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Ring-Opening of Substituted Isoxazolidines: One-Pot Synthesis of Indenes

Francesco Casuscelli,[a] Ugo Chiacchio,[b] Angelo Liguori,[c] Giovanni Romeo,[a] Giovanni Sindona[c] and Nicola Uccella[c]

[a]Dipartimento Farmaco-chimico, Università, 98168 Messina, Italy
[b]Dipartimento di Chimica, Università, 95125 Catania, Italy
[c]Dipartimento di Chimica, Università, 87036 Arcavacata di Rende, Italy

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Abstract: *High yield conversion of 3,5,5-triarylisoxazolidines into indene derivatives has been achieved by 4 h refluxing in aq. H_2SO_4. The rearrangement pathway is interpretable on the basis of a ring-opening process where the crucial step is the protonation of the oxygen atom of the isoxazolidine nucleus. MNDO calculations performed on N,N,O-trimethylhydroxylamine chosen as model system support the proposed mechanism.*

Ring opening of isoxazolidine nucleus, easily accessible by 1,3-dipolar cycloaddition of nitrones to alkenes, constitutes a remarkable powerful approach to the formation of new carbon-carbon and carbon-oxygen bonds.[1-3]

The activation of the system, through cationization of the nitrogen atom,[4-10] opens new alternatives for the chemical conversion of the primary 1,3-dipolar cycloadducts. Isoxazolidinium salts, obtained by independent procedures, undergo chemical modifications leading to hydroxylamines,[6] tetrahydro-1,3-oxazines,[8,11] 1,3-amino alcohols,[4] α,β-enones.[4,5,7,8,10,11]

Recently, an easy entry to tertiary allylic alcohols has been reported based on the ring opening of isoxazolidine nucleus, induced by reaction with trimethyl phosphate and NaH treatment.[12]

Substituted indenes can be prepared by the reaction of aryl-substituted allylic alcohols with concentrated sulphuric acid.[13,14]

An easy synthetic approach towards indene derivatives has been designed as an alternative procedure, starting from suitable isoxazolidine cycloadducts. The exploitation of this new synthetic route from 3,5,5-triarylisoxazolidinium salts, obtained by treatment with mineral acids of the corresponding isoxazolidines, allows the one-pot synthesis of indene systems.

RESULTS AND DISCUSSION

The reaction of 5,5-diphenylisoxazolidine **1** with 30% aqueous H_2SO_4 at reflux for 4 h gave indene **5** in satisfactory yields. Analogous results, although in lower yields, were obtained by treatment of **1** with 30% H_2SO_4 in propanol (Table 1).

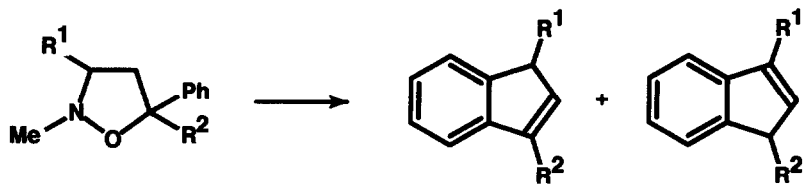
The molecular structure of the reaction product was assigned on the basis of analytical and spectroscopic data (see Experimental) and by comparison with an authentic sample.[15]

The observed reaction route leading to indenes appears to be controlled by the nature of the solvent and temperature. In fact, treatment of **1** with H_2SO_4 in methanol, acetonitrile, dimethoxyethane or dioxane, at reflux, failed to give the expected 1,3-diphenylindene; isoxazolidine **1** was recovered unaltered.

Furthermore, pattern of substitution at position 5 of the heterocyclic nucleus plays a very important role on the reaction course. 5-Aryl-monosubstituted or 5-alkyl-5-aryl-substituted isoxazolidines did not give rise to the

corresponding indenes. On the contrary, no dependence of the reactivity from aryl substituent at position 3 was observed: 3-*p*-chlorophenyl-5,5-diphenylisoxazolidine **2** and 3-*p*-tolyl-5,5-diphenyl-isoxazolidine **3** afforded indenes **6**, **7** and **8**, **9** respectively in good yields (Table 1).

