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Fluoride-Triggered Domino Reactions Involving Ammonium Acetylides and Carbonyl Compounds

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We describe the use of tetrabutylammonium fluoride as a basic trigger for reactions capable of generating structurally diverse products from methyl propiolate and carbonyl derivatives. The processes are based on either chemodifferentiating multicomponent ABB′ three-component reactions or bimolecular domino reactions, and they operate through three different and well-defined autocatalytic cycles. These catalytic cycles share a common property: they are launched by the acid–base reaction of fluoride ions to give catalytic amounts of acetylide or enolate salts, but they are maintained by the autocatalytic generation of these salts.

Introduction

A recent communication from the Reboul group[1] describing the unprecedented in situ formation of cesium acetylides of alkyl propiolates by catalytic amounts of cesium fluoride encouraged us to report our own results dealing with the catalytic formation of ammonium acetylides by using tetrabutylammonium fluoride (TBAF) as the fluoride source. As part of a wide research program aimed at the design and development of new chemodifferentiating ABB′ three-component reactions (3CRs)[2] and higher homologous multicomponent reactions, we were interested in the use of TBAF as a basic trigger for processes that can generate structurally diverse products from alkyl propiolates and carbonyl derivatives. We chose this salt because, in aprotic solvents, it offers a convenient balance between nucleophilicity (low) and base strength (between trialkylamines and alkoxides).[3] We have elsewhere described[4] that these processes can be conveniently triggered by tertiary amines and/or tertiary phosphanes through a novel reactivity generation concept: the in situ generation of a strong base by a good nucleophile. The concept is chemically expressed by the Michael addition of the nucleophile on the alkyl propiolate to generate corresponding β-onium allenolate intermediate **I** (Scheme 1), which is basic enough to deprotonate either a molecule of alkyl propiolate to afford the corresponding acetylide salt **II** (general for aldehydes and ketones), or a molecule of the reactant carbonyl compound to give enolate salt **III** (specific for unbranched 1,2-keto esters).[5] Specific and skeletally different products are obtained from these two salts through well-defined acetylide-driven (structures **1**–**3**)[4] or enolate-driven (isotetronic acid derivative **5**)[4b,5] domino processes. Whereas acid chlorides afford skipped diynes **4** through a similar A_2BB' four-component reaction process,[6] aromatic 1,2-diketones themselves constitute a particular example of this reactivity generation concept, affording cyclobutanes 7 and cyclobutenes **8** through a well-defined domino reaction network involving ambiphilic allenes **6** as discrete intermediates (Scheme 1).[7]

In this communication, we report on our preliminary findings in the use of naked fluoride ions dissolved in an aprotic medium as a convenient trigger for the chemodifferentiation of ABB′ 3CRs and related domino processes.

Results and Discussion

Scheme 2 outlines the chemical outcomes of the fluoride-catalyzed reactions of methyl propiolate (alkynoate source) and a set of carbonyl reactants spanning a wide and conveniently contrasted reactivity profile. Reactions were performed in dichloromethane at room temperature and under an aerobic atmosphere by mixing the two reactants in the presence of catalytic amounts of the ion fluoride source (10 mol-%, 1 M in THF). The stoichiometry was adjusted to that required for optimal product formation under atom-

