Pergamon

Tetrahedron Letters 42 (2001) 1657–1659

TETRAHEDRON LETTERS

Low temperature domino reactions. A ready access to trifluoromethyl substituted butenolides and their thioanalogues†

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Received 22 November 2000; revised 23 December 2000; accepted 28 December 2000

Abstract—Domino reactions are described, including nucleophilic substitution, Claisen rearrangement and Cope rearrangement, which provide ready access to trifluoromethyl substituted butenolides and their thioanalogues, starting from 2-fluoro-3-trifluoromethyl furans and thiophenes, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

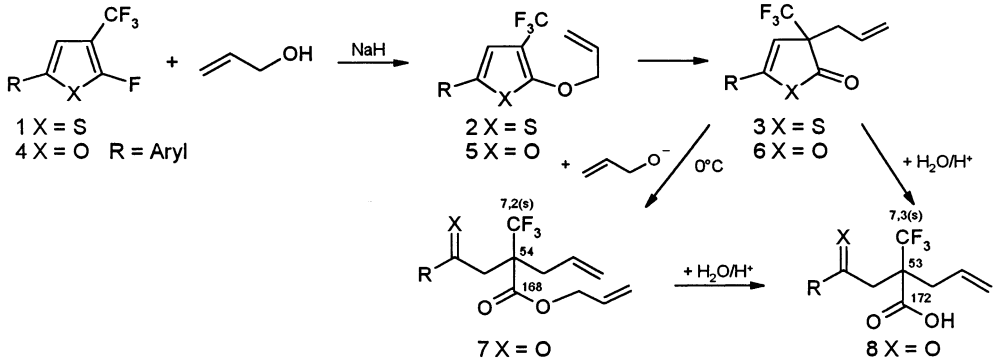
Due to their large abundance and their biological activities butenolides have been studied extensively.[1,2]

The development of synthetic methodology for the regioselective introduction of short-chain perfluoroalkyl groups into organic molecules is of current interest.[3] Fluoromodification often confers unique properties on a molecule, e.g. in terms of increased metabolic stability and lipophilicity, which in turn optimises in vivo absorption and transport rates. As a consequence, the pharmacokinetic profiles are often improved.[4]

We have demonstrated that 5-fluoro-4-trifluoromethyl-1,3-azoles, 2-fluoro-3-trifluoromethylfurans and 2-fluoro-3-trifluoromethylthiophenes are useful building blocks in organic fluorine chemistry.[5] The fluorine atom adjacent to the trifluoromethyl group can be replaced under mild conditions by various nucleophiles, giving ready access to compounds of biological relevance.[6]

When compounds **1** are treated at 0°C with allyl alcohol in the presence of a base, e.g. NaH, allyl ethers **2** are formed in excellent yields, which slowly undergo a Claisen rearrangement at room temperature to give 3-allyl-3-trifluoromethyl-2(3*H*)thiophenones **3**.

Under identical reaction conditions, partially fluorinated furans **4** and allyl alcohol react to give the Claisen product **6**. The intermediate **5** could not be observed even on monitoring the progress of the reaction by ^{19}F NMR spectroscopy. Compounds **6** are stable at room temperature, but in the presence of allyl alcoholate a rapid cleavage of the lactone ring occurs (**6**→**7**). In the presence of an excess of alcoholate, **7** is the main product of the reaction. On hydrolysis compounds **7** are transformed into γ-keto acids **8**, which are preparatively interesting multifunctional, trifluoromethylated building blocks.



Keywords: 3-trifluoromethyl-2(3*H*)furanones; 3-trifluoromethyl-2(5*H*)furanones; 3-trifluoromethyl-2(3*H*)thiophenones; 3-trifluoromethyl-2(5*H*)-thiophenones; domino reactions; membrane transport systems.

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† Dedicated to Professor Ralf Miethchen on the occasion of his 60th birthday.

