-chloroethane in the presence of KOH and a catalytic quantity of 18-crown-6.



EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ solutions with hexamethyldisiloxane as internal standard were recorded with a Varian 200 Mercury (200 MHz) spectrometer. Mass spectra were recorded with an HP 6890 GC-MS instrument with an ionizing voltage of 70 eV. GLC analysis was carried out with a Chrom-5 chromatograph with a flame-ionization detector, with a glass column (1.2 m × 3 mm) filled with OV-101 on Chromosorb W-HP (80-100 mesh), and nitrogen as carrier gas. The analysis temperature was varied within the limits 170-250°C depending on the composition of the reaction mixture. Indole, 3-indolaldehyde, 3-acetylindole, 2-mercaptobenzothiazole, 2-mercaptoimidazole, 2-mercapto-1-methylimidazole, 18-crown-6, and 1-bromo-2-chloroethane (Aldrich) were used without additional purification. 3-Acetylindole oxime was obtained from 2-acetylindole and $NH_2OH·HCl$ in the presence of sodium acetate and ethanol [11], and 3-mercaptoindole from indole in the iodine–KI–NH_2SCNH_2–H_2O analogously to [12].

General Method for the Preparation of Derivatives of 1-Vinylindoles 5-7. 1-Vinylindole (5). Indole (0.176 g, 1.5 mmol), 1-bromo-2-chloroethane (0.25 ml, 3 mmol), 18-crown-6 (0.040 g, 0.15 mmol), powdered KOH (0.25 g, 4.5 mmol), and toluene (2 ml) were placed in a Pierce semimicroreactor. The reaction mixture was stirred for 4 h at 40°C, a second portion of powdered KOH (0.25 g, 4.5 mmol) was added, the reaction mixture was stirred for 6 h at 100°C, filtered, and the filtrate evaporated on a rotary evaporator. The residue was purified by column chromatography (3:1 benzene-ethyl acetate eluent) to give 0.09g (42%) of 1-vinylindole **5** as a yellow oil. The characteristics of compound **5** agreed with those reported in the literature [7, 8, 13].

1-Vinyl-3-indolaldehyde (6) was obtained from 3-indolaldehyde **2** analogously to compound **5**. Reaction time 11 h. Yield 58%. Yellowish oil. ^{1}H NMR spectrum, δ, ppm: 5.15 and 7.09 (3H, m and m, CH_2=CH); 7.29, 7.98, and 8.20 (5H, m, indole protons); 9.98 (1H, s, CH). Mass spectrum, *m/z* (I_{rel}, %): 171 (88) [M^+], 170 (100), 143 (9), 115 (57), 89 (24), 75 (9), 63 (13).

3-Acetyl-1-vinylindole (7) was obtained from 3-acetylindole **3** analogously to compound **5**. Reaction time 11 h. Yield 68%. Colorless crystals; mp 79°C (1:1 benzene–petroleum ether). ^{1}H NMR spectrum, δ, ppm: 2.49 (3H, s, CH_3); 5.04 and 7.06 (3H, m and m, CH_2=CH); 7.22, 7.89, and 8.32 (5H, m, indole protons). Mass spectrum, *m/z* (I_{rel}, %): 185 (38) [M^+], 170 (100) [M - Me]$^+$, 141 (6), 115 (42), 89 (11), 75 (7), 63 (7). Found, %: C 77.26; H 5.94; N 7.52. $C_{12}H_{11}NO$. Calculated, %: C 77.81; H 5.99; N 7.57.

O-(2-Chloroethyl)oxime of 3-acetyl-1-vinylndole (8). 3-Acetylindole oxime **4** (0.054 g, 0.31 mmol), 1-bromo-2-chloroethane (0.077 g, 0.93 mmol), 18-crown-6 (0.008 g, 0.031 mmol), powdered KOH (0.104 g, 1.86 mmol), and toluene (2 ml) were placed in a Pierce semimicroreactor and stirred for 4 h at 40°C, a second portion of powdered KOH (0.104 g, 1.86 mmol) was added, and the mixture was stirred for 6 h at 100°C. The mixture was filtered, the filtrate was evaporated on a rotary evaporator, and the residue was purified by column chromatography (3:1 benzene–ethyl acetate eluent) to give compound **8** (0.05 g, 61%) as a yellowish oil. ^{1}H NMR spectrum, δ, ppm: 2.27 (3H, s, CH_3); 3.79 (2H, t, J = 6.8 Hz, CH_2Cl); 4.44 (2H, t, J = 6.8 Hz, OCH_2); 5.00 and 7.05 (3H, m and m, CH_2=CH); 7.21 and 8.20 (5H, m, indole protons). Mass spectrum, *m/z* (I_{rel}, %): 262 (83) [M^+], 183 (100), 168 (74), 158 (18), 141 (17), 130 (28), 115 (72), 89 (13), 63 (13).