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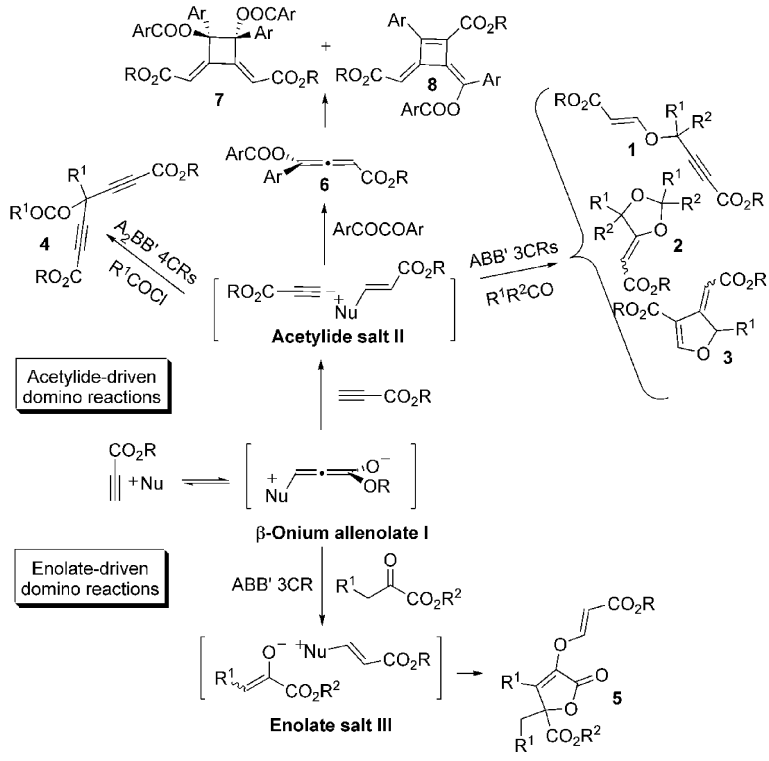


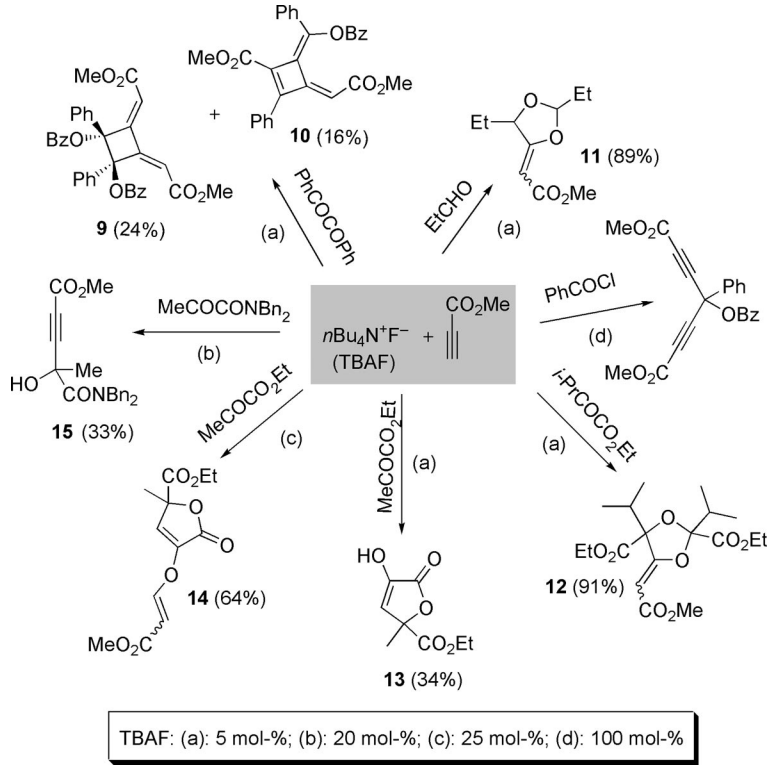
Scheme 1. Lewis base catalyzed acetylide-driven and enolate-driven reactions.

economical conditions. Under these experimental conditions, we were pleased to observe that benzil was stereoselectively transformed into a mixture of highly functionalized cyclobutane **9** and cyclobutane **10** in a modest combined yield (40%). Whereas propionaldehyde and ethyl 3-methyl-2-oxobutyrate afforded the expected 1,3-dioxolane derivatives **11** and **12** in excellent yields (89 and 91%, respectively), ethyl pyruvate gave the corresponding homoaldolic adduct **13** in modest yield (34%).[8] Remarkably, an increase in the amount of fluoride ion from 5 to 25 mol-% (with respect to the carbonyl compound) delivered isotetronic acid derivative **14** in 64% yield. Note that compound **14** incorporates a second unit of alkyl propiolate in the form of an enol ether functionality. In contrast, 1,2-ketoamides, which are transformed into the corresponding propargylic derivative **1** under triethylamine catalysis,[4b] generated propargyl alcohol **15**. Benzoyl chloride did not afford the corresponding 1,3-diyne **4** (R^1 = Ph; R = Me).