PII: S0040-4039(01)00013-2

Although, both compounds **3** and **6** possess a 1,5-hexadiene substructure, no Cope rearrangement could be observed. To weaken the C(3)–C(4) bond of the Cope system we decided to introduce additional substituents via 3-substituted allyl alcohols. Substitution reactions of compounds **1** and **4** with cinnamic alcohol in the presence of NaH proceed readily at 0°C within a few hours. Starting from **1** the first compound of the reaction sequence we were able to isolate was the Claisen product **10**, which slowly undergoes a Cope rearrangement at room temperature to form **11**. Domino reactions[7] involving [3,3]-sigmatropic processes are described.[8] A combination of reaction types, such as Diels–Alder reactions,[9] [3+2]-cycloaddition reactions,[10] and Mannich reactions,[8c] provides a valuable synthetic tool for the construction of complex molecules, often in a stereoselective way.[11] Domino reactions, including sequences like Claisen/Cope rearrangements,[12] and Claisen/aza-Claisen rearrangements,[13] have been applied successfully in organic synthesis. However, it is remarkable that the reaction sequence **1→9→10→11** described, including a Claisen and a Cope rearrangement, proceeds smoothly at room temperature.

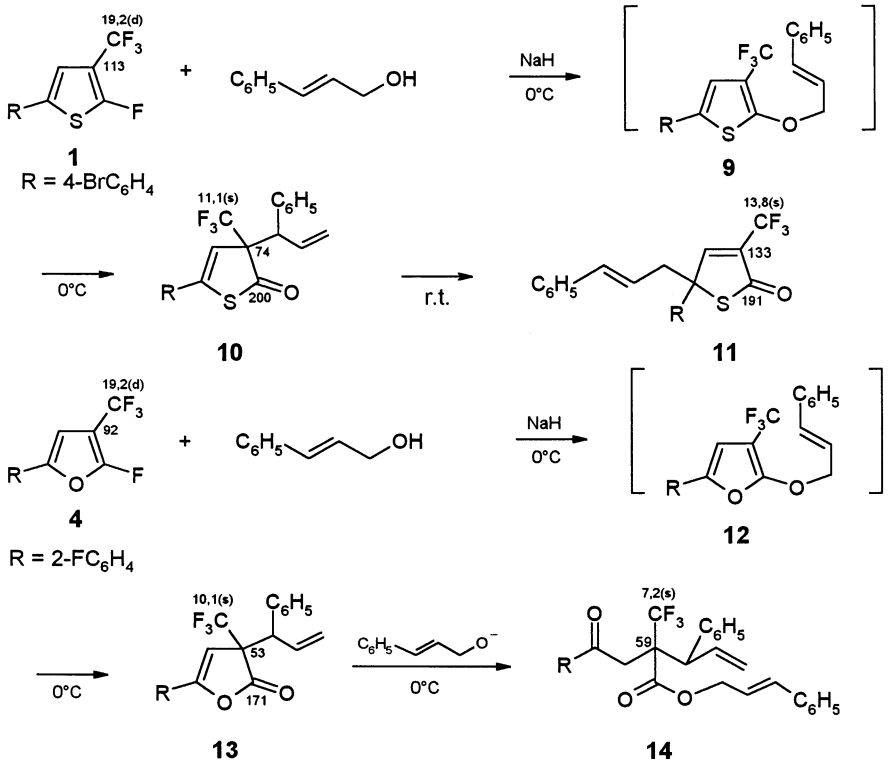
In the furan series we were able to isolate the Claisen product **13** and an open-chain product **14**. The yield of **14** depends on the molar ratio of the starting materials. In the presence of an excess of cinnamic alcohol the ester **14** is the main product of the reaction. These findings demonstrate that cleavage of the lactone ring by the alcoholate is still much faster than the Cope rearrangement.

