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A New Convenient Synthesis of Δ^2-Isoxazolines

Short Communication

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Δ^2-Isoxazolines were obtained from the reaction of alkenes with nitrile N-oxides, generated *in situ* from primary nitroalkane salts in presence of toluenesulfonyl chloride.

(Keywords: Isoxazolines; Nitrile-N-oxides)

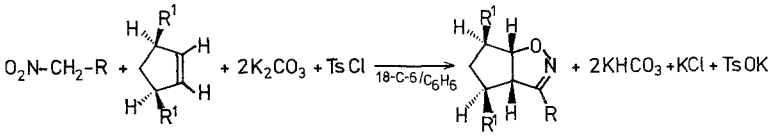
Eine neue, vorteilhafte Synthese von Δ^2-*Isoxazolinen* (*Kurze Mitteilung*)

Aus der Reaktion von Alkenen mit Nitril-N-oxiden, die *in situ* aus primären Nitroalkansalzen in Gegenwart von Toluolsulfonylchlorid erzeugt wurden, wurden Δ^2-Isoxazoline erhalten.

Δ^2-Isoxazolines are useful substrates in the synthesis of complex organic molecules[1]. They can be obtained directly in 1,3-dipolar cycloaddition of nitrile N-oxides and alkenes[2], or in a two step procedure using alkenes and O-silyl nitronates[3]. It is well known that dehydrating agents such as isocyanates, $POCl_3$, etc., can generate nitrile N-oxides from primary nitroalkanes with good to moderate yields[4].

We describe now the use of toluenesulfonyl chloride, potassium carbonate/18-crown-6 system for the conversion of primary nitroalkanes into nitrile N-oxides (Scheme 1) with satisfactory yields.

Scheme 1



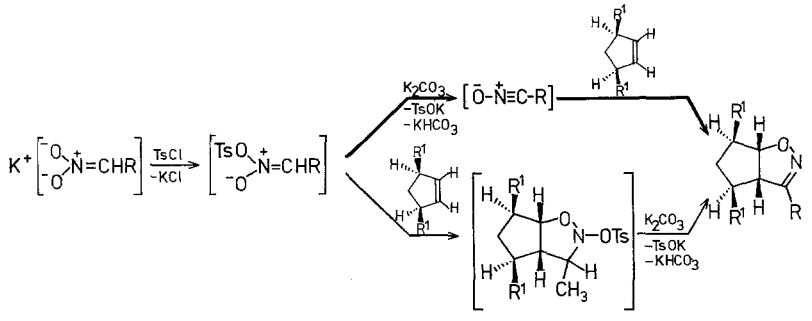
If the reaction is carried out in the presence of cyclopentene or *cis*-1,3-diacetoxycyclopent-4-ene, Δ^2-isoxazolines **3** are formed with satisfactory yields (Table 1). In a typical experiment the toluene solution of equimolar amounts of nitroalkane **1**, toluenesulfonyl chloride and alkene **2** is stirred for 4–6 hours at 60–65 °C with a two-fold molar excess of potassium carbonate and catalytical amount of 18-crown-6.

The simple separation of the Δ^2-isoxazoline **3** formed (dissolved in toluene) from solid (watersoluble) by-products is the main advantage of our method over known methods of Δ^2-isoxazoline preparation.

The method is especially useful in the case of Δ^2-isoxazolines which cannot be purified by distillation. The yields of the Δ^2-isoxazolines **3d–f** obtained by the route described were ~10% higher than under *Mukaiyama's* conditions[2]. All spectral data for the newly synthesized compounds **3c–f** were consistent with the proposed structures.

The method works very well on a small scale. All observations let us assume that the formation of Δ^2-isoxazolines proceeds via the addition of nitrile N-oxides with alkenes rather than through the addition of O-tosylnitronates with alkenes, followed by elimination of the toluenesulfonic acid anion from the adduct under the action of a base (Scheme 2).

Scheme 2



We attempted to separate O-tosylnitronate or the adduct under different reaction conditions, for example: using triethylamine or potassium *tert*-butoxide for the generation of the nitronate anion in the presence or absence of the alkene, but always only Δ^2-isoxazolines or furoxane were detected. The mechanism and the scope and limitation of the Δ^2-isoxazoline formation reaction and the use of **3e** and **3f** in the synthesis of prostaglandine F analogues is still under investigation.

Acknowledgement

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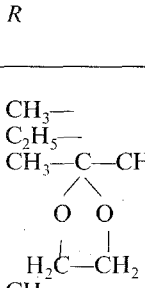
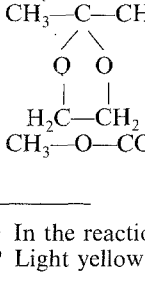
Table 1. *Preparation of* Δ^2*-Isoxazolines*

	R	R^1	Yield (%)	**3** B. p. °C/mm Hg	(Lit. b. p.)
a	CH_3—	H—	62.5	50/0.3	(53.5–55/0.3[5])
b	C_2H_5—	H—	54.2	74–75/1.1	(50–60/0.7[6])
c		H—	64	125–128/0.6	
d[a]	CH_3—	CH_3—CO—O—	62	122–125/0.3	
e[a]		CH_3—CO—O—	57.3	154–157/0.05	
f[a]	CH_3—O—CO—$(CH_2)_5$—	CH_3—CO—O—	68.4	[b]	

[a] In the reactions only the "*anti*" product[7] was obtained.
[b] Light yellow oil purified by column chromatography on SiO_2 (benzene).

Selected ^{1}H *NMR spectral data for* **3** (10% $CDCl_3$ sol., *TMS*, 100 MHz) δ: **3e** (1.41 (s, 3H), 1.98–2.13 (m, 2H), 2.08 (s, 6H), 2.79 (s, 2H), 3.95 (d, 1H, J = 8.8 Hz), 3.98 (s, 4H), 5.00 (d, 1H, J = 8.8 Hz), 5.13–5.25 (m, 2H). **3f** 1.19–1.84 (m, 6H), 1.96–2.14 (m, 2H), 2.06 (s, 6H), 2.18–2.56 (m, 4H), 3.57 (s, 3H), 3.73 (d, 1H, J = 8.8 Hz), 4.87 (d, 1H, J = 8.8 Hz), 5.00–5.16 (m, 2H).

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