A Novel Synthesis of *N*-Styryl Heterocycles

J. Rokach, Y. Girard, and J. G. Atkinson
Merck Frosst Laboratories, Kirkland, Quebec

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Reaction of the anions of a variety of 2-carboethoxy *N*-heterocycles with styrene oxide yields directly the *N*-(*trans*-2-styryl)-2-carboxylic acids. The reaction has been shown to proceed through a lactone intermediate which undergoes rapid elimination to form the unsaturated acid. The reaction has been used to alkylate 2-carboethoxy pyrrole, diethyl pyrazole-3,5-dicarboxylate, ethyl indole-2-carboxylate, ethyl benzimidazole-2-carboxylate, and ethyl 2-pyrrolidone-5-carboxylate. Yields were 82, 88, 93.5, 57, and 5% respectively.

1-(*trans*-2-Styryl)benzimidazole-2-carboxylic acid of m.p. 75–77 °C undergoes an interesting, reversible solid-state transformation to a high melting (255–260 °C), presumably zwitterionic, form.

La réaction d'anions d'une variété de carboéthoxy-2 *N*-hétérocycles avec l'époxide de styrène donne directement les acides *N*-(*trans*-styryl-2) hétérocycles-2 carboxyliques. Le mécanisme de la réaction passe par une lactone intermédiaire qui subit une élimination rapide pour donner ainsi l'acide insaturé. Ont été alkylés par ce procédé le carboéthoxy-2-pyrrole, le dicarboéthoxy-3,5-pyrazole, le carboéthoxy-2-indole, le carboéthoxy-2-benzimidazole et le carboéthoxy-5-pyrrolidone-2 avec des rendements respectifs de 82, 88, 93.5, 57 et 5%.

Il est intéressant de noter que l'acide (*trans*-styryl-2)-1-benzimidazole-2-carboxylique de p.f. 75–77 °C, se transforme réversiblement à l'état solide en un produit de p.f. 255–260 °C, vraisemblablement le zwitterion.

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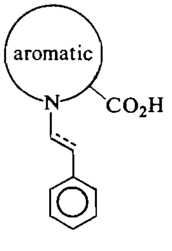
As part of a synthetic program in our laboratories we required an efficient general synthesis of 2-carboxy *N*-heterocycles substituted on nitrogen with β-styryl and β-phenethyl groups (*e.g.* **1**). Accordingly, we investigated the alkylation of a series of 2-carboethoxy *N*-heterocycles and are reporting the discovery of a novel and efficient synthesis of the desired compounds.



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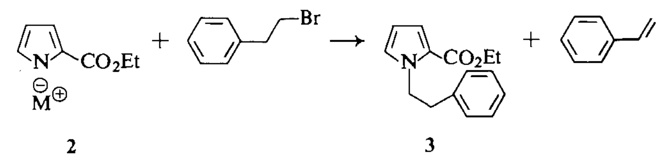
Results

Reaction of the ethyl pyrrole-2-carboxylate anion **2** in DMF with 2-phenethyl bromide gave a low yield (<5%) of the desired *N*-alkylation product, **3** (eq. 1). The main course of the reaction probably involved β-elimination to form styrene. A number of experiments served to confirm the initial result and no conditions were found which gave good yields of the desired product. Omote and co-workers (1) have also reported a similar type of reaction between indole and β-phenethyl bromide (or iodide), and obtained trace amounts of *N*-phenethyl indole. Alkylation of the anion **2** with styrene oxide in DMF was then investigated. It was anticipated that the initially formed alkoxide **4** would ring close to form the lactone **5**. Hydrogenolysis of the lactone was expected to lead to the desired phenethyl carboxylic acid **6** (eq. 2). Alkylation did occur, but surprisingly the product directly isolated was found to be 1-(*trans*-2-styryl)-pyrrole-2-carboxylic acid (**7**) (eq. 3).

