SYNTHESIS OF FUNCTIONALIZED PYRROLIDINES FROM MESOIONIC 4-TRIFLUOROACETYL-1,3-OXAZOLIUM-5-OLATES AND AMINOMALONATE

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Abstract – Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) undergo tandem addition of aminomalonate to afford 3-amido-4-trifluoromethylpyrrolidin-2-ones (**2**) in moderate yields.

During the last two decades the synthesis of trifluoromethyl-substituted compounds has become an important issue in organic chemistry.[1] The building block strategy for synthesis of trifluoromethylated compounds is now the subject of active investigation because selective trifluoromethylation of the target molecules is difficult at a late stage in the synthesis.[2] Recently, we focused on mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) as useful synthons for trifluoromethyl-substituted heterocycles such as imidazoles, pyrazoles, and triazines.[3] In line with this continuing interest, mesoionic oxazoles (**1**) were found to condense with diethyl aminomalonate in refluxing acetic acid to give 3-amino-4-trifluoromethylpyrrolidinones (**2**) in moderate yields. Thus, with the nucleophile, the tandem addition to the C-5 position of the mesoionic ring and to the trifluoromethyl ketone yielded highly substituted pyrrolidines (**2**).

Treatment of **1a** (1 mmol) with diethyl aminomalonate· HCl (3 mmol) and NaOAc (3 mmol) in AcOH (5 mL) at 130 °C for 12 h gave rise to **2a** (62% yield). Several mesoionic **1** reacted in this way and the results are presented in Table 1. In the case of **1b**, 1,5-dihydro-2*H*-pyrrol-2-one (**3b**) was also isolated, in 30% yield, which might be formed *via* dehydration of **2b**. Treatment of **2b** and **3b** with Ac_2O in the presence of pyridine afforded the same **4b** in 89% and 72% yields, respectively. In the case of **1c**, the product (**2c**) could not be purified by column chromatography because **2c** has almost the same polarity as diethyl *N*-acetylaminomalonate formed by the acetylation of diethyl aminomalonate during the reaction. The yield of **2c** was estimated, from the ^{1}H NMR spectrum of the mixture, to be 51%. The

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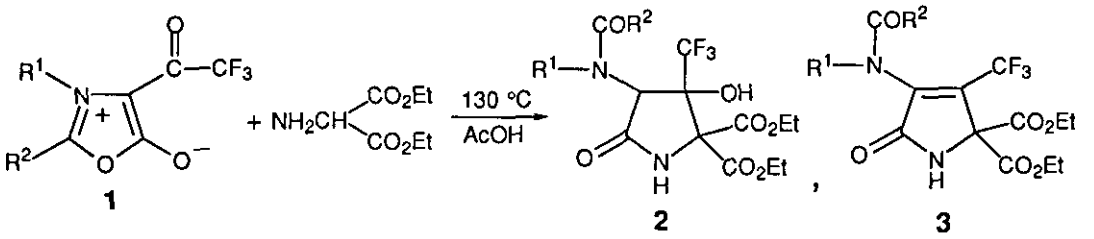
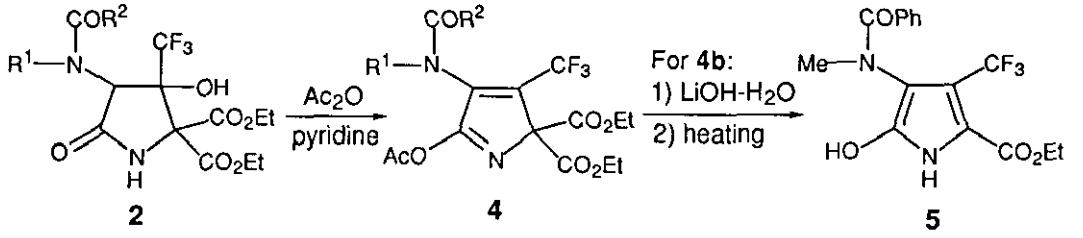
Table1. Reaction of mesoionic compounds (**1**) and aminomalonate



Run	**1**	R^1	R^2	Product, % yield **2**	**3**
1	**a**	Ph	Ph	62	-
2	**b**	Me	Ph	17	30
3	**c**	Me	4-$MeOC_6H_4$	51[a]	-
4	**d**	Ph	Me	44	-
5	**e**	Bn	Me	48	-

[a] The yield was estimated by ^1H NMR due to contamination of *N*-acetylamino-malonate and acetylation of the mixture gave pure **4c** in 47% yield.



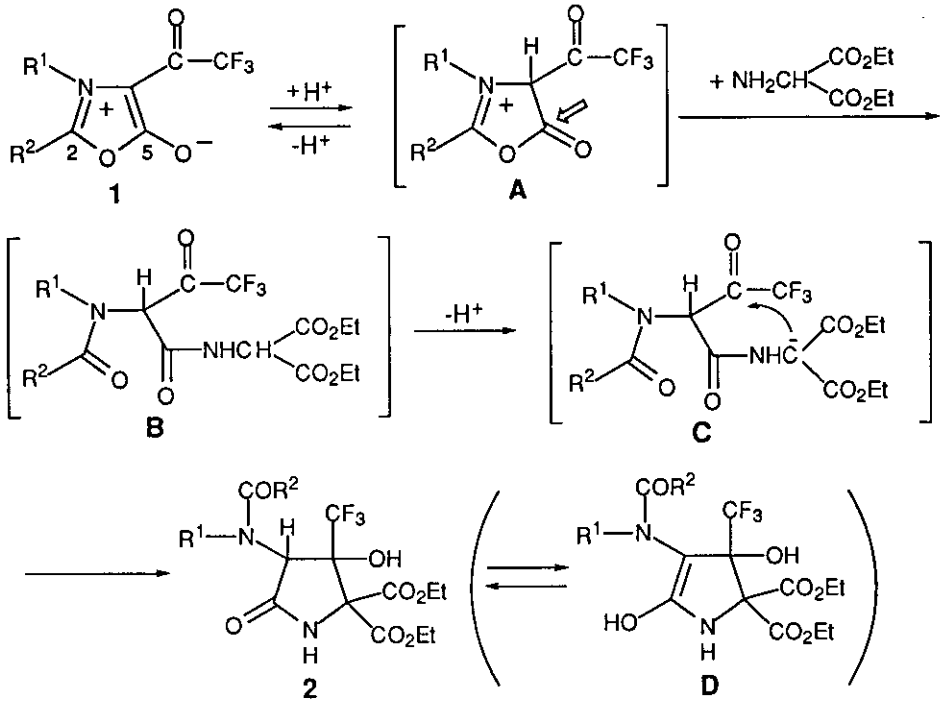
2b: R^1=Me, R^2=Ph **4b**: R^1=Me, R^2=Ph