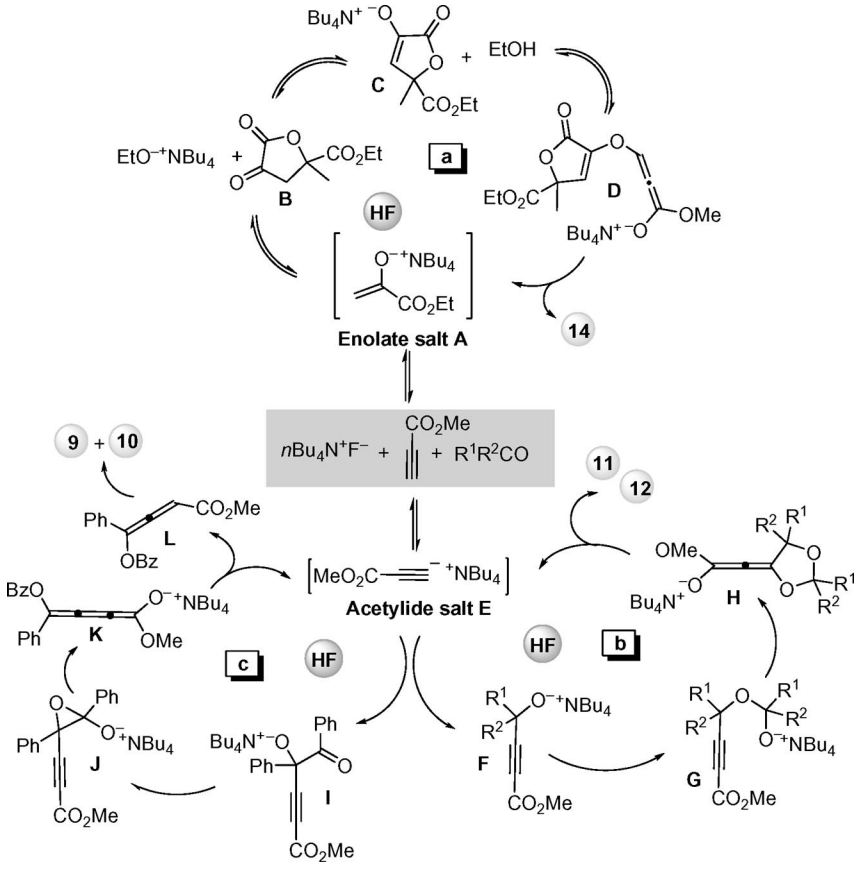
Scheme 3 outlines a mechanistic proposal accounting for these experimental results. As was expected, when methyl propiolate and the carbonyl compound are mixed in the presence of TBAF, an acid–base reaction between fluoride and the more acidic species present in the reaction medium takes place. This acid–base reaction generates either enolate salt **A** or acetylide salt **E** and hydrogen fluoride. The pK_a balance between the alkyl propiolate and the carbonyl partner orchestrates these processes, affording the expected products from either the enolate-driven cycle a or the acetylide-driven cycles b or c. Whereas aliphatic aldehydes, branched 1,2-keto esters, 1,2-ketoamides, and aromatic 1,2-diketones react with methyl propiolate through acetylide-driven processes, unbranched 1,2-keto esters react through the enolate-driven pathway.

