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An efficient and selective route to hybrid trifluoromethyl-substituted γ-lactones or fused nitrogen derivatives via cascade reactions

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ABSTRACT

A straightforward, efficient and selective route for obtaining hybrid trifluoromethyl-substituted γ-lactones and fused nitrogen heterocycles is presented. The reaction could be guided either to γ-lactones with a nitrogen-containing heterocyclic skeleton (for monocyclic systems) or to fused nitrogen heterocycles (for fused bicyclic systems). A new class of γ-lactone with a nitrogen heterocyclic skeleton was obtained. Feasible reaction mechanisms involving cascade reactions are presented.

Pyridazine derivatives have been reported to display a wide range of biological effects; these include activities against viruses (including anti-HIV),[1] cancer,[2] cardiovascular disorders,[3] bacteria, fungi and tuberculosis, as well as anti-inflammatory[4] and other activities.[5] Similarly, fluorine-containing compounds currently feature significantly in the provision of anti-HIV,[6] antiviral and anticancer,[7] antibacterial and antifungal[8] medicines.

One of the strategies adopted for the synthesis of pyridazine derivatives involves nitrogen ylides as reactive species.[4a,c,5,9–11] The reaction pathway involves a Huisgen [3+2] dipolar cycloaddition of ylides to dipolarophiles (activated alkenes and alkynes).

One of our goals is to synthesize a hybrid pyridazine–fluorine moiety, in order to combine their respective biological potentials. As a part of our work in this field,[4,5,11] we report here our results concerning the cycloaddition reactions of diazinium ylides with 2-(trifluoromethyl) acrylic acid.

Pyridazinium ylides **2** (generated in situ from the corresponding cycloimmonium salts **1**, were treated with 2-(trifluoromethyl)acrylic acid (Scheme 1). Unexpectedly, instead of the fused pyridazine **3**, we obtained a new class of organic compounds: fused γ-lactones with nitrogen heterocyclic skeletons, type **4** and **5**. Two stereoisomers were obtained, the reaction being stereoselective (**4** is the major product).

The structures of γ-lactones **4** and **5** were proved by elemental and spectral analyses (IR, ^{1}H NMR, ^{13}C NMR, and two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) and finally single crystal X-ray structure determinations (Figs. 1 and 2).[12]

The mechanism for the formation of γ-lactones **4** and **5** can be explained via a cascade reaction (Scheme 2). Initially, a typical 3+2 dipolar cycloaddition takes place, leading to the intermediate compounds $\boldsymbol{i_a}$. Because of the powerful electronegativity of the CF_3 group, the hydrogen atom from the carboxylic group becomes very acidic and protonate the double bonded nitrogen atom, leading to the tautomeric form $\boldsymbol{i_b}$. A nucleophilic attack of the negative oxygen (from the carboxylate group) to the adjacent endocyclic carbocation is leading to the γ-lactones $\boldsymbol{ii_a}$, which undergoes a subsequent tautomeric rearrangement to $\boldsymbol{ii_b}$.

In order to ascertain if this is a general behaviour for the six-membered nitrogen heterocycles, and whether compounds similar to the γ-lactones **4** and **5** are formed in the related cases, we repeated the reactions with other nitrogen heterocycles. Thus, in the pyrimidine series, when pyrimidinium ylides **7** were treated with 2-(trifluoromethyl) acrylic acid, γ-lactone **8** was obtained, with a structure analogous to lactone **4** (Scheme 3). A single stereoisomer is obtained, the reaction being stereospecific. The mechanistic considerations as for the pyridazine system probably remain valid.

In the case of the fused benzo-pyridazine, phthalazine, the results were different. The reaction starts as a classical [3+2] dipolar

