The selective cleavage/activation of carbon–carbon (C–C) bonds during chemical transformations poses a significant synthetic challenge in traditional organic synthesis. Due to the inherent solidity and stability or unreactivity of the C–C bond, this transformation requires harsh conditions. Moreover, following simultaneous chemical transformations, including the formation of new C–X bond(s), the process can be applied to more complex tasks. In recent years, significant achievements and progress have been reported in the area of transition metal catalysis. However, metal-free conditions to accomplish this, including C–C bond cleavage followed by C–X bond(s) formation, have clear advantages from a green chemistry viewpoint.

Here we disclose the selective C–C bond cleavage and simultaneous formation of two C–F bonds and one C–S bond in β-keto esters with nucleophilic fluorination reagents such as DAST under metal-free/catalyst-free conditions (Scheme 1). Double fluorination at two remote carbons with additional dialkylamino-sulfonylation provided unique fluorinated compounds in good to high yields. This method can be applied for the successive C–C bond cleavage/fluorination/trifluoromethylthiolation of β-keto esters using trifluoromethyl-DAST (CF₃-DAST) providing different type of fluorinated and trifluoromethylthiolated compounds via a shunt pathway. Doubly fluoro-functionalized compounds obtained in these reactions are unique and difficult to synthesize by other methods.

The selective C–C bond cleavage and simultaneous formation of two C–F bonds and one C–S bond in β-keto esters with nucleophilic fluorination reagents such as DAST under metal-free/catalyst-free conditions is disclosed. Double fluorination at two remote carbons with additional dialkylamino-sulfonylation provided unique fluorinated compounds in good to high yields. This method can be applied for the successive C–C bond cleavage/fluorination/trifluoromethylthiolation of β-keto esters using trifluoromethyl-DAST (CF₃-DAST) providing different type of fluorinated and trifluoromethylthiolated compounds with a tri-substituted carbon center (Scheme 1b). Doubly fluoro-functionalized compounds obtained in these reactions are unique and are difficult to synthesize by other methods. A pentafluorophenylthiolated analogue was also synthesized using pentafluorophenyl-DAST (C₆F₅-DAST). Our results suggest that unique sequential transformation that provides attractive fluorinated compounds is possible without any state-of-the-art catalyst, energy of the ring-strain or heating. Instead, it simply involves a suitable choice of substrates and reagents.

A large number of commercial applications for fluorinated organic compounds have induced much interest in developing novel synthetic methods to incorporate fluorine or fluorinated groups into organic compounds. Fluorination (F₃C)⁵ trifluoromethylation (CF₃)⁶ and trifluoromethylthiolation (SCF₃)⁷ reactions are among the three most important chemical transformations investigated in recent years due to the impressive electron-withdrawing effects and lipophilicity of the groups being introduced. While developing novel methodologies for

Successful C–C bond cleavage, fluorination, trifluoromethylthiolation and pentafluorophenylthiolation under metal-free conditions to provide compounds with dual fluoro-functionalization†

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† Electronic supplementary information (ESI) available. CCDC 1415530 and 1415531. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc04208a
fluoro-functionalization reactions, we unexpectedly transformed ethyl indanone carboxylate (1a) with DAST10 in CH2Cl2 to acyclic acid fluoride 2a with a tetra-substituted carbon center with C-F and C-S bonds. Although the chemical yield was low, only 31%, the reaction was unique enough for further investigation since it effectuated four important chemical transformations without any catalysis: C-C bond cleavage, the formation of two C-F bonds at remote positions, and a C-S bond.11 We thus envisioned that this strategy might be viable for the synthesis of new types of fluoro-functionalized acid fluoridae from ubiquitous carboxylic carboxyl esters. With this idea in mind, we set out to investigate the use of β-keto ester 1a and DAST,12,13 after thoroughly surveying reaction conditions, including temperature, solvent, concentration, etc. (see ESI, Table S1†), we found that the use of 2.0 equivalents of DAST in THF at room temperature gave the best result (2a, 85% yield).

We proceeded to evaluate the scope of these four metal-free, sequential transformations by DAST with a wide variety of β-keto esters 1 (Table 1). The sequential transformation of indaneone substrates with DAST was in general independent of the size of the ester moiety (Me, Et, Bn), and a substitution on the benzene ring (MeO, Me, Br, Cl) provided the corresponding products 2a–2g in good to high yields. Substrate 1h, which is very rich in electrons, also underwent the same four sequential transformations to give the corresponding product in good yield (2h, 54%). Tetralone carboxylate 1i and benzosuberanone carboxylate 1j were also good substrates for transformation to furnish the desired products 2i and 2j in 30% and 39% yield, respectively. Non-aromatic benzyl 2-oxocyclopentanecarboxylate (1k) was also converted to fluorinated-sulfenylated acid fluoride 2k in 39% yield. Other nucleophilic fluorination reagents such as [MeOCH2CH2Cl]2SF3 (DeoxoFluor®),14,15 4-morpholinsulfur trifluoride (Morph-DAST)16,17 and N,N-dimethylaminosulfur trifluoride (Me-DAST)18 were equally effective for these transformations, yielding the corresponding fluorinated dialkylaminosulfenylated acid fluoride products 3a–3c in moderate to high yields. Finally, this strategy was also effective for an acyclic substrate, methyl 2-benzyl-3-oxobutanone (1o) in DMF at 50 °C to provide the C–C bond cleavage, two fluorinations, and sulfenylation of 1 with nucleophilic fluorination reagents.4a,b,c The reaction of 1o with DAST (2.0 equiv.) was carried out overnight in THF (0.1 M) at room temperature. Isolated yields are indicated. For detailed reaction conditions, see ESI.19 19F NMR yields. The reaction of 1o with DAST (2.0 equiv.) was carried out overnight in DMF (0.1 M) at 50 °C.

