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## Graphical Abstract

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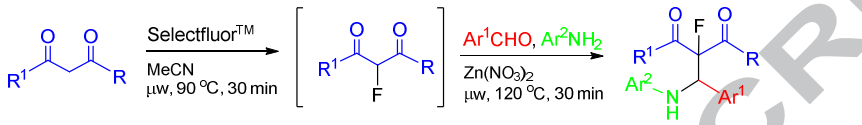

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# One-pot fluorination and Mannich reactions of 1,3-dicarbonyl compounds

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ABSTRACT

One-pot fluorination of 1,3-dicarbonyl compounds with Selectfluor™ followed by the Mannich reaction with anilines and benzaldehydes is developed for the synthesis of α-fluoro and aminomethylated 1,3-dicarbonyl compounds.



Organofluorine molecules could have significantly different physical, chemical, and biological properties from their non-fluorinated parent compounds.[1] The synthesis of fluorinated small molecules has become increasingly important in medicinal chemistry[2] and agricultural chemistry.[3] Shown in Figure 1 are biologically interested α-fluorinated 1,3-dicarbonyl compounds, including schizophrenia and anxiety agent **I**,[4] human Kv1.1/Kvβ1.3 potassium channel inhibitor **II**,[5] antimalarial candidate compound **III**,[6] and antibacterial erythromycin compound **IV**.[7] Compounds **3** with a tertiary fluorinated carbon at the 2-position of 1,3-dicarbonyl could be prepared by the Michael or Mannich reactions of fluorinated substrates **2** (route 1),[8,9] or by fluorination of the tertiary carbon of substrates **4** (route 2) (Scheme 1).[10] However, to the best of our knowledge, no one-pot fluorination and intermolecular Mannich reactions of 1,3-dicarbonyl compounds **1** to form both C-F and C-C bonds have been reported.

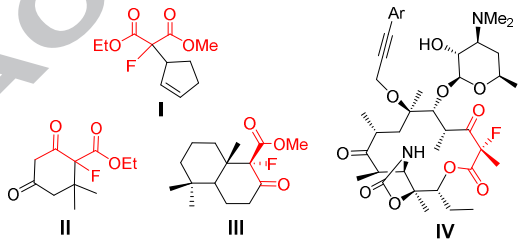
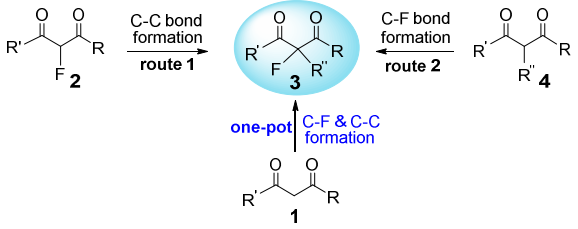



**Figure 1.** α-Fluorinated 1,3-dicarbonyl compounds.

One-pot synthesis is a green technique with a good step economy.[11,12] It saves reaction time and energy, and reduces the amount of waste solvent by eliminating the intermediate purification step. As part of our continuous efforts in the development of efficient and green synthetic methods,[13,14] we have recently reported a one-pot fluorination and Michael addition for the synthesis of α-fluoro-β-ketoesters.[8,15] Introduced in this paper is the extension of the method for one-pot fluorination and Mannich reaction of 1,3-dicarbonyl compounds **1** for the synthesis of α-fluoro and aminomethylated 1,3-dicarbonyl compounds **3**.




**Scheme 1.** C-F & C-C bond formation for 1,3-dicarbonyl compounds **3**

The Mannich reaction of an enolizable carbonyl compound, an amine, and a nonenolizable aldehyde is a good method for the synthesis of aminomethylated 1,3-dicarbonyl compounds. An α-fluorinated and enolizable carbonyl compound has an acidic proton, which is favorable for the Mannich reaction. We first screened a range of salts as potential catalysts for the Mannich reaction of α-fluorinated β-keto ester **2aa** for the formation of **3ac**. Under microwave heating at 120 °C for 30 min with 20 mol% of salt, only a trace or small amount of product was detected from the reactions using $AlCl_3$, $CuCl_2$, $TiCl_2$, $Fe(NO_3)_3$, $Mg(NO_3)_2$, and $Zn(OAc)_2$ (see Supporting Information). The reaction with $Zn(NO_3)_2$ gave much high product yield. Further exploring of reaction time (20-40 min), temperature (100-140 °C), and catalyst amount (0.1-0.4 equiv) confirmed that 20 mol% of $Zn(NO_3)_2$ under microwave heating at 120 °C for 30 min was the best condition which gave product in 89% yield (Table 1,

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entry 5). Regular heating at 120 °C only gave 60% product even after 18 h (entry 9).