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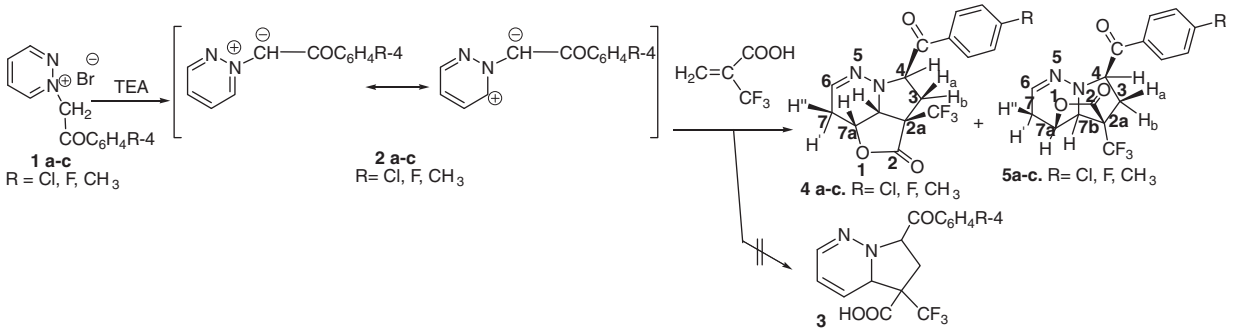


Scheme 1. Reaction pathway to γ-lactones with nitrogen heterocyclic skeleton.

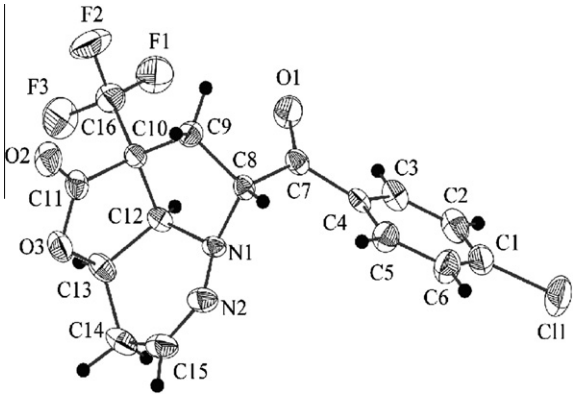


Figure 1. The ORTEP diagram of compound **4a** including atom numbering scheme.

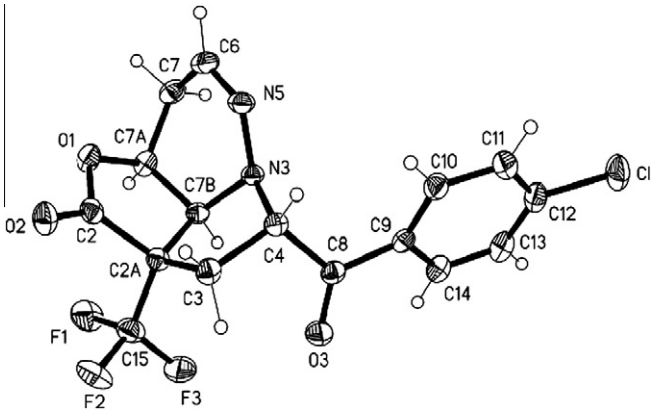


Figure 2. The ORTEP diagram of compound **5a** including atom numbering scheme.

cycloaddition of phthalazinium ylide **9** to the dipolarophile, and finally the aromatized pyrrolophthalazine compounds **12** were obtained (Scheme 4).

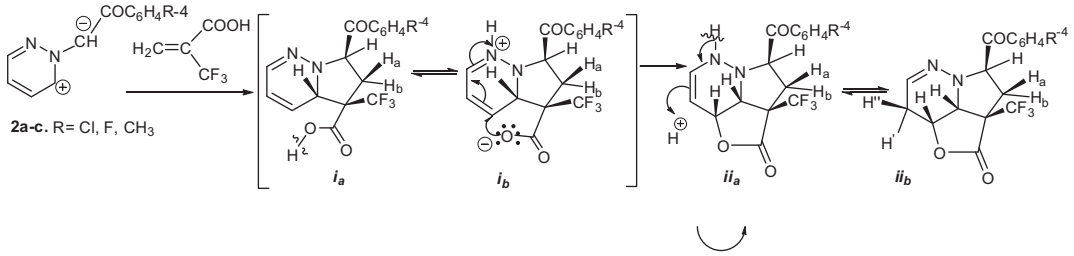
The structures of compound **12** were proved by elemental and spectral (IR, ^{1}H NMR, ^{13}C NMR, and two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) and X-ray analyses (Fig. 3).

Concerning the reaction mechanism we presume that such a different behaviour is related to the influence of the nitrogen heterocycle. After an initial cycloaddition of ylide **9** to 2-(trifluoromethyl)acrylic acid, the formation of the γ-lactone is prevented by the benzene ring fused with pyridazine (its aromatic nature prevents canonical structures such as ***i*$_b$**). The intermediate **10** undergoes subsequent decarboxylation to the tetrahydropyrrolophthalazine **11**, which via spontaneous oxidative dehydrogenation (by air) generates the aromatized pyrrolophthalazine compound **12**.

