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Synthesis of Cyclopropyl-substituted Heterocyclic Compounds

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When vinyl-substituted heterocyclic aromatic compounds with electron deficient vinyl double bond were treated with sulfur ylides formation of the corresponding cyclopropyl derivatives occurred in fair to good yields. The reaction of dichlorocarbene with 2-vinylpyridine afforded 3-chloroindolizine.

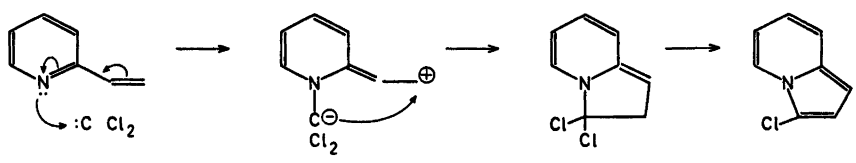
Simple syntheses of cyclopropylpyridines from vinylpyridines have recently been reported.[1,2] The present study describes some attempts to prepare cyclopropyl-substituted *N*-heterocyclic aromatic compounds starting from vinyl-substituted 5- and 6-membered heterocyclic rings.

The vinyl compounds were prepared according to known methods with two exceptions. Eisch *et al.*[3] recently reported a convenient preparation of the unstable 2-vinyl-1,2-dihydroquinoline, and it was easily oxidized with chloranil to give 2-vinylquinoline (*1*) in 35 % yield. 2-Vinylbenzoxazole (*2*) was chosen as an example of a vinyl-substituted 5-membered ring with an sp^2-hybridized nitrogen. 3-Chloro-2′-hydroxypropananilide (*3*), prepared from 3-chloropropionyl chloride and *o*-aminophenol, was treated with catalytic amounts of *p*-toluenesulfonyl chloride to give ring closure with loss of water and hydrogen chloride producing compound *2* in 54 % yield.

The addition of carbenes to double bonds is an easy approach to cyclopropanes; however, the vinyl double bond attached α or γ to an sp^2-hybridized ring nitrogen is electron deficient, and it was not surprising that the reaction of these compounds with dichlorocarbene[4] gave no isolable yield of the corresponding cyclopropyl derivatives. In all cases a black tarry product resulted from which no pure substance could be obtained with one exception. From the reaction of 2-vinylpyridine a small amount of 3-chloroindolizine (*4*) was isolated. The compound was unstable and structural proof was based on spectroscopic data. The UV spectrum was quite similar to that reported for indolizine itself[5] and the NMR spectrum showed only the presence of aromatic protons. The fragmentation pattern of the mass spectrum was as expected for a 3-substituted indolizine.[6] A reasonable explanation for its formation is depicted in Scheme 1.

The nitrogen lone pair attacks dichlorocarbene to give a zwitterion which cyclizes; under the strong alkaline condition hydrogen chloride is eliminated to give the product *4*.

Conjugation of a vinyl double bond with an sp^2-hybridized nitrogen atom as in 2-vinylpyrrole (*5*) and *N*-methyl-2-vinylpyrrole (*6*) or a sulfur atom as in 2-vinylthiophene (*7*) makes the former more electron rich and should therefore be more inclined to carbene additions. Indeed the thiophene *7* reacted readily with dichlorocarbene to give 2-(2,2-dichlorocyclopropyl)thiophene (*8*)[7] in 42 % yield. The



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Scheme 1.

Table 1. Yields of cyclopropanes in the reaction of dichlorocarbene and of the ylides *9* and *10* with vinyl-substituted heterocyclic compounds.

Vinyl compound	% Yield of the cyclopropyl product with :CCl_2	Ylide *9*	Ylide *10*
2-Vinylpyridine (*11*)	[a]	63[b]	7[b]
4-Vinylpyridine (*12*)	0	60[b]	19[b]
2-Vinylpyridazine (*13*)	0	42	20
4-Vinylpyrimidine (*14*)		8	
2-Vinylquinoline (*1*)	0	46	18
2-Vinylbenzoxazole (*2*)		37	7
2-Vinylpyrrole (*5*)		[c]	
N-Methyl-2-vinylpyrrole (*6*)	0	0	0
2-Vinylthiophene (*7*)	42	0	0

[a] Low yield of 3-chloroindolizine. [b] From Ref. 2. [c] 60 % yield of *N*-methyl-2-vinylpyrrole.

pyrrole *6*, however, gave only a black tarry product.

In addition to the carbene route to cyclopropanes sulfur ylides have long proved their significance.[8] Dimethylsulfonium (*9*) and dimethylsulfoxonium methylide (*10*) afford cyclopropyl derivatives from vinyl- and styrylpyridines.[1,2] The reaction can be envisioned as a Michael-type condensation where the intermediate carbanion undergoes ring closure with loss of dimethyl sulfide or dimethyl sulfoxide.