2c: R^1=Me, R^2=4-$MeOC_6H_4$ **4c**: R^1=Me, R^2=4-$MeOC_6H_4$

mixture was acetylated with Ac_2O/pyridine and the pure **4c** was isolated in 47% yield. Attempts to condense **1** with ethyl glycinate or *N*-methylglycinate were unsuccessful. The failure of these reactions can be attributed to the weakness of the nucleophilic character of the methylene carbon of the glycine. The successful condensation of aminomalonate must be due to the highly acidic methylene group.

The use of an aprotic solvent such as DMF and benzene did not give any characterized product, but led to complete destruction of the munchnone ring system. The critical role of AcOH as the solvent may be due to its function as a proton donor to the mesoionic **1** and the equilibrium from the mesoionic form (**1**) to the keto form (**A**) may be favored.

This highly substituted pyrrolidine (**4a**) could be converted into the corresponding pyrrole ester (**5**) in 51% yield by treatment with LiOH-H_2O-THF followed by heating in refluxing toluene.



Scheme 1

Structures of all compounds were confirmed by elemental analyses, ^{1}H- and ^{13}C-NMR, MS, and IR spectroscopy.[4] The product (**2**) is a single isomer due to the keto-enol tautomerism (**2** ⇄ **D** in Scheme 1). However, the stereochemistry of **2** has not yet been determined.

A plausible mechanism for the formation of **2** is illustrated in Scheme 1. Mesoionic **1** is probably in equilibrium with the keto form (**A**) in the polar protic solvent. Then, the amino group of aminomalonate would attack at the carbonyl of **A** to give an adduct (**B**). Deprotonation of **B** affords an anion (**C**). Subsequently, intramolecular cyclization of **C** leads to the product (**2**).

In our previous work, *N*-nucleophiles such as ammonia,[3b] amidines,[3a] and phenylhydrazine[3c] usually attacked at the C-2 position of **1** in polar aprotic solvent DMF. The site was changed in the aprotic solvent. In the reaction of **1** with phenylhydrazine in refluxing benzene, the attacking position is C-5 of **1**, because the mesoionic **1** is in equilibrium with the trifluoroacetylketene in which the ketene carbony is attacked by phenylhydrazine. However, in the polar protic solvent, mesoionic **1** is in equilibrium with the keto form (**A**) and the attacking position is C-5 of **1**.

Recently, functionalized pyrrolidinones have attracted considerable interest, principally because of the wide-ranging biological activity of this class of compounds.[5] Some of them are psychotropic agents, muscarinic acid antagonists, and antihypertensive agents.[5f] Especially, 3-amino-γ-lactams are of interest as the conformationally restricted dipeptide mimics for the study of the relationship between biological activity and peptide structures.[6]

The reported new cyclization reaction of mesoionic oxazoles (**1**) with aminomalonate extended the scope of the use of fluorinated synthons (**1**) in the synthesis of new heterocycles. The reaction is practical since the starting materials (**1**) are readily available from α-amino acids and the reaction procedure is operationally simple.

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4. All new compounds exhibited IR, ^{1}H- and ^{13}C-NMR spectra, MS spectral or combustion data in agreement with the structures indicated. For **2a**: mp 155-158 °C (Et_2O-hexane), Anal. Calcd for $C_{24}H_{23}N_2O_7F_3$: C, 56.69; H, 4.56; N, 5.51. Found: C, 56.79; H, 4.63; N, 5.48. MS m/z 508 (M^+, 44), 105 (100); IR υ_{max}/nujol (cm^{-1}) 1620, 1740, 1760, 3100, 3200; ^{1}H NMR δ 1.24 (t, 3H, *J*=7.0), 1.34 (t, 3H, *J*=7.0), 4.22 (q, 2H, *J*=7.0), 4.38 (q, 2H, *J*=7.0), 5.03 (s, 1H), 7.10-7.30 (m, 6H), 7.14 (t, 2H, *J*=7.6), 7.32 (t, 2H, *J*=7.6), 7.40 (s, 1H), 8.72 (s, 1H); ^{13}C NMR δ 13.5 (CH_3), 13.6 (CH_3), 63.0 (CH_2), 63.6 (CH_2), 68.6 (CH), 83.3 (CH, $^2J_{CF}$=31.0), 123.0 (CF_3, $^1J_{CF}$=285.5), 126.5 (CH), 127.7 (CH), 127.7 (CH), 129.0 (CH), 129.4 (CH), 130.7 (CH), 133.4 (C), 143.8 (C), 164.2 (C), 165.9 (C), 166.9 (C), 175.3 (C).
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