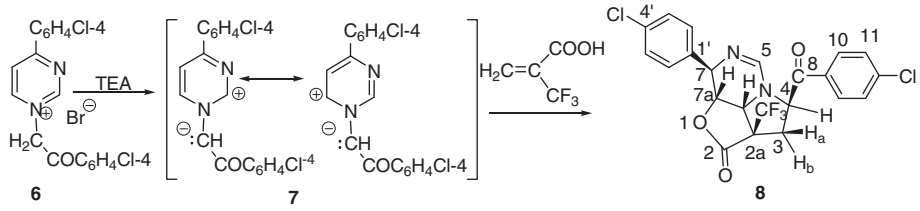
In conclusion, a straightforward, efficient and selective route for obtaining hybrid fluorine nitrogen heterocycle is presented. A new class of γ-lactone with a nitrogen heterocyclic skeleton was obtained. The reaction mechanism for γ-lactone formation was explained via a cascade reaction: a 3+2 dipolar cycloaddition, followed by a concomitant protonation of the nitrogen atom and nucleophilic attack of the carboxylate oxygen at the adjacent endocyclic carbocation. The reaction pathway is straightforward, efficient and stereoselective (for pyridazine) or stereospecific (for pyrimidine). Depending on the nature of the heterocycle, the reaction leads to either γ-lactones with a nitrogen heterocyclic skeleton (for monocycles) or to fused nitrogen heterocycle (for fused bicyclic systems).

The corresponding cycloimmonium salt (**1**) (2 mmol) was suspended in 50 mL of chloroform. A solution of 2-(trifluoromethyl)acrylic acid (2 mmol) and triethylamine (2.2 mmol) in the same solvent (5 mL) was then added. The solution was refluxed for 3 h, then the solution was filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica, CH_2Cl_2–MeOH) and then crystallized from an appropriate solvent.

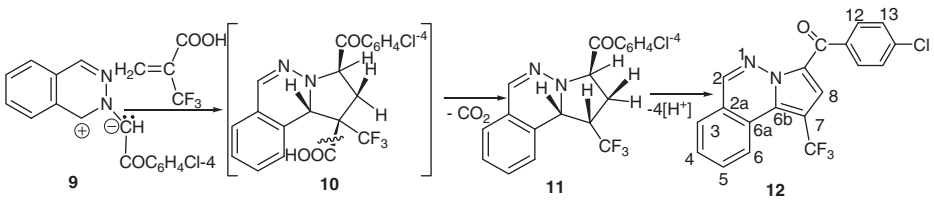
Compound (**4a**): White crystals, mp 183–184 °C. IR (KBr, cm^{-1}): 3042, 2976, 1778, 1686, 1596, 1509, 1467, 1152. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.18–2.13 (dd, J = 4.8, J = 16.4 Hz, 1H, H7″), 2.61–2.56 (dd, J = 6.0, J = 14.4 Hz, 1H, H3b), 2.78–2.72 (ddd, J = 4.8, J = 8.0, J = 16.4 Hz, 1H, H7′), 3.00–2.93 (dd, J = 11.2, J = 14.4 Hz, 1H, H3a), 4.62–4.60 (d, J = 7.6 Hz, 1H, H7b), 4.82–4.78 (dd, J = 6.0,



Scheme 2. Reaction mechanism to γ-lactones with nitrogen heterocycle skeleton.



Scheme 3. Reaction pathway of pyrimidinium ylides with 2-(trifluoromethyl)acrylic acid.



Scheme 4. Reaction pathway of phthalazinium ylides with 2-(trifluoromethyl)acrylic acid.

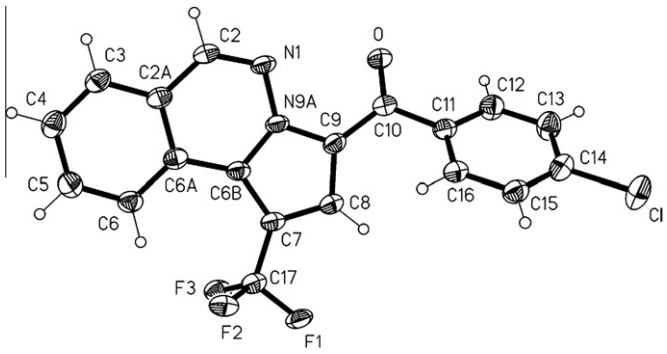


Figure 3. The ORTEP diagram of compound **12** including atom numbering scheme.

