ONE-POT PREPARATION OF 1-CHLOROVINYLISOCYANIDES FROM CARBONYL COMPOUNDS

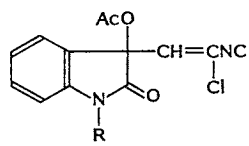
Sir:

Recently, we found a new antibiotic indisocin[1] (**1**) which has a unique 1-chlorovinylisocyanide group in its structure (Fig. 1). Indisocin, which shows broad and strong antimicrobial activity, is very unstable because of the presence of a labile 1-chlorovinylisocyanide moiety which has never been found before. We now wish to report a new method for synthesizing 1-chlorovinylisocyanide derivatives. The stereochemistry of the vinyl group was determined as based on the PASCUAL's rule[2].

SCHÖLLKOPF *et al.* reported the general method for preparation of α,β-unsaturated isocyanides[3] from diethyl(isocyanomethyl)phosphonate (**2**) and carbonyl compounds, and applied it to the synthesis of the antibiotic B371[4]. We also applied it to the synthesis of 1-chlorovinylisocyanides. For example, 2-(4-methoxyphenyl)-vinylisocyanide (**3**) was prepared by the reaction of **2** with *p*-anisaldehyde in the presence of sodium bis(trimethylsilyl)amide as a mixture of *cis*- and *trans*-isomers[3] which were separated by silica gel column chromatography (CCl_4) (Scheme 1). [*cis*-**3**: ^{1}H NMR (CCl_4) δ 3.83 (3H, s), 5.68 (1H, d, J=9.5 Hz), 6.22 (1H, br d, J=9.5 Hz), 6.88 (2H, d, J=9 Hz), 7.63 (2H, d, J=9 Hz), *trans*-**3**: ^{1}H NMR (CCl_4) δ 3.80 (3H, s), 6.12 (1H, d, J=15 Hz), 6.80 (2H, d, J=9 Hz), 6.85 (1H, br d, J=15 Hz), 7.23 (2H, d, J=9 Hz)]. Unfortunately, the following halogenation of **3** was too difficult to give the corresponding 1-halovinylisocyanide, because the isocyanide group as well as olefinic portion, possessed undesirable reactivity[5] with halogenating reagents such as chlorine or *N*-chlorosuccinimide. The alternative method was developed as follows. Since SAVIGNAC *et al.*[6] have prepared diethyldichloromethylphosphonate by chlorination of diethyl chloromethylphosphonate, we examined halogenation of phosphonate (**2**) and obtained the diethyl haloisocyanomethylphosphonates (**4** and **5**). Compound **2** was treated with one equivalent of butyllithium (1.6 N in hexane, Merck, Art 801660) in THF at -78°C and the resulting anion of **2** was quenched by addition of one equivalent of tetrachloromethane or tetrabromomethane to give **4** or **5**. [**4**: Electron impact mass spectra (EI-MS) *m/z* 214 and 212 $(M+H)^+$; IR $\nu_{max}^{CCl_4}$ cm^{-1} 2120 (NC); ^{1}H NMR (CCl_4) δ 1.43 (6H, t), 4.32 (4H, m), 5.20 (1H, d, J=9.0 Hz), **5**: EI-MS *m/z* 258 and 256 $(M+H)^+$; IR $\nu_{max}^{CCl_4}$ cm^{-1} 2120 (NC); ^{1}H NMR (CCl_4) δ 1.43 (6H, t), 4.30 (4H, m), 5.15 (1H, d, J=8.5 Hz)]. Compounds **4** and **5** were so unstable and volatile substances that they were stored in CCl_4 solutions after silica gel column chromatography (CCl_4 - EtOAc, 10:1). Without isolation of the halogenated compound (**4** or **5**), the THF solution which contained above compound (**4** or **5**) was again treated with butyllithium (one equivalent) to yield the anion which reacted with various carbonyl compounds **6a**~**6f** at -78°C to give the desired 1-halogenated vinylisocyanides **7a**~**7f** (Scheme 2). All of these were as unstable as indisocin. The aldehyde **6f** was prepared from indole-3-carboxaldehyde by methylation (CH_3I - NaH in THF at 0°C). [**6f**: ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 7.20~7.40 (3H, m), 7.62 (1H, s), 8.20~8.45 (1H, m), 10.0 (1H, s)]. Physico-chemical properties of compounds **7a**~**7f** are summarized in Table 1. The *Z*- and *E*-configurations of the above compounds were determined by substituent constants Zi in the PASCUAL's equation (I) on chemical shifts of olefinic protons[2].

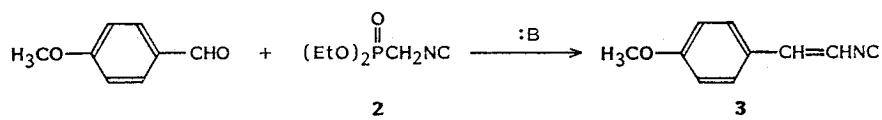
$$\delta\,(\text{ppm}) = 5.28 + \sum_i \text{Zi} \cdots\cdots\cdots\cdots \text{(I)}$$

Fig. 1. The structure of indisocin.