The results from reactions of dichlorocarbene and of the ylides *9* and *10* with the vinyl-substituted heterocyclic compounds are summarized in Table 1. Polymerization to varying degrees accompanied most of the reactions.

The ylide *9* gave under identical conditions more than twice the yields of cyclopropanes than the ylide *10*. When the vinyl group was α or γ to an sp^2-hybridized ring nitrogen in a 5- or 6-membered ring cyclopropanes were formed in moderate to good yields, except in the reaction with 4-vinylpyrimidine where polymerization was the predominant reaction. The conjugation of the vinyl group with the electronegative nitrogen and the aromatic ring enables these compounds to be efficient in Michael-type additions.

With compound *5*, however, the ylide *9* acted as a methylating agent, and compounds *6* and *7* were, as expected, both recovered unchanged after prolonged treatment with the ylides.

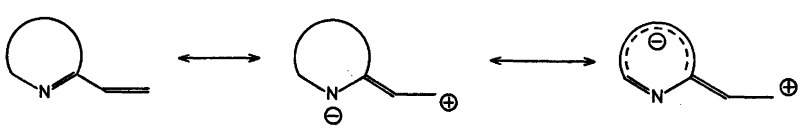
EXPERIMENTAL

Melting points were determined on a micro hot stage. UV spectra were recorded on a Cary 14 Spectrophotometer, IR spectra on a Perkin-Elmer 457 Grating Infrared Spectrophotometer, NMR spectra on Varian A-60 and HA-100 Spectrometers with TMS as internal standard, and the mass spectra on an AEI/EC MS 902 instrument, 70 eV. Elemental analyses were performed by I. Beetz, West Germany.

2-Vinylquinoline (1). To the solution of dried, crude 2-vinyl-1,2-dihydroquinoline in tetrahydrofuran, prepared from 9 g (70 mmol) quinoline,[3] chloranil (17.4 g, 70 mmol) and xylene (40 ml) were added and the mixture was refluxed for 30 min. After removal of the solvents the crude product was dissolved in light petroleum (100 ml), washed with 10 % aqueous sodium hydroxide (2 × 20 ml) and water (2 × 15 ml) and then dried. The black liquid residue was distilled to give 2.3 g of unreacted quinoline and 1.9 g (35 % based on the quinoline used) of compound *1*, b.p. 63–65 °C/0.01 mmHg, (lit:[13] 100–101 °C/2 mmHg). The NMR spectrum was identical with that previously reported.[3]

3-Chloro-2'-hydroxypropananilide (3). 3-Chloropropionyl chloride (15.2 g, 120 mmol) was added dropwise with stirring to a dispersion of *o*-aminophenol (25 g, 240 mmol) in benzene (100 ml) and left at room temperature for 4 h. The mixture was filtered and the white solid washed thoroughly with ether and recrystallized from water to give 13 g (54 %) of the anilide *3*, m.p. 124–125 °C. Anal. $C_9H_{10}ClNO_2$: C, H. MS (*m/e*): 199 (M). ^{1}H NMR (DMSO-d_6): δ 2.94 (2 H, t, J 6.5 Hz), 3.88 (2 H, t, J 6.5 Hz), 6.57–7.05 (4 H, complex), 7.58–7.82 (1 H, complex), 9.37 (1 H, broad s).

2-Vinylbenzoxazole (2). The anilide *3* (11 g, 55 mmol) and *p*-toluenesulfonyl chloride (0.2 g) in xylene (200 ml) were refluxed in a flask equipped with a water separator for 6 h until



Scheme 2.

1 ml (55 mmol) of water was collected. The solvent was removed and the residue distilled to give 4.3 g (54 %) of compound *2*, b.p. 69 °C/0.2 mmHg. Anal. C_9H_7ON: C, H. MS [*m/e* (% rel. int.)]: 145 (100, M), 144 (43.5), 64 (36.0), 63 (38.5), 39 (11.3), 38 (14.5). ^1H NMR ($CDCl_3$): δ 5.77 (1 H, dd, J 2.6 and 9.5 Hz), 6.37 (1 H, dd, J 2.6 and 17.0 Hz), 6.78 (1 H, dd, J 9.5 and 17.0 Hz), 7.15–7.80 (4 H, complex). IR (film): 1530 (s), 1450 (s), 1240 (s), 935 (s), 830 (s) cm^{-1}.

2-Vinylpyrrole (5),[9] *N-methyl-2-vinylpyrrole (6)*,[9] *2-vinylthiophene (7)*,[10] *2-vinylpyrazine (13)*,[11] and *4-vinylpyrimidine (14)*[12] were prepared according to known methods.