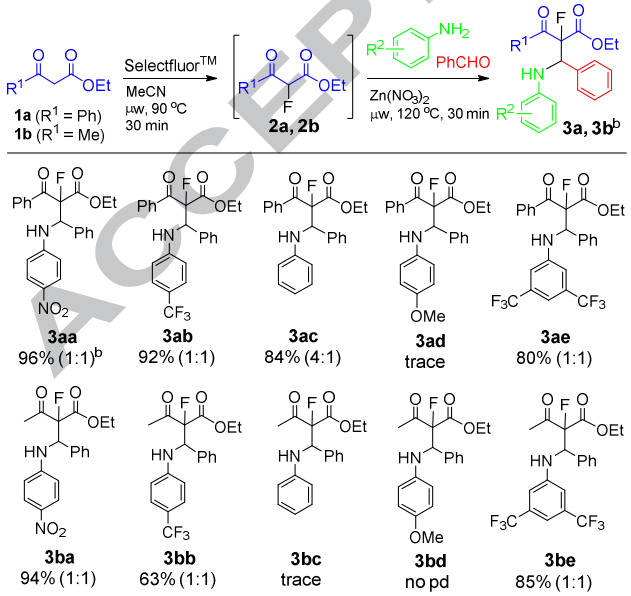
**Table 1.** Optimization of the reaction conditions[a]


| Entry | $Zn(NO_3)_2$ (equiv) | Temp (°C) | Time (min) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 0.2 | µw, 120 | 30 | 85 |
| 2 | 0.2 | µw, 120 | 20 | 62% |
| 3 | 0.2 | µw, 120 | 40 | 85% |
| 4 | 0.2 | µw, 100 | 30 | 73% |
| **5** | **0.2** | **µw, 120** | **30** | **89%** |
| 6 | 0.2 | µw, 140 | 30 | 89% |
| 7 | 0.1 | µw, 120 | 30 | 62% |
| 8 | 0.4 | µw, 120 | 30 | 87% |
| 9 | 0.2 | heating,120 | 18 h | 60% |

[a] Reactions were carried out using 0.2 mmol each of benzaldehydes and aniline, and 20 mol% of $Zn(NO_3)_2$.
[b] LC-MS yield.

With an optimized condition for the Mannich reaction in hands, we then explored the one-pot fluorination and Mannich reactions (Table 2). The fluorination of **1a** was conducted following the reported procedure of heating a $\beta$-ketoester with one equiv. of Selectfluor™ under microwave heating at 90 °C for 30 h.[15] After completion of the fluorination, one equiv. each of aniline and benzaldehyde, and 0.2 equiv. of $Zn(NO_3)_2$ was added to the reaction mixture for the Mannich reaction. The reaction mixture was then heated under microwave at 120 °C for 30 min to afford $\alpha$-fluoro and aminomethylated $\beta$-ketoesters **3**.[16] It was found that products with Ph as $R^1$ (**3aa-3ad**) have slightly better yields than that with Me as $R^1$ (**3ba-3bd**) except for **3ae** and **3be** which have strong electron-withdrawing $CF_3$ groups on aniline (Table 2). Anilines bearing an electron-withdrawing $R^2$ group such as $NO_2$ or $CF_3$ gave good to excellent product yields because of increased electrophilicity of imines are more favorable for the reaction with the enoles, whereas anilines without an electron-withdrawing group gave trace or no products (**3ad, 3bc** and **3bd**) due to low electrophilicity of the imines. The Mannich products **3a** or **3b** have two stereogenic centers. The ratio of two diastereomers determined by $^1$H MNR is in the range of 1:1 to 4:1.

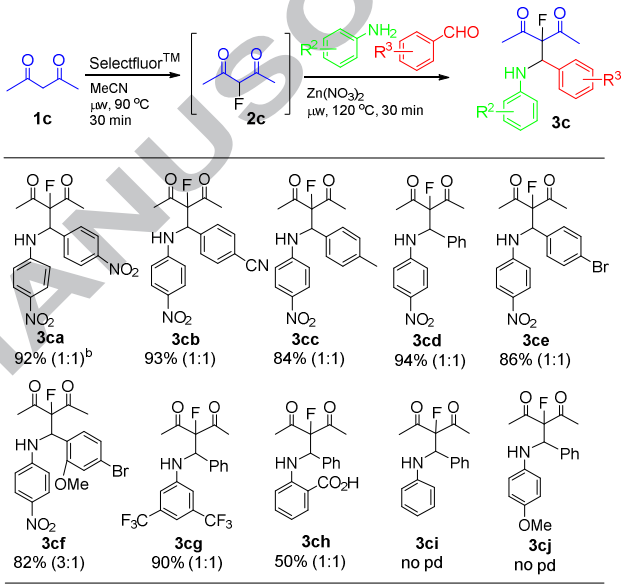
**Table 2.** One-pot reactions of $\beta$-ketoesters **1a** and **1b**[a]




[a] Reactions were carried out using 0.5 mmol each of $\beta$-ketoester and Selectfluor™, followed by addition of 0.5 mmol each of benzaldehydes and aniline, and 20 mol% of $Zn(NO_3)_2$.
[b] Isolated yield, diastereomeric ratio in parenthesis was determined by $^1$H NMR.

