Synthesis of α-trifluoromethyl-β-keto phosphonates by electrophilic trifluoromethylation with Togni reagent

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ABSTRACT
A new synthetic method of trifluoromethylated phosphonates was developed via electrophilic trifluoromethylation with Togni reagent. A variety of β-keto phosphonates were converted into the corresponding α-trifluoromethyl-β-keto phosphonates in moderate to good yields. This protocol could also be extended to other fluoroalkylation reactions, such as pentafluoroethylolation.

GRAPHICAL ABSTRACT

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Introduction
Phosphonic acids and their diesters have received increasing attention in medicinal and synthetic chemistry. Phosphonates were considered in many instances as analogs of naturally occurring phosphates, with enhanced metabolic stability. Consequently, research interest in phosphonate analogs has grown tremendously to develop new biological compounds. It is well known that the incorporation of fluorine atom and/or fluorine-containing groups into an organic molecule often changes the chemical, physical, and biological properties of the parent compound. Therefore, fluorinated phosphonate analogs including α-monofluorinated, α,α-difluorinated, and α-trifluoromethylated phosphonates I–III have been intensively investigated (Scheme 1).

Because of the unique properties of trifluoromethyl group, such as strong electron-withdrawing effect, high lipophilicity, and excellent metabolic stability, trifluoromethylated phosphonates are of particular interest. However, the synthetic methods of trifluoromethylated phosphonates mainly relied on phosphorylation of CF3-containing building blocks (Scheme 2a) and transformation of trifluoromethylated iminophosphonates (Scheme 2b).
Compared to these indirect methods, the direct trifluoromethylation is more attractive. To the best of our knowledge, only one example was reported of the synthesis of trifluoromethylated phosphonates by a direct trifluoromethylation approach, in which nucleophilic trifluoromethylation of acyl phosphonates was involved (Scheme 2c).[8] Thus, it is highly desirable to develop other direct methods to synthesize trifluoromethylated phosphonates. In continuation of our recent research interest in trifluoromethylation reactions,[9] herein we report a new approach to trifluoromethylated phosphonates via electrophilic trifluoromethylation of β-keto phosphonates (Scheme 2d). This method provides a variety of previous unknown and potentially useful α-trifluoromethyl-β-keto phosphonates.

Results and discussion

We began our study by examining the reaction of β-keto phosphonate 1a with different electrophilic trifluoromethylating reagents in the presence of various bases and solvents (Table 1). Among several electrophilic trifluoromethylating reagents, Togni reagent B was the most effective, providing the trifluoromethylated product 2a in 32% yield (entries 1–4). To our delight, the addition of hexamethylphosphoramide (HMPA), a common cosolvent used to accelerate otherwise slow S_N2 reactions by solvating cations,[10] could improve the yield to 53% (entry 5). To further improve the reaction yield, different organic and inorganic bases were investigated and t-BuONa was found to be the optimal base to afford 2a in 67% yield (entries 6–10). The subsequent solvent screening demonstrated that CH_2Cl_2 was superior to tetrahydrofuran (THF), Et_2O, and toluene (entries 11–13). Finally, reducing the amounts of t-BuONa and extending the reaction time could improve the yield to 79% (entry 14).
With the optimized reaction conditions in hand (Table 1, entry 14), we next investigated the substrate scope of this reaction. As summarized in Scheme 3, the electrophilic trifluoromethylation of various β-keto phosphonates 1 proceeded well, affording the corresponding products 2 in moderate to good yields. Several tetralone derivatives 1a–d were successfully converted to the trifluoromethylated products 2a–d. The reaction of acyclic β-keto phosphonates 1e–f showed comparable yields to cyclic ones. Substrates 1e and 1f bearing α-methyl and α-ethyl groups were both compatible with the reaction conditions. This protocol allowed the direct trifluoromethylation of substrates 1g–i bearing different substituents including methyl, chloro, and acetoxyl on the arene rings. It was noteworthy that different ester groups in 1j–l had no obvious influence to the yield. In the cases of non-aromatic β-keto phosphonates, the desired trifluoromethylated products were isolated in poor yields.

Furthermore, this method can be further extended to the synthesis of pentafluoroethylated phosphonates (Scheme 4). Cyclic and acyclic β-keto phosphonates 1a and 1e reacted with electrophilic pentafluoroethylyating reagent E to give the corresponding products 3a and 3e, respectively. These results showed that this protocol should be extended to other perfluoroalkylation reactions.

Table 1. Optimization of reaction conditions.

| Entry | CF3 reagent | Additive | Base | Solvent | Yield (%) |
|-------|-------------|----------|------|---------|-----------|
| 1     | A           | —        | NaH  | THF     | 0         |
| 2     | B           | —        | NaH  | THF     | 32        |
| 3     | C           | —        | NaH  | THF     | 14        |
| 4     | D           | —        | NaH  | THF     | 20        |
| 5     | B           | HMPA     | NaH  | THF     | 53        |
| 6     | B           | HMPA     | DBU  | THF     | 0         |
| 7     | B           | HMPA     | LDA  | THF     | 32        |
| 8     | B           | HMPA     | t-BuOLi | THF  | 16        |
| 9     | B           | HMPA     | t-BuONa | THF   | 67        |
| 10    | B           | HMPA     | t-BuOK | THF  | 0         |
| 11    | B           | HMPA     | t-BuONa | Et2O| 40        |
| 12    | B           | HMPA     | t-BuONa | CH2Cl2 | 72       |
| 13    | B           | HMPA     | t-BuONa | Toluene | 29       |
| 14    | B           | HMPA     | t-BuONa | CH2Cl2 | 79       |

*aReactions were carried out using 1a (0.2 mmol), CF3 reagent (0.3 mmol), base (0.6 mmol), and additive (1.2 mmol) in solvent (2.0 mL) for 12 h.

*bYields were determined by 19F NMR spectroscopy of the crude reaction mixture using benzotrifluoride as an internal standard.

c-t-BuONa (0.3 mmol), 18 h.
Conclusions

In conclusion, we have developed a new method for the preparation of trifluoromethylated phosphonates. The reaction of cyclic and acyclic β-keto phosphonates with Togni reagent in the presence of t-BuONa and HMPA provided various α-trifluoromethyl-β-keto phosphonates in moderate to good yields. This protocol could also be extended for the preparation
of pentafluoroethylated phosphonates. All these fluorinated products are previously unknown and might be used as building blocks in organic synthesis and drug development.

**Experimental**

A 25-mL Schlenk tube was charged with a stir bar and t-BuONa (28.8 mg, 0.3 mmol) under N₂ atmosphere. Phosphonate (0.2 mmol), HMPA (215.0 mg, 1.2 mmol), and CH₂Cl₂ (2.0 mL) were added to the tube. The reaction mixture was cooled 0 °C and stirred for 30 min. Then, Togni reagent B (94.8 mg, 0.3 mmol) was added to the reaction mixture. After stirring at room temperature for 18 h, the reaction mixture was quenched with 10% NH₄Cl aqueous solution and extracted with CH₂Cl₂ three times. The combined organic layer was dried over Na₂SO₄, and the organic solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product.

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