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PAPER

Catalyst-free and highly selective electrophilic mono-fluorination of acetoacetamides: facile and efficient preparation of 2-fluoroacetoacetamides in PEG-400†

Jingjing Bi, Zhiguo Zhang,* Qingfeng Liu and Guisheng Zhang*

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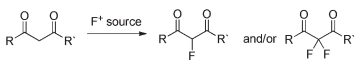
Series of α-mono-fluorinated acetoacetamides were synthesized under mild condition with industrialized Selectfluor as the F^+ source in PEG-400. The approach avoided the use of base or metal catalyst, and most of cases proceeded in nearly quantitative conversions regardless of the electronic nature of the diversity substituent.

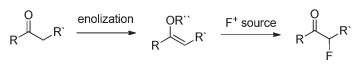
Introduction

"Green and sustainable chemistry" aims to develop environmentally benign syntheses and processing, to reduce steps and consequently minimize toxic waste and byproducts, to produce simpler and safer experimental procedures and to design energy efficient syntheses.[1] At the same time, these greener approaches should still take into account high atom economy, selectivity (chemoselectivity, regioselectivity, stereoselectivity) and efficiently convert to larger-scale preparations which are of crucial importance for industrial applications. According to Trost's enigmatic atom economy[2] and Sheldon's E-factor,[3] the two most famous "green chemistry parameters", organic solvents should be minimized or even avoided. So naturally, water,[4] polyalcohols, polyethers,[5] ionic liquids,[6,7] and supercritical fluids are therefore employed in organic reactions, and solvent-free reaction (SFR) seems to be another good choice.

To date, fluorine-containing compounds play an increasingly important role, introduction of fluoride atom(s) into a molecule brings out valuable properties, which are applicable to pharmaceuticals,[8] agrochemicals,[9] and materials[10] bearing an outstanding properties.[11] Nucleophilic fluorination[12] and electrophilic fluorination[13,14] are the two most direct and useful methods to introduce fluorine selectively into organic compounds.[15] Many of them, such as electrophilic fluorinating agents $FClO_3$,[16] NF_3O,[17] XeF_2,[18] AcOF,[19] PhIO/HF[20] and NFSI,[21] are dangerous or expensive. So, over the past decade, easily-handled cost-effective bis(tetrafluoroborate) [F-TEDA-BF_4 (TEDA = triethylenediamine)],[14] commonly called Selectfluor, rapidly become a commercial chemical[22] with established applications in the pharmaceutical industry and asymmetric synthesis,[23,24] and has attracted much attention as a stable electrophilic fluorination reagent.



(1)

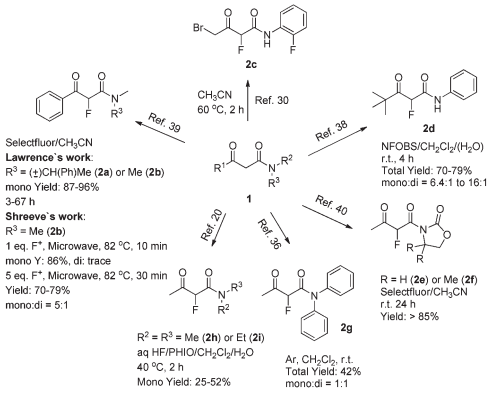


(2)