The three catalytic cycles share a common property: they are launched by the acid–base reaction of fluoride ions with propiolate or pyruvate to give catalytic amounts of enolate or acetylide salts, but these processes are maintained by the autocatalytic generation of these salts.[4] This property is chemically expressed in the form of an acid–base reaction between the most advanced allenolate intermediate (**D**, **H**, or **K**) and the starting material to afford the product in the neutral final state and enolate (or acetylide) salt to reinitiate the catalytic cycle. Note that in these processes, the only hydrogen source is the carbonyl compound itself or methyl propiolate.

Cycle a (Scheme 3) is followed when the carbonyl partner is more acidic than methyl propiolate. This is the case of ethyl pyruvate, which in the presence of ion fluoride forms the corresponding enolate **A**, which reacts with another molecule of ethyl pyruvate to afford the homoaldol adduct, which lactonizes to give the corresponding lactone **B** and ammonium ethoxide salt. An acid–base equilibrium involving these species and enolate **C** is then established. If the amount of fluoride is low (5 mol-%), enolate salt **A**, lactone **B**, enolate **C**, ammonium ethoxide, and ethanol coexist in equilibrium. Enolate **C** is a mild nucleophile and it needs a high concentration to productively add to methyl propiolate to keep the cycle going. If the amount of fluoride is increased, the concentration of enolate **C** increases and the Michael addition of this enolate to the starting alkynoate



Scheme 2. Fluoride-catalyzed reactions involving methyl propiolate and carbonyl compounds.



Scheme 3. Fluoride-triggered domino process involving autocatalytic generation of acetylide or enolate salts.

shifts the equilibrium towards the formation of allenolate **D**. In this step, HF could activate the alkynoate through H-bond interactions.[3] Protonation of allenolate **D** affords isotetronic acid derivative **14** and enolate salt **A** to reinitiate the cycle (autocatalysis). Isotetronic acid derivative **14** is obtained as a mixture of *E*/*Z* isomers, which is the expected outcome from the Michael addition of alkoxide ions to alkyl propiolates.[9] Because ethyl pyruvate is incorporated into product **14** in the form of two chemodifferentiated structural motives, we categorize this reaction as an ABB′ 3CR.[2]

Cycle b (Scheme 3) operates through acetylide salt formation. Obviously, it requires that the carbonyl partner be less acidic than methyl propiolate. Once a catalytic amount of acetylide salt **E** forms, it adds to the carbonyl compound to generate propargylic alkoxide **F**, which in turn reacts with a second unit of the carbonyl compound to give intermediate **G**. Intramolecular Michael addition yields allenolate **H**, which in turn reacts with methyl propiolate to afford 1,3-dioxolane derivatives **11** (or **12**) and acetylide salt **E** to reinitiate the cycle (autocatalysis). 1,3-Dioxolane derivatives **11** and **12** are obtained as an isomeric mixture of the four possible isomers (*syn*/*anti*, *E*/*Z*) through a common chemodifferentiated ABB′ 3CR reaction. We can point out that the isomeric mixtures of 1,3-dioxolanes were conveniently converted into tetronic acid derivatives.[10] 1,2-Ketoamides constitute a particular case of activated carbonyl compounds. They react through cycle b (Scheme 3) to give the corresponding quaternary alkoxide intermediate **F** (R^1 = Me; R^2 = $CONBn_2$), which is a much stronger base than nucleophile and it deprotonates the starting propiolate to reinitiate the cycle. In this case, cycle b (Scheme 3) affords propargylic amide **15**, which incorporates just one unit of propiolate and one unit of 1,2-ketoamide and it cannot be considered a domino process. Cycle c (Scheme 3) is particular for aromatic 1,2-diketones and it also operates by acetylide salt formation. The catalytic cycle involves 1,2-addition of acetylide to the 1,2-diketone to form propargylic alkoxide **I**, which rearranges into cumulenolate **K**. Acid–base protonation of this intermediate generates ambiphilic allene **L** and a new unit of acetylide salt **E** to reinitiate the cycle. Allene **L** slowly dimerizes to give a mixture of C_4-carbocycles **9** and **10**. Overall, the reaction constitutes an impressive example of a complexity-generating domino process.