The one-pot reactions of 1,3-diketone **1c** were also carried out using a 1:1:1 ratio of diketone, aniline, and benzaldehydes under similar conditions developed for the reactions of $\beta$-ketoesters **1a** and **1b.** It was found that the $R^2$ group of anilines has a significant impact on the yields, whereas the $R^3$ of benzaldehydes only have a minimal impact (Table 3). 1,3-Diketones **1c** seems to have a similar reactivity as $\beta$-ketoesters **1a** and **1b**. Again the reactions of anilines without an electron-withdrawing group gave no product (**3ci** and **3cj**).

**Table 3.** One-pot reactions of 1,3-diketone **1c**[a]

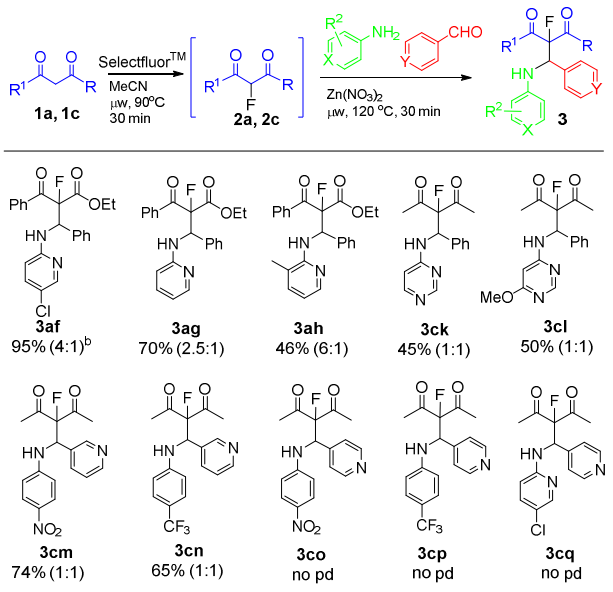



[a] Reactions were carried out using 0.5 mmol each of 1,3-ditekone and Selectfluor™, followed by addition of 0.5 mmol each of benzaldehyde and aniline, and 20 mol% of $Zn(NO_3)_2$
[b] Isolated yield, diastereomeric ratio in parenthesis was determined by $^1$H NMR.

Heteroaromatic amines and aldehydes were also employed for the one-pot reactions (Table 4). 2-Aminopyridine with an electron-withdrawing Cl gave **3af** in a better yield than that of 2-aminopyridine and 2-aminopyridine with a Me group to form **3ag** and **3ah**. 2-Aminopyrimidine and its MeO analog gave products **3ck** and **3cl** in 45% and 50% yield, respectively. Pyridinecarboxaldehydes were also employed for the one-pot reactions. 3-Pyridinecarboxaldehyde gave products **3cm** and **3cn** in good yields, but no products **3co-3cq** were observed from the reaction of 4-pyridinecarboxaldehyde under the same reaction condition.

In summary, a one-pot and two-step reaction process involving electrophilic fluorination of an enolizable 1,3-dicarbonyl compound followed by the Mannich reaction with aromatic amine and nonenolizable aromatic aldehyde has been developed. This simple and efficient method has been demonstrated in the synthesis of a series of $\alpha$-fluoro and aminomethylated 1,3-dicarbonyl compounds. The extension of this method for asymmetric one-pot fluorination and Mannich reactions is currently under investigation and will be reported in due course.

**Table 4.** One-pot reactions with heteroaromatic amines and aldehydes[a]




[a] Reactions were carried out using 0.5 mmol each of 1,3-dicarbonyl compounds and Selectfluor™, followed by addition of 0.5 mmol each of benzaldehydes and aniline, and 20 mol% of $Zn(NO_3)_2$.
[b] Isolated yield, diastereomeric ratio in parenthesis was determined by $^1H$ NMR.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## Supplementary data

Supplementary data associated with this article can be found in the online version at

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16. General procedure for the one-pot synthesis: 1,3-dicarbonyl compound **1** (0.5 mmol) and Selectfluor™ (from Sigma, 0.5 mmol) in 1.0 mL of $CH_3CN$ was heated under Biotage Initiator microwave reactor at 90°C for 30 min. Then a benzaldehyde (0.5 mmol), an aniline (0.5 mmol) and $Zn(NO_3)_2$ (20 mol%) were carefully added to the fluorinated reaction mixture at room temp. The mixture was then heated under microwave at 120 °C for another 30 min. After an aqueous work up, the crude product was purified by flash column chromatography on silica gel to give fluorinated Mannich product **3**.