General Method for the Preparation of 2-Vinylthio Derivatives of 1-Methylimidazole and Benzothiazole. 1-Methyl-2-vinylthioimidazole (11). A solution of 2-mercapto-1-methylimidazole **9** (3.42 g, 30 mmol), 1-bromo-2-chloroethane (4.97 ml, 60 mmol), 18-crown-6 (0.39 g, 1.5 mmol), powdered KOH (6.72 g, 0.12 mol), and toluene (20 ml) was stirred at 40°C for 4 h, then a second portion of powdered KOH (3.36 g, 60 mmol) was added. The mixture was stirred at 100°C for 7 h, filtered, and the filtrate was evaporated on a rotary evaporator. The residue was distilled in vacuum to give compound **11** (2.00 g, 48%); bp 140-142°C (10 mm Hg). ^{1}H NMR spectrum, δ, ppm: 3.65 (3H, s, CH_3); 5.20 and 6.45 (3H, m and m, CH_2=CH); 7.16 (2H, m, imidazole protons). Mass spectrum, *m/z* (I_{rel}, %): 140 (41) [M^+], 139 (100), 114 (21), 107 (8), 95 (8), 81 (20), 72 (34), 58 (13), 54 (12), 42 (28).

2-Vinylthiobenzothiazole (12) was obtained from 2-mercaptobenzothiazole **10** analogously to compound **11.** Reaction time 9 h. Yield 16%; bp 163°C (10 mmHg). Yellowish oil. The characteristics of compound **12** correspond to those cited in the literature.

General Method for the Preparation of N,S-Divinyl Derivatives of 2-Mercaptobenzimidazole and 3-Mercaptoindole. 1-Vinyl-2-vinylthiobenzimidazole (15). 2-Mercaptobenzimidazole **13** (0.255 g, 1.5 mmol), 1-bromo-2-chloroethane (0.49 ml, 6 mmol), 18-crown-6 (0.040 g, 0.15 mmol), powdered KOH (0.25 g, 4.5 mmol) and toluene (2 ml) were stirred in a Pierce semimicroreactor for 4 h at 40°C, then a second portion of powdered KOH (0.25 g, 4.5 mmol) was added and the mixture was stirred for 10 h at 100°C. The mixture was filtered, the filtrate was evaporated on a rotary evaporator, and the residue was purified by column chromatography (3:1 benzene–ethyl acetate as eluent) to give compound **15** (0.15 g, 56%) as a yellowish oil. Characteristics of compound **15** correspond to those cited in the literature [15].

1-Vinyl-3-vinylthioindole (16) was obtained from 3-mercaptoindole **14** analogously to compound **15**. Reaction time 9 h. Yield 43%. Yellowish oil. Characteristics of compound **16** correspond to those cited in the literature [16].

REFERENCES

1. E. S. Domnina, G. G. Skbortsova, N. G. Glazkova, and M. F. Shostakovskii. *Khim. Geterotsikl. Soedin.,* 390 (1966).
2. E. Wainer, J. M. Lewis, and J. E. Shirey. GER. Pat 2112416; *Chem. Abstr.,* **76**, 8694 (1972).
3. K. Muto, H. Tsuiki, A. Noguchi, and Y. Tsujimoto. Jpn. Pat 7514333; *Chem. Absts.,* **83**, 88755 (1975).
4. M. Kosmin. US Pat 2637647; *Chem. Abstr.,* **47**, 7726 (1953).
5. M. F. Shostakovskii, E. N. Prilezhaeva, and V. M . Karavaeva. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk,* 1250 (1958).
6. G. G. Skovortsova, B. V. Trzhtsinskaya, and N. D. Abramova. USSR Inventor's Certificate 427010; *Chem. Abstr.,* **81**, 77918 (1974).
7. L. S. Hegedus, P. M. Winton, and S. Varaprath. *J. Org. Chem.,* **46**, 2215 (1981).
8. F. N. Zeiberlikh, N. E. Starostenko, M. N. Polyakova, adn N. N. Suvorov. *Zh. Org. Khim.,* **19**, 206 (1983).
9. V. A. Trofimov and A. I. Mikhaleva. *Heterocycles,* **37**, 1193 (1994).
10. N. P. Ramzaeva, M. Yu. Lidak, Yu. Sh. Gol'dberg, and M. V. Shimanskaya, *Zh. Org. Khim.,* **24**, 1090 (1988).
11. M. N. Preobrazhenskaya, K. G. Zhirnova, N. P. Kostyuchenko, O. S. Anisimova, and N. N. Suvorov. *Khim. Geterotsikl. Soedin.,* 778 (1971).
12. R. L. N. Harris. *Org. Synth.,* **53**, 1834 (1973).
13. K. Kawasaki. *Ann. Rept. Shionogi Research Lab.,* No. 5, 57 (1955); *Chem. Abstr.,* **50**, 16748 (1956).
14. G. E. Ham, US Pat. 2643990; *Chem. Abstr.,* **47**, 9026 (1953).
15. N. D. Abramova, B. V. Trzhtsinskaya, and G. G. Skvortsova, *Khim. Geterotsikl. Soedin.,* 1670 (1975).
16. G. G. Skvortsova, L. F. Teterina, B. V. Trzhtsinskaya, and V. K. Voronov, *Khim. Geterotsikl. Soedin.,* 352 (1979).