Unusual Ring Expansion observed during the Dakin–West Reaction of Tetrahydroisoquinoline-1-carboxylic Acids using Trifluoroacetic Anhydride: an Expedient Synthesis of 3-Benzazepine Derivatives bearing a Trifluoromethyl Group

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The reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids with trifluoroacetic anhydride proceeds through mesoionic 1,3-oxazol-5-one intermediates followed by ring expansion to form 2-trifluoromethyltetrahydro-3-benzazepinone derivatives in good yields.

The 3-benzazepine ring system has long been of interest to a variety of investigators because of the physiological effects of certain of its derivatives[1] and because it is the basic ring system of various alkaloids.[2] Although several synthetic routes to 3-benzazepines have been reported in order to develop central nervous system and cardiovascular pharmaceutical agents,[3] syntheses of 3-benzazepines with a trifluoromethyl group on the azepine unit have not been reported. From a biological point of view, trifluoromethyl substitution often confers unique properties to a molecule in terms of increased lipophilicity, which in turn changes *in vivo* absorption and transport rates.

We have already described[4] the autoxidation of intermediary mesoionic 1,3-oxazol-5-ones obtained from a number of *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids **1** and *N*,*N*′-dicyclohexylcarbodiimide (DCC). In continuing this study, we have now found that the use of trifluoroacetic anhydride (TFAA) instead of DCC leads to a new, preparatively useful synthesis of tetrahydro-3-benzazepinone derivatives bearing a trifluoromethyl group.

Thus, treatment of **1a** (1 mmol) with TFAA (5 mmol) in benzene (5 ml) containing pyridine (10 mmol) at 20 °C for 12 h gave rise to the 3-benzazepine **2a** in 98% yield. Pyridine was not essential, but the absence of base lowered the yield (48%). 5 equiv. of TFAA with respect to **1a** were needed to obtain a high yield of **2a**, the use of 3 equiv. reducing the yield (50%). The structure of **2a** was determined from spectral and analytical data. The precise assignments of the carbon signals in **2a** were performed by ^{1}H–^{13}C shift correlated 2D NMR (COSY) and ^{1}H–^{13}C long-range COSY (COLOC) spectral analysis.† In particular, the carbonyl carbon signal at δ 158.83 was correlated with the 9-H signal at δ 7.61 in the COLOC spectrum ($^{3}J_{C-H}$). Therefore, the carbonyl group must be located at C–1.

Variation of the *N*-acyl groups was briefly examined and it became obvious that the nature of N-substituents influenced

† For **2a**: ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 9H, Bu^t), 2.67–2.74 (m, 2H, 5-H_2), 3.62–3.74 (m, 1H, 4-H^a), 3.85–3.96 (m, 1H, 4-H^b), 6.28 (q, *J* 6.9 Hz, 1H, 2-H), 7.20 (d, *J* 7.3 Hz, 1H, 6-H), 7.34 (dt, *J* 1.4, 7.3 Hz, 1H, 7-H), 7.36 (dt, *J* 1.4, 7.3 Hz, 1H, 8-H) and 7.61 (d, *J* 7.3 Hz, 1H, 9-H); ^{13}C NMR ($CDCl_3$): δ 25.62 (t, C-5), 26.86 (q, 3 × Me), 38.84 (s, CMe_3), 47.33 (t, C-4), 70.89 (dq, $^{2}J_{C,H}$ 32.4 Hz, C-2), 122.99 (q, $J_{C,H}$ 277.8 Hz, CF_3), 125.03 (d, C-9), 126.74 (s, C-5a), 127.03 (d, C-7), 127.80 (d, C-6), 131.36 (d, C-8), 137.36 (s, C-9a), 158.83 (s, C-1) and 176.46 (s, $COBu^t$).