Table 1. Reaction of Isoxazolidines **1-4** with 30% H_2SO_4

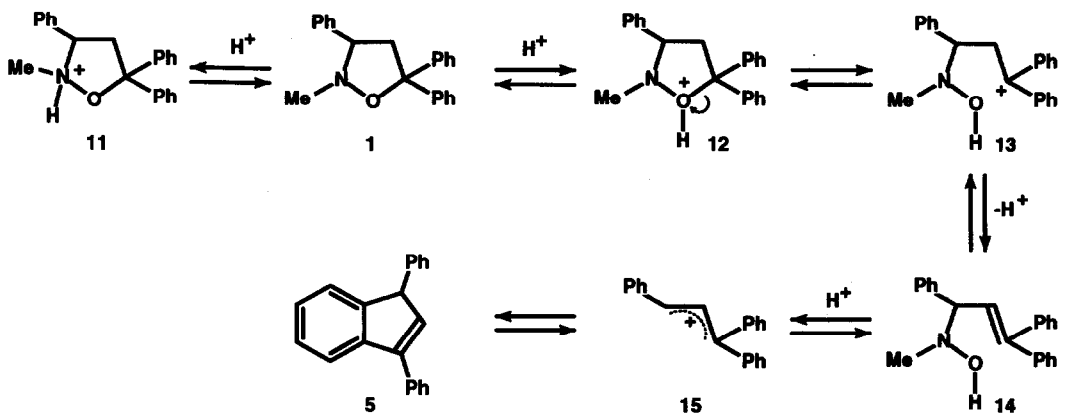


1-4 **5,6,8,10** **7,9**

Isoxazolidines	R^1	R^2	Indenes (Yield %)
1	Ph	Ph	**5** (75)
2	*p*-ClC_6H_4	Ph	**6** (76); **7** (20)
3	*p*-$CH_3C_6H_4$	Ph	**8** (50); **9** (45)
4	*p*-ClC_6H_4	*p*-ClC_6H_4	**10** (70)

Structures of obtained compounds were attributed on the basis of spectroscopic data; in particular, compounds **6** and **8** were confirmed by comparison with authentic samples, prepared by treatment of the corresponding allylic alcohols (1,1-diphenyl-3-*p*-chlorophenyl-2-propen-1-ol and 1,1-diphenyl-3-*p*-tolyl-2-propen-1-ol) with H_2SO_4, followed by quenching of the reaction mixture with aqueous sodium hydroxide.[13]

On the basis of the obtained results we postulate a ring-opening mechanism where protonation at the oxygen atom of the isoxazolidine nucleus is followed by the heterolytic cleavage of the C_5-O bond as the rate-determining step of the process.



Scheme 1

The obtained tertiary carbocation **13**, whose formation is promoted by the high temperature and assisted by the protic polar solvent and the two phenyl groups in conjugation with the charged carbon, is in equilibrium with the olefin **14**, formed by deprotonation; the subsequent acid attack at the nitrogen atom generates the N-methylhydroxylamine as a good leaving group and drives the reaction towards the formation of the highly stabilized 1,1,3- triphenylpropenyl cation **15**, which cyclize very rapidly to 1,3-diphenylindene **5**[15](Scheme 1).

The alternative ring closure of the 1,1,3-triphenylpropenyl cation **13** could lead to the isomeric 1,1-diphenyl indene which has not been detected in the reaction mixture. The observed regioselectivity is imputable to the steric interactions between two phenyl groups on the transition state promoted by the electrophilic attack of the more substituted benzylic carbon atom in cation **12** on the aromatic nucleus.

Our findings are in agreement with literature data[13,14] which state that cyclization of triphenyl-substituted allylic cations always proceeds from the less substituted end of the allylic system.

The protonation pre-equilibrium (Scheme 1), interpretated on the basis of HSAB, postulates the initial formation of cations **12** according to the higher charge density on oxygen atom, as reported on Table 2, being H^+ an hard acid.[16] Values of energy levels, coefficients, and charge densities, have been performed on the model system N,N,O-trimethylhydroxylamine using MNDO calculations.[17]

Table 2. HOMO-LUMO Energies of *N,N,O*-trimethylhydroxylamine.

		E (eV)	C_1	C_2
	N-HOMO	- 11.15	- 0.18	0.8
Me, Me, N, O, Me (1 2)				
	HOMO	- 10.07	0.75	- 0.26

Net charge density on oxygen atom: - 0.249; net charge density on nitrogen atom: - 0.220.

As reported in Table 1, the reaction of 2-methyl-3-*p*-chlorophenyl-5,5-diphenylisoxazolidine **2** and 2-methyl-3-*p*-tolyl-5,5-diphenylisoxazolidine **3** with aqueous 30% H_2SO_4 at reflux gave a mixture of indene **6** and **7** (relative ratio 76:20) and **8**, **9** (relative ratio 50:45) respectively. The crude reaction mixtures have been subjected to flash chromatographic separation to give pure indenes.

Formation of isomeric **7** and **9**, besides the expected **6** and **8**, and their relative distribution have been explained on the basis of the following experimental evidence.

The major isomers **6** and **8** were further reacted in 30% H_2SO_4 at reflux to give a mixture of indenes **6** and **7** and **8** and **9** respectively, in the above reported ratios.