This mechanistic proposal diverges from that advanced by Reboul et al.[1] in the fluoride-catalyzed synthesis of 1,3-benzothiazines from alkyl propiolates and cyclic sulfonamides. The authors propose a catalytic cycle triggered and maintained by fluoride ions. This proposal requires that the fluoride ion must be regenerated during the catalytic cycle to keep the process going. It is not easy to explain that if the fluoride ion can deprotonate the starting alkynoate, which means that the fluoride is a stronger base than the generated acetylide, hydrogen fluoride can be deprotonated in the presence of alkyl propiolate (hydrogen fluoride should be a milder acid than alkyl propiolate). We believe that a catalytic mechanism involving fluoride triggering and autocatalytic maintenance would be more appropriate. Our own results confirm this idea.

Conclusions

In summary, we have described our results on the use of TBAF as a basic trigger for domino processes involving methyl propiolate and carbonyl derivatives. Although the efficiency of these processes is sometimes lower than that described for the Lewis base catalyzed versions,[4–7] fluoride catalysis offers some advantages: (1) reactions are performed at room temperature and under aerobic atmospheres (bench-economy); (2) THF solutions of TBAF are easily handled without especial care (CsF is a highly hygroscopic solid); (3) fluoride accumulates in the form of HF (weak acid), which can participate as an H-bond donor[3] (H-bond catalysis); (4) TBAF in aprotic solvents behaves as a bad nucleophile and it is not expected to compete with other nucleophiles for the electrophilic intermediates generated in these domino processes (i.e., allenes) (feasibility of novel multicomponent reaction); (5) the results are complementary to those obtained when a much stronger base such as *n*BuLi is utilized;[4a] (6) the ammonium counterion actively participates in each one of the three catalytic cycles and it can be conveniently utilized as a chiral transfer catalyst (ion-pair-based chiral implementation).[11]

Experimental Section

Compounds **9**–**14** have been fully described elsewhere.[4–7]

Fluoride-Catalyzed Reaction of *N*,*N*-Dibenzyl-2-oxopropanamide and Methyl Propiolate: TBAF (1.0 M in THF, 0.080 mmol) was added to a solution of methyl propiolate (0.40 mmol) and *N*,*N*-dibenzyl-2-oxopropanamide (0.40 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1 h before it was quenched with a NH_4Cl solution. After extraction with CH_2Cl_2 followed by removal of the solvent under reduced pressure, the products were purified by flash column chromatography (silica gel; *n*-hexane/EtOAc, 90:10) to yield **15** (33%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.75 (s, 3 H), 3.65 (s, 3 H), 4.47 (d, $^3J_{H,H}$ = 14.8 Hz, 1 H), 4.67 (d, $^3J_{H,H}$ = 16.2 Hz, 1 H), 4.69 (d, $^3J_{H,H}$ = 14.8 Hz, 1 H), 4.88 (d, $^3J_{H,H}$ = 16.2 Hz, 1 H), 5.29 (s, 1 H), 7.10–7.12 (m, 2 H), 7.19–7.21 (m, 2 H), 7.28–7.39 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 28.0, 49.2, 50.8, 52.7, 66.5, 76.7, 85.7, 127.2, 127.8, 127.9, 128.0, 128.7, 128.8, 128.9, 134.6, 135.7, 170.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3360.1, 3023.8, 2929.0, 2238.8, 1716.9, 1645.2, 1436.3, 1363.3, 1261.4 cm^{-1}. MS (70 eV): *m*/*z* (%): 333 (20) [M – H_2O]$^+$, 224 (55), 127 (17), 95 (20), 92 (65), 91 (100), 65 (33). HRMS: calcd. for $C_{21}H_{19}NO_3$ [M – H_2O]$^+$ 333.1352; found 333.1365.

Supporting Information (see footnote on the first page of this article): General experimental details and characterization data for compounds **9**–**12** and **14**; ^{1}H and ^{13}C NMR spectra of compound **15**.

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