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An unexpected result in an intramolecular Ritter reaction induced by triflic anhydride

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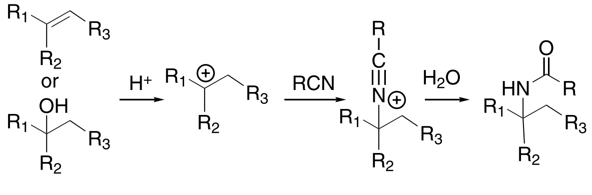
Abstract—The treatment of the methyl 2-(cyanoethyl)-1-hydroxy-2-indane-carboxylate **1b** in dichloromethane solution with triflic anhydride at 20°C afforded the tricyclic enone **3** in 65% yield, instead of the expected lactam **2b** produced under the 'classic' conditions of the Ritter reaction.

In 1948, Ritter and Minieri reported that the reaction of alkenes with nitriles in the presence of concentrated sulfuric acid yields an amide by simple dilution with water.[1] Since alcohols can also be used as substrates instead of the alkenes, the Ritter reaction provides a particularly versatile synthetic method for the preparation of a variety of amides (Scheme 1).[2,3]

Several alternative methodologies were later developed for the Ritter reaction[4–9] and very recently, the use of *tert*-butyl acetate, as a non-alcoholic source of *tert*-butyl cation, in presence of a catalytic amount of sulfuric acid as the proton source, have been reported.[10]

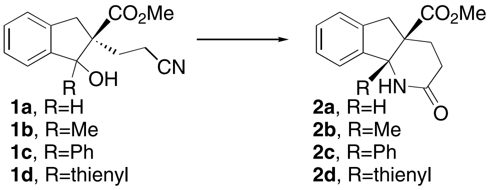
The Ritter reaction was applied to the enantiospecific synthesis of 3-aza-bicyclic compounds using chiral terpenes,[11] to the chiral synthesis of *cis* aminoindanol[12] and also a safe procedure for the preparation of acrylamides has been scaled up.[13]



Scheme 1.

Our primary interest in this research project resulted from some initial students investigations in the mechanism of the Ritter reaction[14] followed by the analysis of the reaction induced by triflic anhydride in dichloromethane solution,[7] to control the Wagner–Meerwein rearrangement that undergoes an α-isopropylbenzyl alcohol.[15]

Later on and in view that no publications on intramolecular Ritter reactions induced by triflic anhydride were reported in the literature, it seemed to us interesting to analyze, under these conditions, a specific example that had been studied under 'classic' conditions.



1a, R=H
1b, R=Me
1c, R=Ph
1d, R=thienyl

2a, R=H
2b, R=Me
2c, R=Ph
2d, R=thienyl

Recently Compernolle et al.[16] reported the intramolecular Ritter reactions of several methyl 2-(cyanoethyl)-1-hydroxy-2-indane-carboxylates **1**, using various acid reaction conditions, for the synthesis of the tricyclic lactams **2**.

It seemed to us that the analysis of the reactivity of the substrates described by Compernolle et al.[16] under conditions induced by triflic anhydride was an ideal case for the comparison of both type of reaction conditions. Our first choice was to work with substrate **1b**. This

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Keywords: intramolecular Ritter reaction; triflic anhydride; enone.

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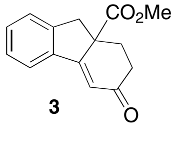
substrate is readily prepared and is obtained with a very high diastereoisomeric excess and furthermore, it is surprising that the acid treatment of **1b** to give lactam **2b**, required a considerable difference in heating time (23 h) in comparison with the transformation of **1a** into **2a** (4 h). Since it is known that allylic alcohols in dichloromethane solution afford allyl cations upon treatment with triflic anhydride[17] we therefore expected to obtain lactam **2b** under milder conditions than those previously described.

However, when a solution of **1b** in dichloromethane was subjected to the treatment with triflic anhydride at room temperature no lactam **2b** was formed, instead, the tricyclic α,β-unsaturated ketone **3**[18] was isolated in 65% yield.



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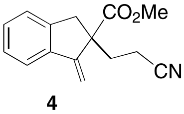

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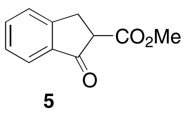

5

The analysis of the transformation of **1b** into **3** by ^{1}H NMR in $CDCl_3$ solution showed that immediately after the addition of triflic anhydride, the signals at δ 5.68 and 5.18 attributed to alkene **4** were observed. Under these conditions, **1b** is readily dehydrated giving exclusively **4**. After 40 min, three new signals at δ 7.06, 9.84 and 9.99 started to appear, indicating the presence of a three substituted double bond conjugated with a protonated imino group. During the work-up the imino group was hydrolyzed giving the α,β-unsaturated enone moiety present in **3**. Undoubtedly, the formation of **3** is the result of the addition of the nitrile carbon atom across the olefinic linkage instead of the normal addition of the nitrile to the intermediate carbonium ion to produce the lactam.

To the best of our knowledge, the report of Hill et al.[19] in which they described an unusual intramolecular Ritter reaction of unsaturated nitriles that gave α,β-unsaturated enones, on treatment with polyphosphoric acid at 120–130°C, is the only publication related to this transformation.

Interestingly, tricyclic **3** is structurally equivalent to the Robinson annulation product of the β-keto ester **5**[16] with methylvinylketone.

Work is in progress to study the scope and limitations of this interesting variant of the intramolecular Ritter reaction induced by triflic anhydride, a promising reaction for accessing six–five–six fused-ring structures.[20]

Acknowledgements

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18. To a stirred solution of triflic anhydride (0.14 mL, 0.85 mmol) in anhydrous CH_2Cl_2 (5 mL) at 20°C a solution of **1b** (220 mg, 0.85 mmol) in CH_2Cl_2 (3 mL) was slowly added. After 4 h of stirring an aqueous saturated solution of $NaHCO_3$ was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue (188 mg) was purified by column chromatography (silica gel, hexane–EtAcO) to give **3** (132 mg, 65%) as a crystalline solid, mp 127.4–128.1°C, ^{1}H NMR δ: 7.63–7.59 (m, Ar, 1H), 7.38–7.33 (m, Ar, 3H), 6.30 (s, 1H) 3.63 (s, 3H), 3.57 (d, $J=16.5$ Hz, 1H), 3.04 (d, $J=16.5$ Hz, 1H), 2.76 (dt, $J=12.5$ and 3.5 Hz, 1H), 2.57–2.50 (m, 2H), 2.23–2.08 (m, 1H). ^{13}C NMR δ: 198.32 (CO), 173.59 (CO) 164.19 (s), 145.43 (s), 137.88 (s), 131.68 (d), 127.54 (d), 125.13 (d), 122.67 (d), 118.91 (d), 54.28 (s), 52.59 (q), 42.85 (t), 34.93 (t), 32.71 (t). HRMS calcd for $C_{15}H_{14}O_3$ (M^+): 242.0943, found: 242.0939.
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