Reactions with dichlorocarbene

3-Chloroindolizine (4). To a solution of 2-vinylpyridine (*11*) (5.3 g, 50 mmol) and triethylbenzylammonium chloride (TEBA) (150 mg) in chloroform (18 g, 155 mmol) was added 50 % aqueous sodium hydroxide (10 ml, 125 mmol). The mixture was vigorously stirred for 14 h. The two layers of the black mixture were separated and the organic phase chromatographed on Silica gel 60 with chloroform to give colourless liquid *4* which turned black within 1 h. MS [*m/e* (% rel. int.)]: 153 (35), 151 (100, M), 116 (39.9), 115 (23.6), 89 (35.2), 63 (19.6). ^1H NMR ($CDCl_3$): δ 6.40–8.10 (complex). UV (abs. ethanol): 233.5, 294.0, 282.0, 348.5 nm; for indolizine itself[5] (log ε): 237.5 (4.51), 295 (3.56), 285 (3.45), 275.5 (3.34), 346.5 (3.29) nm.

2-(2,2-Dichlorocyclopropyl)thiophene (8). To a solution of 2-vinylthiophene (*7*) (0.55 g, 5 mmol), 1-nitroso-2-naphthol (20 mg), and TEBA (20 mg) in chloroform (3.6 g, 32 mmol) was added 50 % aqueous sodium hydroxide (2 ml, 25 mmol). The mixture was vigorously stirred for 5 h. The two layers were separated and the organic phase was dried. Distillation gave 0.4 g (42 %) of compound *8*, b.p. 97 °C/9 mmHg, (lit.:[7] b.p. 64–65 °C/49 mmHg). Anal. $C_7H_6Cl_2S$: C, H. MS [*m/e* (% rel. int.)]: 196 (2.4), 194 (14.6), 192 (21.5, M), 159 (35.0), 157 (100), 122 (40.7), 121 (46.1), 69 (10.1), 60 (10.5), 45 (30.4), 39 (13.0). ^1H NMR (CCl_4): δ 1.73 (1 H, dd, J 7.0 and 8.5 Hz), 1.98 (1 H, dd, J 7.0 and 10.0 Hz), 2.90 (1 H, dd, J 8.5 and 10.0 Hz), 6.75–6.98 (2 H, complex), 7.12 (1 H, dd, J 2.0 and 4.7 Hz). IR (film): 1430 (s), 1118 (s), 1055 (s), 850 (s) cm^{-1}.

Reactions with ylides

Reactions with dimethylsulfonium (*9*) and sulfoxonium methylide (*10*) are performed as described previously.[2]

2-Cyclopropylpyridazine (15). B.p. 68 °C/11 mmHg. Anal. $C_7H_8N_2$: C, H. MS [*m/e* (% rel. int.)]: 120 (40.0, M), 119 (100), 118 (4.2), 94 (5.3), 78 (5.4), 65 (6.3), 52 (5.4), 39 (11.1). ^1H NMR (CCl_4): δ ~1.05 (4 H, m), ~2.00 (1 H, m), ~8.33 (3 H, m). IR (film): 1418 (s), 1140 (s), 1042 (s), 1010 (s) cm^{-1}.

4-Cyclopropylpyrimidine (16). M.p. 43–45 °C. Anal. $C_7H_8N_2$: C, H. MS [*m/e* (% rel. int.)]: 120 (16.3, M), 119 (100). ^1H NMR (CCl_4): δ ~1.08 (4 H, m), ~1.90 (1 H, m), 7.20 (1 H, dd, J 1.5 and 5.0 Hz), 8.61 (1 H, d, J 5.0 Hz), 9.10 (1 H, broad s). IR (film): 1585 (s), 1030 (m), 991 (s) cm^{-1}.

2-Cyclopropylquinoline (17). B.p. 65–70 °C/0.01 mmHg (lit.:[14] b.p. 145–148 °C/17 mmHg). MS [*m/e* (% rel. int.)]: 169 (49.1, M), 168 (100), 167 (30.0), 83.5 (13.5). Mol.wt., obs. 169.0868, calc. for $C_{12}H_{11}N$ 169.0891. IR (film): 1601 (s), 1502 (s), 1425 (s), 1030(sh), 1020 (m), 819 (s) cm^{-1}.

2-Cyclopropylbenzoxazole (18). B.p. 73 °C/0.07 mmHg. Anal. $C_{10}H_9NO$: C, H. MS [*m/e* (% rel. int.)]: 159 (100, M), 158 (72.5), 133 (52.3), 130 (13.8). ^1H NMR (CCl_4): δ 1.18 (4 H, m), 2.18 (1 H, m), 7.12–7.68 (4 H, m). IR (film): 1618 (s), 1575 (s), 1452 (s), 1240 (s), 1155 (s), 1078 (s), 1030 (m), 940 (s) cm^{-1}.

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