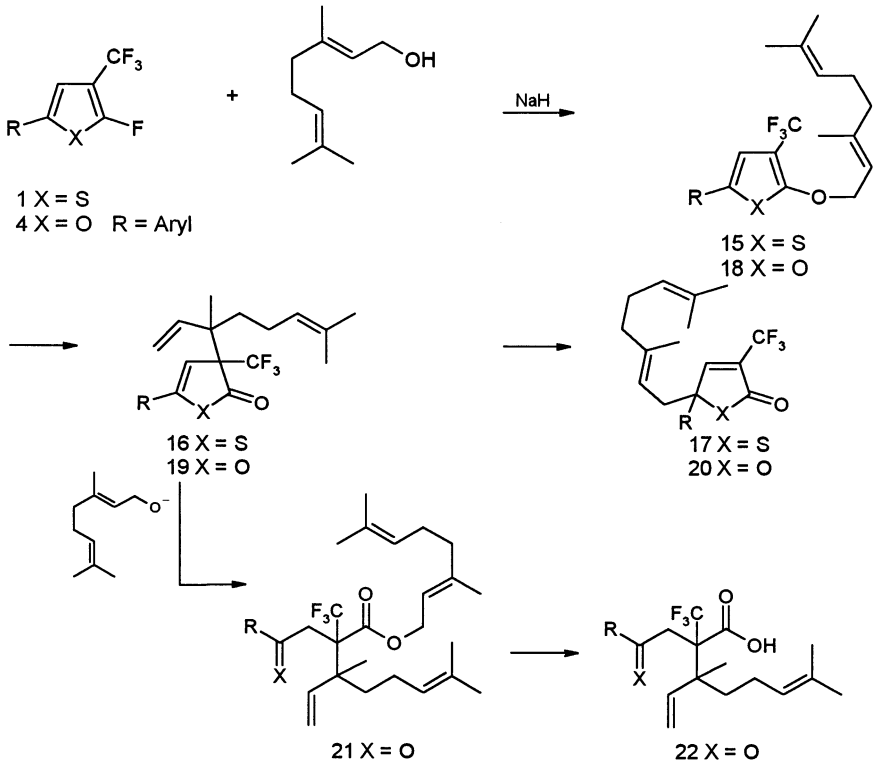
Substitution product **15** was obtained from **1** and geraniol at room temperature in 78% yield. On heating **15** up to 65°C a rearrangement can be initiated. Via the Claisen product **16** which can be detected on monitoring the reaction by ^{19}F NMR spectroscopy [$\delta = 17.9$ ppm (s)], the Cope product **17** [$\delta = 13.9$ ppm (s)] is formed in 79% isolated yield.

When **4** and geraniol are reacted at 0°C in the presence of NaH two products are obtained: the Cope product **20** and product **21** formed by transesterification of the Claisen product **19**. In case of the reaction of 3,3-disubstituted allyl alcohols, the Cope reaction (**19→20**) can successfully compete with lactone cleavage via the alcoholate (**19→21**). The reaction sequence consisting of nucleophilic substitution, Claisen rearrangement and Cope rearrangement (**4→18→19→20**) is, to the best of our knowledge, the first example of a domino reaction where two [3,3]-sigmatropic reactions proceed at 0°C.

Claisen and Cope rearrangements of fluorinated systems often take place at low temperatures.[14] The correct location of the trifluoromethyl group within the rearrangement system can result in a significant rate enhancement.[15]

The reaction sequence provides an elegant method for incorporation of lipophilic anchors with up to 20 carbon atoms into the C-5 position of butenolides and their thioanalogues. Likewise, compounds **22**, obtained on hydrolysis from **21**, are equipped with a trifluoromethyl group together with a long lipophilic carbon side chain. Therefore, compounds of this type may be considered as interesting candidates for the development of transport systems to guide drugs with poor pharmacokinetic profiles through membranes and across the blood/brain barrier. The Michael system present in compounds of type **17** and **20** provides an ideal functionality to form conjugates, i.e. with peptides





and peptidomimetics. Furthermore, the presence of the trifluoromethyl group enables us to monitor the passage of such species through membranes by ^{19}F NMR spectroscopy.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (Bu 277/20-1) and the Fonds der Chemischen Industrie for financial support.

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