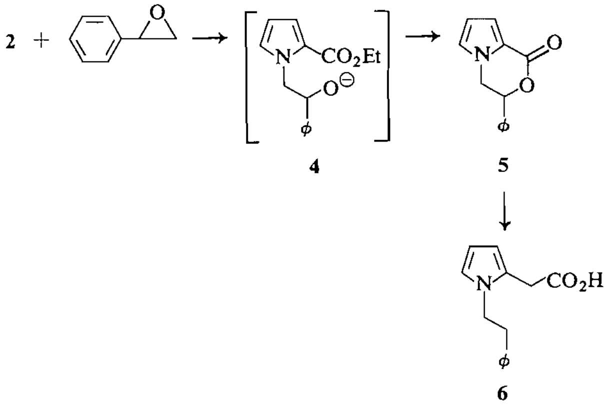
Using NaH or potassium *t*-butoxide as the base and running the reaction in DMF at 110° for 1–2 h gave rise to an excellent yield (82%) of the product **7**. The elevated temperature was found to be very advantageous as at room temperature the yield was only about 25% after 24 h, and longer reaction times did not substantially improve the yield.

Further investigation with a series of 2-carboethoxy *N*-heterocycles showed that the reaction was of general applicability and that excellent yields of the *N*-(*trans*-2-styryl)-2-

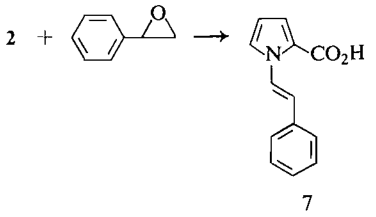
[1]



[2]



[3]

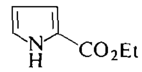
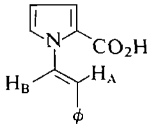
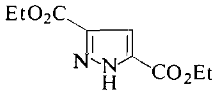
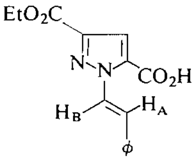
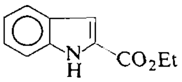
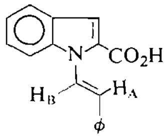
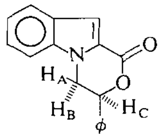
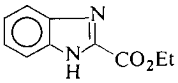
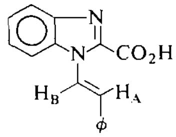
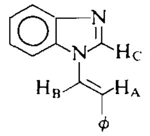
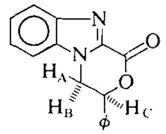
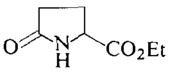
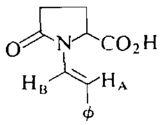


carboxylic acids could be readily obtained by this procedure (Table 1). Entry 5 of Table 1 (ethyl 2-pyrrolidone-5-carboxylate) indicates that the reaction is applicable to aliphatic as well as aromatic systems, although in lower yield. As can be seen in the Experimental, a particularly pleasing aspect of the reaction is the purity of the products as isolated directly from the reaction mixture. In all cases, there was no indication of impurities in the crude products as judged by the n.m.r. spectra and t.l.c., and there was little or no improvement in the m.p. upon recrystallization. The *N*-(2-styryl)carboxylic acids thus obtained could be hydrogenated quantitatively to *N*-(2-phenethyl)carboxylic acids (thus completing the original aim of the work in high overall yields).

At the time that our work was nearing completion, a publication by Irwin and Wheeler (2) appeared describing the reaction of the anion of ethyl pyrrole-2-carboxylate with a series of epoxides, and our work confirms and extends the results of these authors. Our assignments agree with those of Irwin and Wheeler (2), and in all cases the *trans* configuration is assigned to the styryl double bond on the basis of the large (~15 Hz) coupling constant between the two protons of the vinyl moiety.

A careful search was made in order to isolate the proposed lactone intermediates of type **5**. In the cases of the indole and benzimidazole compounds (entries 3 and 4, Table 1), it was possible to isolate low yields (~2%) of the lactones directly from the reaction mixture. The major product in each case was still the *N*-(*trans*-2-styryl)-2-carboxylic acid. The lactones were highly crystalline compounds and their structures could be unambiguously assigned on the basis of the i.r. and n.m.r. spectra, the details of which are given in Table 1. The assignment of shifts to the protons H_A and H_B in the lactones is based on the assumption that the *trans* hydrogens will have the larger of the two coupling constants with the tertiary proton H_C. The fact that there is a significant difference in the vicinal coupling constants indicates that