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into the desired products 4l–4n under the same conditions. Acyclic methyl 2-benzyl-3-oxobutanoate 1o was converted into the desired C–C bond cleavage triﬂuoromethylthiolation product 4o in acceptable yield (19%) after the release of the acid ﬂuoride part. The isolated yields are somewhat lower than the NMR yields due to instability during puriﬁcation by silica-gel chromatography. The structures of the triﬂuoromethylthiolated acid ﬂuorides were assigned by spectroscopy and clearly determined by X-ray crystallographic analysis of 4h (CCDC 1415531).†

Acid ﬂuorides are versatile building blocks. In particular, they are popular for peptide coupling reactions without epi- merization, and thus a range of more complex ﬂuorinated compounds can be synthesized. As shown in Scheme 2, 2b and 4b easily underwent alkylation, amination, and esteriﬁcation to form the corresponding ﬂuorinated and sulfonylated products 5a,b and triﬂuoromethylthiolated products 6a–6c in good to high yields (Scheme 2).

It is interesting to note that this methodology was effectively extended to the reaction of 1b with in situ generated, previously unknown pentaﬂuorophenyl-DAST (C6F6-DAST) to provide SC6F5-analogue 7b in 53% isolated yield (Scheme 3).

Moreover, 1,3-diketone 8 also reacted with DAST or CF3-DAST to provide the corresponding unexpected ﬂuorinated or sulfonylated product 9 or triﬂuoromethylthiolated product 10 in 63% and 54% yield, respectively. Although it was possible to isolate both compounds, 9 was not very stable during silica-gel column chromatography. Decacylation was observed in this case, similar to the reaction of acyclic substrates 1o to 2o or 1o to 4o (Scheme 4).

A possible reaction mechanism (Fig. 1) is based on the unexpected formation of two diﬀerent types of products 2 and 4. Initially, the ﬂuorine anion generated from DAST or CF3-DAST selectively attacks the ketone moiety of 1a to give the acid ﬂuoride enolate A via a ring-opening reaction through a retro-Dieckmann type reaction (for acyclic substrates 2o and 1,3-diketone 8, a “retro-Claisen” type reaction might be suitable due to the de-acetylation). The enolate rapidly attacks the sulfur atom of the DAST or CF3-DAST residue providing unstable intermediate B. In the case of the reaction with DAST (X = F), intermediate B promptly releases HF initiated by the attack from the internal nitrogen moiety. This is followed by intramolecular ﬂuoro-Pummerer-type rearrangement to furnish ﬁnal product 2a as an HF salt via thionium intermediate C.
A plausible reaction mechanism.

Fig. 1 A plausible reaction mechanism.

(route a). On the other hand, the reaction with CF3-DAST (X = CF3) enters route b instead of route a due to the presence of diisopropylethylamine (iPr2NEt). CF3-DAST should be prepared in situ from an equivalent mixture of DAST, CF3SiMe3, and iPr2NEt. A molar equivalent of iPr2NEt is crucial for complete transformation to CF3-DAST, and iPr2NEt is presumably required to initiate the reaction and stabilize the generated CF3-DAST.16 The acidic proton in intermediate B needs to be removed by iPr2NEt to furnish D rather than the elimination of HF before heading into route a. Unstable intermediate D promptly releases HF as an N-ethylidene ethanamine salt,16 resulting in trifluoromethylthiolation product 4a via enolate E.

Conclusions

In summary, we have efficiently synthesized acid fluorides with a tetra-substituted fluorinated and sulfenylated carbon center at a remote position via a metal- or catalyst-free ring opening reaction of β-keto esters with DAST. The chemical transformation undergoes a sequence of C–C bond cleavages, two C–F bonds form at the remote positions of C1 to C5–C6 and C–S bond formation affords a wide range of unique fluorinated acid fluorides in good to high yields under mild reaction conditions. This sequential transformation was extended to the reaction of β-keto esters with CF3-DAST. More interestingly, trifluoromethylthiolated acid fluorides with a tri-substituted carbon center were produced under the same reaction conditions. 1,3-Diketones are also acceptable substrates in these transformations with DAST and CF3-DAST. All these reactions are triggered by an attack by fluoride on the carbonyl through a retro-Dieckmann or retro-Claisen type reaction. Both fluorofunctionalized compounds unexpectedly obtained here are otherwise difficult to prepare. Although a large number of reactions have been reported using DAST and related reagents with a variety of substrates16–18 including β-keto esters,15,16 the present sequential reaction has never been reported. The reaction mechanism, the utility of this strategy for the development of new chemical transformations and the synthesis of biologically attractive molecules using these fluorinated products are under investigation.

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