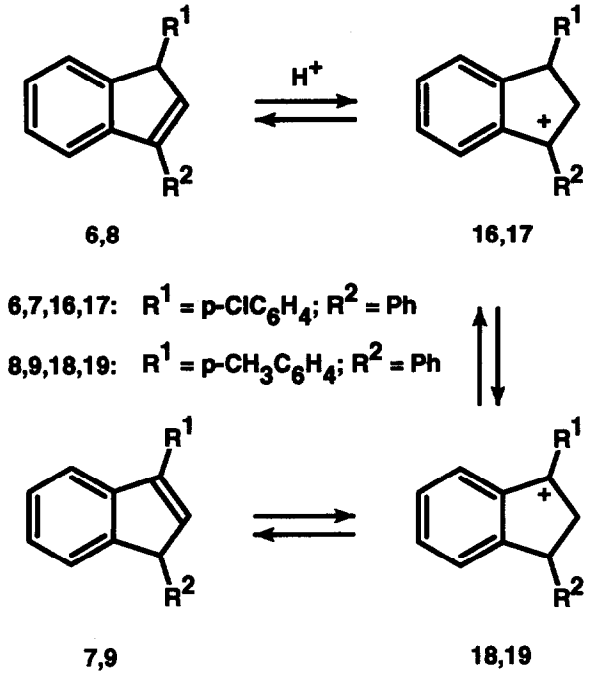
Furthermore, the analogous reaction performed with D_2SO_4 (30% in D_2O) at reflux showed the complete H/D exchange for proton at C-2.

These experimental data clearly point out that in acidic medium the initially formed indenes **6** and **8** are subsequently protonated; the so generated indanyl cations **16** and **18** equilibrate with cations **17** and **19** respectively from which formation of indenes **7** and **9** proceeds (Scheme 2).

The observed ratios **6/7** and **8/9** reflects the relative stability and hence the equilibrium position between two

indanyl cations **16**, **17** and **18**, **19**.

The rearrangement process occurs *via* a 1,3-hydride shift, as supported by deuteration labelling. No deuterium was found at C-3 as required by a mechanism involving two consecutive 1,2-hydride shifts.[13]



Scheme 2

Noteworthy, it has been reported that 1-phenyl-3-*p*-tolylindanyl cation **17** does not undergo rearrangement to 1-*p*-tolyl-3-phenylindanyl cation **19** at room temperature in H_2SO_4, despite of the greater stability of the latter with respect to the former.[13] In our experiments, the rearrangement takes place in H_2SO_4 at reflux; this experimental condition accounts for the observed increase of the rearrangement rate.

Finally, the reaction of 2-methyl-3,5-di-*p*-chlorophenylisoxazolidine **4** with H_2SO_4 at reflux afforded 1,3-di-*p*-chlorophenylindene **10**. The NMR spectrum of the crude reaction mixture rules out the presence of the isomeric 5-chloro-1-phenyl-3-*p*-chlorophenylindene.

This result is in agreement with an intramolecular electrophilic aromatic sustitution mechanism which originates by the attack of the less substituted end of the allylic cation onto the more activated aromatic ring.

In conclusion, acidic treatment of 5,5-diarylsubstituted isoxazolidines affords an easy entry to 1,3-diarylindenes. The validity of this synthetic approach relies on the availability of isoxazolidine precursors, easily accessible by 1,3-dipolar cycloaddition of nitrones to suitably substituted alkenes.

EXPERIMENTAL

M.p.s. were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed

with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 225 spectrophotometer and ^{1}H NMR on Bruker WP 200 SY instrument; chemical shifts are reported in ppm from internal Me_4Si and refer to $CDCl_3$ solution. Mass spectra were determined on a Varian Mat CH-5 DF and GC-MS HP 5859 A instruments. Reaction mixtures were analyzed by t.l.c. on silica gel GF 254 (Merck) and the spots were detected under UV light (254 nm). Flash chromatography was carried out with Kieselgel. The substituted isoxazolidines used have been already reported in literature.[12,18]

Ring-opening Reactions of Isoxazolidines 1-4 with 30% Aqueous H_2SO_4.

General procedure. A solution of isoxazolidine (1 mmol) and 25 ml of aqueous H_2SO_4 (30%) was stirred at reflux temperature for 4 h. The solution was then cooled and extracted with ether. The organic layer was washed with saturated aqueous sodium carbonate solution, dried over $MgSO_4$ and concentrated under reduced pressure to give a residue which was subjected to silica gel chromatography, using an ethyl ether/hexane 55:45 mixture as eluent.