TABLE 1. Synthesis of *N*-styryl derivatives from styrene oxide

Entry	Starting material	Product	Yield (%)	M.p. (°C)	Spectral data
1			82	183–185*	J_{AB} 15 Hz
2			88	165–167	J_{AB} 15 Hz
3			93.5	222–224	J_{AB} 15 Hz
				180–182	($CDCl_3$) δ_A 4.20 J_{AB} 13 Hz δ_B 4.58 J_{AC} 10.5 Hz δ_C 5.80 J_{BC} 4 Hz ν(C=O) 1735 cm^{-1} (KBr)
4			57	75–77 (dec.)	J_{AB} 15 Hz (Na salt)
			quantitatively from acid	93–95	($CDCl_3$) δ_C 8.84 J_{AB} 15 Hz
				215–217	(DMSO-d_6) δ_A 4.63 J_{AB} 13.5 Hz δ_B 5.05 J_{AC} 10.5 Hz δ_C 6.25 J_{BC} 4 Hz ν(C=O) 1740 cm^{-1} (KBr)
5			5	165	J_{AB} 14.5 Hz

*Literature (1) m.p. 178–179 °C.

H_C is in fact in a pseudoaxial configuration. Figure 1 shows a photograph of the n.m.r. spectrum of the indole lactone with a proposed configuration for the molecule.

Discussion

The results of Irwin and Wheeler (2) taken with those presently reported show that the reaction of 2-carboethoxy *N*-heterocycles is a

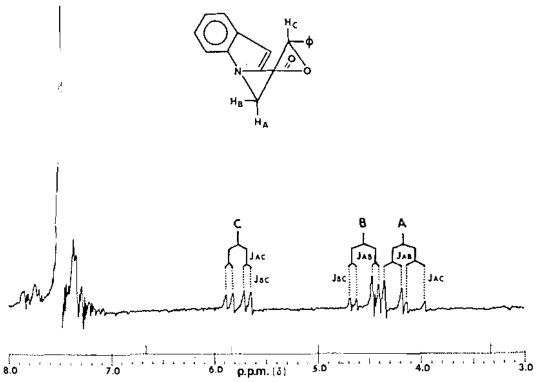


FIG. 1. N.m.r. spectrum of the lactone from the reaction of ethyl indole-2-carboxylate with styrene oxide (60 MHz, $CDCl_3$ solvent).

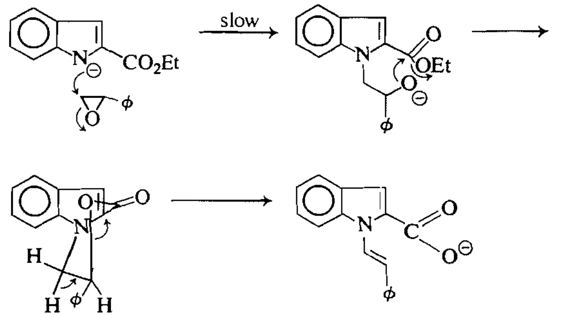
generally applicable reaction for the synthesis of 2-carboxy *N*-(β-styryl) compounds. The previous workers employed mainly ethyl pyrrole-2-carboxylate with a variety of epoxides and we have demonstrated, using styrene oxide, that the heterocyclic molecule can be varied considerably.

Irwin and Wheeler had reasonably proposed that the formation of the styryl carboxylic acids must go through a lactone intermediate which then undergoes β-elimination under the basic conditions of the reaction. They were able to isolate a lactone from the reaction with cyclohexene oxide, but this lactone did not undergo the elimination reaction because, as the authors point out, the stereochemistry of the material does not permit a transoid transition state.

We have been able to complete the mechanistic picture by isolation of the lactones from the reaction of styrene oxide with ethyl indole-2-carboxylate and ethyl benzimidazole-2-carboxylate. Both of these lactones, when treated under the conditions of the original reaction, were converted rapidly and in high yields to the styryl carboxylic acids. The ease of the conversion of the lactones to the final product indicates why they are normally isolated in very low yields or not at all.

The mechanistic picture thus derived is shown in Scheme 1 using styrene oxide and ethyl indole-2-carboxylate and is essentially identical to that proposed by Irwin and Wheeler.

Given the demonstrated rapidity of the last step of the scheme and the fact that starting material can be seen by t.l.c. until near the end of the reaction, one can also reasonably propose that the slow step is the initial alkylation by the the epoxide.