J = 11.2 Hz, 1H, H4), 5.14–5.12 (dd, J = 7.6, J = 8.0 Hz, 1H, H7a), 6.92–6.91 (dd, J = 4.8 Hz, 1H, H6), 7.43–7.41 (d, J = 8.8 Hz, 2H, H11), 8.10–8.08 (d, J = 8.8 Hz, 2H, H10). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.73 (C7), 33.89 (C3), 58.83 (C2a), 65.86 (C7b), 71.27 (C7a), 72.43 (C4), 123.33 (CF_3), 128.87 (C11), 130.59 (C10), 134.07 (C9), 139.79 (C12), 142.30 (C6), 170.31 (C2), 192.02 (C8).

Compound (**5a**): White crystals, mp 140–142 °C. IR (KBr, cm^{-1}): 3044, 2982, 1778, 1688, 1590, 1510, 1475, 1182. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27–2.22 (dd, J = 4.8, J = 17.2 Hz, 1H, H7″), 2.84–2.80 (dd, J = 2.8, J = 14.4 Hz, 1H, H3b), 2.76–2.70 (dd, J = 4.0, J = 7.2, J = 17.2 Hz, 1H, H7′), 2.92–2.86 (dd, J = 9.2, J = 14.4 Hz, 1H, H3a), 4.42–4.41 (d, J = 6.0 Hz, 1H, H7b), 5.04–5.03 (d, J = 2.8 Hz, 1H, H4), 5.43–5.40 (dd, J = 4.0, J = 5.2 Hz, 1H, H7a), 6.83–6.82 (dd, J = 4.8 Hz, 1H, H6), 7.48–7.46 (dd, J = 8.8 Hz, 2H, H11), 7.99–7.97 (dd, J = 8.8 Hz, 2H, H10).^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.00 (C7), 32.26 (C3), 62.23–61.40 (C2a), 63.28 (C7b), 69.80 (C7a), 72.10 (C4), 125.23–122.43 (CF_3), 129.20 (C11), 130.56 (C10), 132.84 (C12), 135.77 (C6), 140.44 (C9), 171.06 (C2), 194.31 (C8).

Compound (**8**): White-beige crystals, mp 218–220 °C. 1H NMR ($CDCl_3$, 400 MHz): δ 2.00–1.96 (dd, 1H, H7), 3.04–3.01 (dd, 1H, H3b), 3.07–3.04 (dd, 1H, H3a), 4.82–4.80 (d, 1H, H7b), 5.63–5.62 (d, 1H, H7a), 6.00–5.98 (d, 1H, H4), 7.45–7.43 (dd, J = 8.0 Hz, 2H, H11), 7.72–7.67 (m, 5H, H1, 2H2, 3H$_3$), 7.74–7.73 (d, 1H, H5), 8.09–8.07 (dd, J = 8.0 Hz, 2H, H10).

Compound (**12**): White crystals, mp 172–174 °C. 1H NMR ($CDCl_3$, 400 MHz): δ 7.42 (s, 1H, H8), 7.51–7.49 (d, J = 8.4 Hz, 2H, H13), 7.78–7.75 (dd, J = 7.6 Hz, 1H, H4), 7.89–7.87 (d, J = 8.4 Hz, 2H, H12), 7.95–7.91 (dd, 2H, H3, H5), 8.45–8.43 (d, J = 7.2 Hz, 1H, H6), 8.77 (s, 1H, H2).^{13}C NMR ($CDCl_3$, 100 MHz): δ 116.81 (C8), 119.78 (C7), 121.61 (C6), 124.57 (CF_3), 125.37 (C3), 126.16 (C6a), 128.27 (C6b), 128.79 (C13), 129.62 (C4), 131.05 (C12), 133.63 (C5), 137.18 (C11), 138.98 (C14), 146.49 (C2), 183.06 (C10).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.093.

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12. The following crystal structures have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers: **4b**: CCDC 679536, **5b**: CCDC 691746, **14**: CCDC 827693.