Indisocin (**1**) R = H

Scheme 1.



2 **3**

Scheme 2.

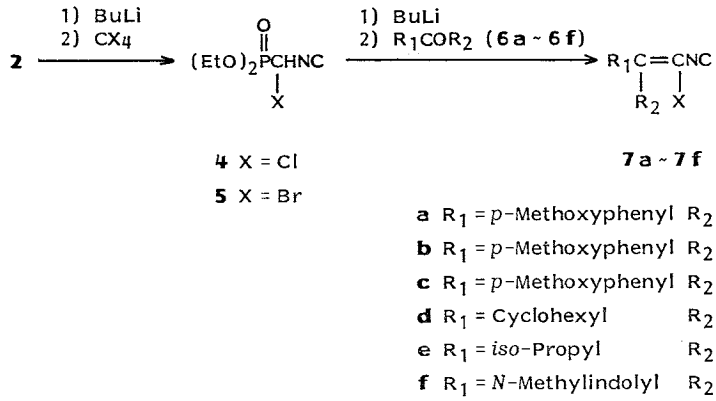


Table 1. Physico-chemical properties of 1-halovinylisocyanides and calculated chemical shifts of olefinic protons.

Compounds	EI-MS (m/z)	IR $\nu_{max}^{CCl_4}$ cm^{-1}	^1H NMR (CCl_4) δ (ppm)[a]		Calcd shifts[b]	
			E	*Z*	*E*	*Z*
7a	193, 195	2095 (NC), 2850, 1605, 1515, 1305, 1260, 1180, (*E*)	3.83 (3H, s), 6.54 (1H, s), 6.92 (2H, d, *J*=9 Hz), 7.54 (2H, d, *J*=9 Hz)	3.84 (3H, s), 6.88 (1H, s), 6.91 (2H, d, *J*=9 Hz), 7.58 (2H, d, *J*=9 Hz)	6.41	6.88
7b	237, 239	2090 (NC), 2960, 2940, 2340, 1605, 1510, 1260, (*E*)	3.81 (3H, s), 6.67 (1H, s), 6.88 (2H, d, *J*=9 Hz), 7.54 (2H, d, *J*=9 Hz)	3.83 (3H, s), 6.87 (2H, d, *J*=9 Hz), 7.12 (1H, s), 7.57 (2H, d, *J*=9 Hz)	6.62	7.40
7c	207, 209	2090 (NC), 2960, 2850, 1610, 1510, (*E*, *Z*)	2.28, 2.19 (3H, s), 3.80, 3.82 (3H, s), 6.82, 6.86 (2H, d, *J*=9 Hz), 7.21, 7.29 (2H, d, *J*=9 Hz)			
7d	—	2100 (NC), 2930, 2860, 1630, 1450, (*E*)	0.9~2.0 (10H, m), 2.2~2.7 (1H, m), 5.65 (1H, d, *J*= 9.5 Hz)	0.9~2.0 (10H, m), 2.1~2.6 (1H, m), 5.87 (1H, d, *J*=9.5 Hz)	5.50	5.97
7e	—	2100 (NC), 2970, 2930, 2870, 2100, (*E*, *Z*)	1.06, 1.09 (3H, d, *J*=7 Hz), 2.5~3.0 (1H, m), 5.62, 5.85 (1H, d, *J*=7 Hz)		5.50	5.97
7f	216, 218	2090 (NC), 2960, 1630, 1530, 1480, 1340, (*Z*)	3.85 (3H, s), 6.86 (1H, s), 7.15~7.30 (3H, m), 7.5~7.65 (1H, m), 7.69 (1H, s)	3.87 (3H, s), 7.12 (1H, s), 7.15~7.30 (3H, m), 7.50~7.65 (1H, m), 7.74 (1H, s)	6.41	6.88

[a] Varian EM-390 (90 MHz) (ppm from TMS).

[b] Zi values in equation (I) for Cl, Br and aromatic ring are used according to data of PASCUAL *et al.*[2].

—: No useful data because of their volatility.

The Zi values of isonitril were determined to be $NC_{cis}=0.22$ and $NC_{trans}=-0.41$ from the observed chemical shifts of olefinic protons in the ^1H NMR spectra of *cis*- and *trans*-**3**. The chemical shifts of olefinic protons in 2-substituted-1-halovinylisocyanide compounds (**7a**, **7b** and **7d**~**7f**) were calculated using above Zi values of isonitrile. The calculated chemical shifts corresponded with the observed shifts for compounds **7a**, (*E*)-**7b**, **7d** and **7e** within ±0.15 ppm. The calculated chemical shifts for (*Z*)-**7b**, **7f** have rather large error (±0.45 ppm), however, the chemical shifts of the proton in *Z*-isomers of chloro- and bromo-derivatives are theoretically downfield from those of *E*-isomers respectively[2]. Thus, the configuration of those compounds could be determined as the *Z*-isomer.

The application of this synthetic strategy for the construction of indisocin-related antibiotics as well as some of their potentially therapeutically interesting analogs is an exciting prospect[7].

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