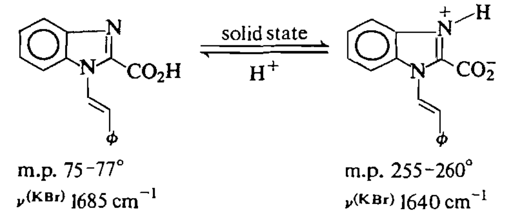


SCHEME 1

The properties of the product derived from ethyl benzimidazole-2-carboxylate and styrene oxide were found to be somewhat unusual and merit some discussion.

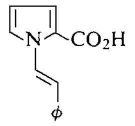
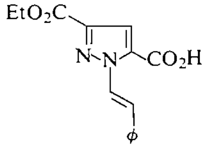
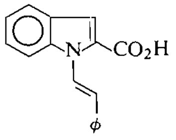
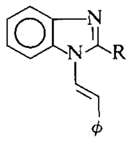
The product undergoes decarboxylation with extreme ease and if the work-up is done as usual with HCl, only the decarboxylated product is isolated (Table 1, entry 4). If acetic acid is used, the product can be isolated in good yield. Upon dissolving in organic solvents at room temperature, the acid decarboxylates neatly and quantitatively to 1-(2-styryl)benzimidazole in the time required to run the n.m.r. spectrum. The sodium salt, in contrast, is quite stable, and a satisfactory n.m.r. spectrum could be obtained in DMSO-d_6.

The solid acid of m.p. 75–77°, upon standing for several days at room temperature, undergoes a transformation to a high melting, very insoluble form. There is a concomitant change of the carboxyl band in the i.r. spectrum (KBr) from 1685 (sharp) to 1640 cm^{-1} (broad). Careful treatment with acetic acid regenerates the original form. This indicates that on standing the material is changing from a free acid to a zwitterionic form as shown in Scheme 2.



SCHEME 2

TABLE 2. Ultraviolet spectra of *N*-styryl heterocycle (EtOH)

Structure		λ max (nm)	log Σ
		208 221 243 305	4.12 4.14 4.02 4.24
		209 226 sh 317	4.25 4.17 4.23
		211 sh 225 284 327	4.30 4.40 4.30 3.98
	R = CO_2Na	213 275*	4.37 4.19
	R = CO_2H†	211 271 302	4.30 4.25 4.13
	R = H	212 270 303	4.32 4.37 4.30

*Tailed out to 340 nm.
†The acid has undoubtedly largely decarboxylated during the spectrum.

Experimental

Melting points are uncorrected.

Ethyl benzimidazole-2-carboxylate was prepared according to Copeland and Ray (3). Ethyl 2-pyrrolidone-5-carboxylate and ethyl pyrrole-2-carboxylate were prepared by esterification of the corresponding acids. All the remaining starting materials were commercially available. All new compounds gave correct elemental analysis. The u.v. spectra are collected in Table 2.

N-(trans-Styryl)pyrrole-2-carboxylic Acid

Ethyl pyrrole-2-carboxylate (11.7 g, 0.084 mol) was dissolved in 50 cc dry DMF and sodium hydride powder (2 g, 0.084 mol) added to the stirred solution. When hydrogen evolution had ceased (2–3 h), styrene oxide (14 g, 0.115 mol) was added and the solution warmed at 110–120 °C for 1 h. (Reaction followed by t.l.c. for disappearance of starting material.) The reaction mixture was cooled, ice-water added (~300 cc), the resulting solution extracted with ether, and the water layer cooled and acidified with dilute HCl. The precipitated white solid was filtered, washed with water, and dried, yielding 14.6 g of pure product (82% yield), m.p. 183–184 °C. A sample recrystallized from methanol had m.p. 183–185 °C.

1-(trans-Styryl)pyrazole-3-carboethoxy-5-carboxylic Acid

Diethyl pyrazole-3,5-dicarboxylate (24 g, 0.113 mol) was dissolved in 300 cc dry DMF and potassium *t*-butoxide (13.2 g, 0.116 mol) added to the stirred solution. After 15 min, styrene oxide (18 g, 0.150 mol) was added and the mixture heated at 120 °C for 1–2 h (reaction followed by t.l.c. for disappearance of starting material). The cooled reaction mixture was diluted with ice-water (1000 ml), extracted with ether, and the water layer cooled and acidified with dilute HCl. The precipitated white solid was filtered, washed with water, and dried, yielding 28.4 g of pure product (88% yield), m.p. 165–167 °C, unchanged by recrystallization from methanol.