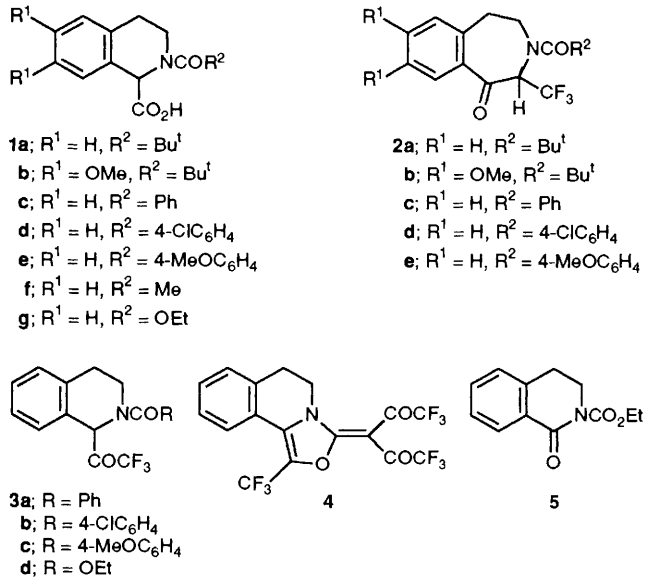


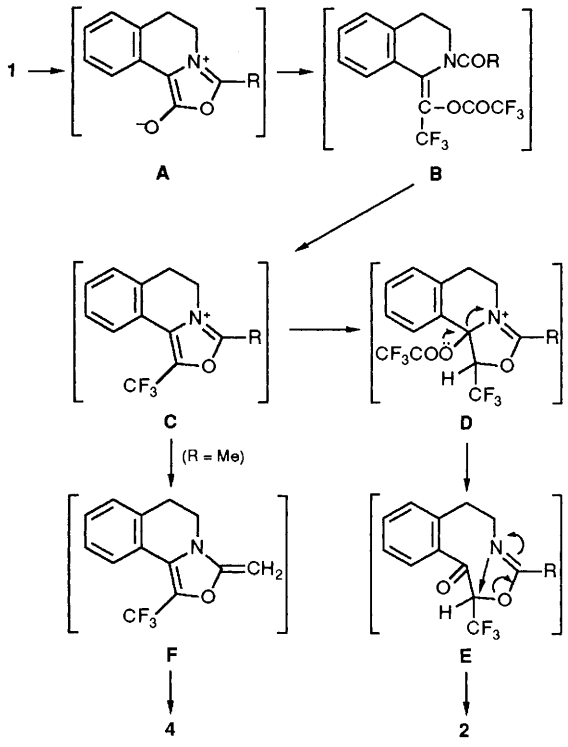
Table 1 Reactions of carboxylic acids with TFAA[a]

Entry	Starting material	Product (% yield)[b]	M.p. or b.p.,*t*/°C[c] (*p*/mmHg)	^{13}C NMR δ_C (C=O)	
1	**1a**	**2a** (98)	150 (3)	158.83	176.46
2	**1b**	**2b** (92)	62–63	158.20	176.45
3	**1c**	**2c** (61)[d]	185 (2)	158.72	164.67
4	**1d**	**2d** (58)[e]	185 (1)	158.50	163.87
5	**1e**	**2e** (52)[f]	91–92	158.88	164.22
6	**1f**	**4** (28)	174–176	175.12 (q, *J* 36.1 Hz)	
7	**1g**	**3d** (61)[g]	135 (1)	156.24	189.32

[a] The reactions were carried out according to the general procedure described in the text. All new compounds have satisfactory spectroscopic data and elemental analyses. [b] Isolated yields of pure products. [c] B.p. refers to the bath temperature in a 'Kugelrohr' apparatus. [d] Plus 28% of **3a**, m.p. 131–132 °C. [e] Plus 15% of **3b**, b.p. 150 °C (bath temp.) at 1 mmHg. [f] Plus 24% of **3c**, m.p. 114–115 °C. [g] Plus 17% of **5**, b.p., 145 °C (bath temp.) at 1 mmHg, an autoxidation product of intermediate **A** (R = CO_2Et).[4]

the reaction. As shown in Table 1, *N*-acyl derivatives **1a–e**, containing pivaloyl or benzoyl groups, were easily transformed to the 3-benzazepines **2a–e** in good yields. In the case of *N*-benzoyl derivatives **1c–e**, small amounts of the 1-trifluoroacetyl-tetrahydroisoquinolines **3a–c**, respectively, were obtained as by-products. The *N*-acetyl derivative **1f** afforded not the expected 3-benzazepine derivative but the oxazoline **4**, whose structure was confirmed by spectral and analytical data.

Clues to the possible mechanism of this reaction are provided by the isolation of **3**, a product of the Dakin–West reaction,[5] and **4**. It was also observed that **3a** yielded the 3-benzazepine **2c** in 56% yield under the same reaction condition as **1c**. A plausible mechanism is shown in Scheme 1. This reaction involves a mesoionic 1,3-oxazol-5-one **A** formed through the cyclodehydration of **1** by TFAA. Intermediate **A** undergoes trifluoroacetylation followed by decarboxylation to give the enol trifluoroacetate **B** which is an enol form of **3**; a similar mechanism has been postulated in the Dakin–West reaction.[5] Cyclization of **B** gives the oxazolinium salt **C** whose existence is supported by the isolation of **4** in the reaction of **1f**. Intermediate **C** (R = Me), bearing α-hydrogens, isomerizes to **F** which undergoes trifluoroacetylation. A similar type of



Scheme 1 Possible mechanism

bistrifluoroacetylation has been reported in the reaction of other vinyl ethers with TFAA in the presence of pyridine.[6] It is difficult to find a definitive explanation for the ring expansion of **C** to **2**. However, as the R groups do not possess α-hydrogens, the isomerization of **C** is no longer possible. It is postulated that the ring expansion of **C** proceeds *via* oxazoline salt **D**, formed by the addition of trifluoroacetic acid, in a concerted fashion as shown in **E** leading to the azepine **2**. A similar ring expansion was postulated in the oxidative rearrangement of naturally occurring oxyberberine into chilenine, an isoindolobenzazepine alkaloid.[7]

In summary, the reaction offers a unique and attractive synthesis of 3-benzazepine derivatives with a trifluoromethyl group α to nitrogen by a novel rearrangement, making these compounds easily accessible from readily available precursors.[4] The details of the mechanism of the ring expansion are currently under investigation.

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