Reaction of isoxazolidine **1** *with H_2SO_4.* First fractions gave *1,3-diphenylindene* **5**, 75% yield; m.p. 70-71°C (lit.,[18] 69-70° C); ν_{max} 3036- 3020, 1940, 1590, 1440, 1070, 1030, 740, 690 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 4.70 (d, 1H, H_3, J= 3.0 Hz), 6.65 (d, 1H, H_2, J= 3.0 Hz), 7.10-7-70 (m, 14H, Ar-H). MS: m/z 268 (M^+, 100). (Found: C, 93.92; H, 6.07%. Calc. for $C_{21}H_{16}$: C, 93.99; H, 6.01%).

Reaction of isoxazolidine **2** *with H_2SO_4.* First eluted product was *1- phenyl-3-p-chlorophenylindene* **6**, 76% yield; m.p. 74-75° C; ν_{max} 3040-3020, 1490, 1460-1440, 1080, 1020, 830, 770, 740, 700 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 4.66 (d, 1H, H_3, J= 4.0 Hz), 6.00 (d, 1H, H_2, J= 4.0 Hz), 7.12-7-73 (m, 13H, Ar-H). MS:[19] m/z 302 (M^+, 100). (Found: C, 83.35; H, 5.01; Cl 11.76%. Calc. for $C_{21}H_{15}Cl$: C, 83.30; H, 4.99; Cl, 11.71%). Further elution gave *1-p-chlorophenyl-3-phenylindene* **7**, 20% yield; mp 68-70° C; ν_{max} 3040-3020, 1490, 1460-1430, 1070, 1025, 830, 770, 740, 700 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 4.70 (d, 1H, H_3, J= 3.0 Hz), 6.65 (d, 1H, H_2, J= 3.0 Hz), 7.10-7-70 (m, 13H, Ar-H). MS:[19] 302 (M^+, 100). (Found: C, 83.32; H, 4.97; Cl, 11.67%. Calc. for $C_{21}H_{15}Cl$: C, 83.30; H, 4.99; Cl, 11.71%).

Reaction of isoxazolidine **3** *with H_2SO_4.* First eluted product was *1-phenyl-3-p-tolylphenylindene* **8**, 50% yield; m.p. 58-60° C; ν_{max} 3030-3010, 2910, 1640, 1580, 1500-1440, 1270, 1010, 930, 820, 760, 740, 700 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 2.32 (s, 3H, Ar-CH_3), 5.66 (d, 1H, H_3, J= 4.1 Hz), 6.63 (d, 1H, H_2, J= 4.1 Hz), 7.02-7.63 (m, 13H, Ar-H). MS: m/z 282 (M^+, 100). (Found: C, 93.53; H, 6.38%. Calc. for $C_{22}H_{18}$: C, 93.57; H, 6.42%). Further elution gave *1-p-tolylphenyl-3-phenylindene* **9**, 45% yield; m.p. 60-62° C; ν_{max} 3030-3010, 1490, 1460, 1450, 1440, 1180, 1020, 830, 760, 750, 700 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 2.43 (s, 3H, Ar-CH_3), 5.70 (d, 1H, H_3, J= 4.1 Hz), 6.66 (d, 1H, H_2, J= 4.1 Hz), 7.00-7-68 (m, 13H, Ar-H). MS: m/z 282 (M^+, 100). (Found: C, 93.52; H, 6.37%. Calc. for $C_{22}H_{18}$: C, 93.57; H, 6.42%).

Reaction of isoxazolidine **4** *with H_2SO_4.* First fractions gave *1,3- di-p-chlorophenylindene* **10**, 70% yield; m.p. 68-70° C; ν_{max} 3030-3020, 2910, 2830, 1460, 1440, 1380, 1330, 1170, 1080, 1010, 870, 840, 820, 780, 750, 740, 730, 710 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 4.69 (d, 1H, H_3, J= 4.5 Hz), 6.64 (d, 1H, H_2, J= 4.5 Hz), 7.62-7.06 (m, 12H, Ar-H) MS:[19] m/z 337 (M^+, 52), 105 (100). (Found: C, 74.73; H, 4.15, Cl, 21.00%. Calc. for $C_{21}H_{14}Cl_2$: C, 74.79; H, 4.18; Cl, 21.02%).

Reaction of 1-p-chlorophenyl-3-phenylindene **7** *with D_2SO_4 (30%).* A solution of 50 mg of **7** and 2 ml of D_2SO_4 (30%) in D_2O was stirred for 4 h at reflux temperature. After usual work-up the crude NMR showed complete deuteration at C_2. ^{1}H NMR: δ ($CDCl_3$) 4.65 (s), 4.70 (s), 7.10-7.73 (m). MS:[19] m/z 303 (M^+, 100).

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