N-Styrylindole-2-carboxylic Acid

Sodium hydride powder (3.5 g, 0.146 mol) was added to a stirred solution of ethyl indole-2-carboxylate (25 g, 0.132 mol) in 250 ml dry DMF. After the hydrogen evolution had stopped, styrene oxide (30 g, 0.250 mol) was added and the mixture heated at 110 °C for 1½ h. The mixture was cooled, water added, and the solution extracted with ether. The water layer was acidified with excess dilute HCl. The precipitated solid was filtered, washed with water, and dried, yielding 32.5 g (93.5% yield), m.p. 222–224 °C, unchanged on recrystallization from methanol.

In a separate run ethyl indole-2-carboxylate (1.89 g, 10 mmol) and sodium hydride (260 mg, 11 mmol) were heated at 110° with styrene oxide (2.4 g, 20 mmol) and the reaction stopped before completion. The reaction was worked-up as above and the ether extracts dried and evaporated to dryness. The residue (1.6 g) was triturated with ether – petroleum ether. The precipitated crystals (50 mg) were filtered to yield the lactone, m.p. 180–182 °C. Recrystallization from methanol did not improve the melting point.

The lactone (45 mg) was dissolved in $\frac{1}{2}$ cc DMF and 19 mg potassium *t*-butoxide (1 equiv.) added and the mixture stirred at room temperature for 15 min. The reaction was diluted with water, acidified, and extracted with ether. The ether solution yielded 40 mg of a yellowish solid, identical by t.l.c. to the acid isolated above. This was recrystallized from methanol, m.p. 218–222 °C, mixed melting point 220–222 °C, with an i.r. spectrum identical to that of the authentic acid.

1-Styrylbenzimidazole-2-carboxylic Acid

To a stirred solution of ethyl benzimidazole-2-carboxylate (3.8 g, 0.020 mol) in 60 ml dry DMF, was added sodium hydride powder (520 mg, 0.022 mol). After 1 h styrene oxide (4.8 g, 0.040 mol) was added and the mixture heated at 110 °C for 2 h. The mixture was cooled, ice-water added, and the mixture extracted with ether. A suspended solid was filtered (30 mg) and proved to be the lactone, m.p. 215–217 °C. The ether extracts were dried and evaporated to dryness and the oily residue (2.6 g) treated with some ether and filtered to yield a further 30 mg of lactone.

The water layer was carefully acidified with acetic acid and the precipitated white solid was dried under vacuum at room temperature to yield the acid (3 g, 57% yield), m.p. 75–77 °C (dec.).

If the acidification is done with HCl, decarboxylation occurs and 1-styrylbenzimidazole is obtained, m.p. 93–94 °C. A sample of the acid recrystallized from cyclohexane similarly yielded the decarboxylated material, m.p. 93–94 °C.

When the acid is stored for a few days the m.p. increases to 255–260 °C and the i.r. spectrum shows a shift in the C=O absorption from 1685 to 1640 cm^{-1}. This compound, treated with AcOH in the cold, regenerates the original form of the acid, m.p. 74–76 °C, and the C=O band is restored to its original position and sharpness.

1-Styryl-2-pyrrolidone-5-carboxylic Acid

Ethyl 2-pyrrolidone-5-carboxylate (1.57 g, 10 mmol) was dissolved in DMF (20 cc) and sodium hydride (260 mg) added. After 1 h a two-fold excess of styrene oxide (2.4 g) was added and the mixture heated at 180 °C for $\frac{1}{2}$ h. Ice-water was added to the cooled reaction mixture which was then extracted with ether. The water layer was acidified with dilute HCl, extracted with ether, and the ether dried and evaporated. The oily residue (350 mg) solidified on standing, m.p. 165 °C ($CHCl_3$).

1. Y. Omote, T. Nakamura, K.-T. Kuo, and N. Sugiyama. Chem. Abstr. **65**, 16928b (1966).
2. W. J. Irwin and D. L. Wheeler. Tetrahedron, **28**, 1113 (1972).
3. R. A. B. Copeland and A. R. Ray. J. Am. Chem. Soc. **65**, 1072 (1943).