α-Fluoro-1,3-dicarbonyl compounds, especially α-mono-fluorinated 1,3-dicarbonyl compounds, are widely used in asymmetric synthesis[25–29] and construction of biologically active molecules.[30,31] They have been synthesized by treating the parent dicarbonyls (eqn (1)) or their enolates with fluorine (eqn (2)),[32–35] base (commonly used strong base, such as NaH, LiHMDS *etc.*) and/or metal as catalysts, acetonitrile and dichloromethane being the two most commonly used solvents.[24] But most of the reaction inevitably produced a mixture of mono and di-fluorinated products that must be troublesome to separate (eqn (1)).[36–38] Therefore, high yielding of mono-fluorinated products remains a much more challenging task. Currently, a few cases have so far focused on the preparation of α-mono-fluorinated acetoacetamides, in which acetoacetamides were a special case of β-dicarbonyl compounds (Scheme 1). Lawrence *et al.*[39] demonstrated that 1,3-dicarbonyl compounds including β-ketoamides **2a** and **2b** are converted efficiently to 2-monofluoro derivatives, and thence to 2,2-difluoro derivatives. Xiao and Shreeve[37] also showed that the mono-fluorination of less reactive ketoamide **2b** could be accelerated dramatically under microwave assistance, but at the end of the reaction process traces of 2,2-difluorinated products often formed in these reactions judging from the NMR spectral analyses. ω-Bromoacetoacetanilide **1c** can be regiospecifically fluorinated at the α-position in organic solvent.[30] In Davis *et al.*'s[38] study of the electrophilic fluorinations by using *N*-fluoro-*o*-benzenedisulfonimide (NFOBS), mono- (**2d**) and difluorination (**3d**) are both observed

College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education; Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, PR China. E-mail: zhangzhiguo3030@yahoo.com.cn, zgs6668@yahoo.com; Fax: (+86) 373-3325250

†Electronic supplementary information (ESI) available: Detailed experimental procedure, including ^1H NMR, ^{13}C NMR and IR spectra for all compounds. See DOI: 10.1039/c2gc16661e



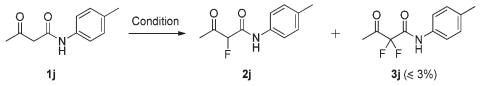
Scheme 1 Related works of other researchers.

in the best ratio of 16 : 1 when using water as a cosolvent, mono-fluorination increases at the expense of difluorination. *N*-Aceto-acetylated oxazolidinones **1e** and **1f** also give **2e** and **2f** in good yield in CH_3CN.[40] Togni *et al.*[36] isolated a 1 : 1 mixture of mono (**2g**) and difluorination (**3g**) of β-ketoamide with Selec-tfluor using $CpTiCl_3$ as a catalyst. Very recently, Kitamura's group[20] reported that 3-ketoamides underwent fluorination to give the corresponding 2-fluorinated products **2h** and **2i** in yields of 25% and 52%, respectively, by direct use of 55% aqueous hydrofluoric acid and iodosylbenzene (PhIO). To the best of our knowledge, there is no detailed investigation of the controlled synthesis of α-mono-fluorination of acetoacetamides, especially consideration of greener methods such as avoiding the use of alkali, organic solvent, and minimizing fluoride reagents and with enhanced selectivity, *etc*. Herein, we wish to report an efficient catalyst-free α-electrophilic mono-fluorination of aceto-acetamides under green conditions.

Results and discussion

On the basis of our studies on acetoacetamides in recent years,[41–45] we found α-fluorination of β-keto amides is a very important class of reaction. But the intolerable reaction mixture often is annoying to isolate. In some cases, the ratio of mono to di-fluorinated products was significantly lower as well as the yield.[20,36–38] DesMarteau *et al.*'s findings[46] showed that the enol content of 1,3-dicarbonyl compounds was the key factor, which could affect the number of fluorine atoms at the α-position. And solvent is one of the factors affecting enol content of the sub-strates. So we hypothesize that selecting the appropriate solvent (s) should be able to control the final fluorinated products.[47] Under the guidance of this assumption, we examined the direct fluorination of acetoacetamides under a variety of green reaction conditions, using a commercially available Selectfluor as the fluorine source. The attempts are summarized in Table 1. α-Monofluorinated β-keto amide **2j** could be obtained with 95% yield when we treated **1j** with Selectfluor (1.1 equiv.) in PEG-400 (3 mL) for 8 h at 60 °C, while it will take a longer time at room temperature (entry 3 *vs.* 4). If water was chosen as solvent, at room temperature, the yield of **2j** was significantly lower and the reaction time was very long (entry 1). Even heating at 60 °C, the yield of **2j** was not higher than in PEG-400

Table 1 Survey of reaction conditions[a]



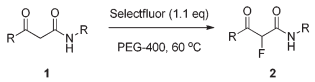
Entry	Condition	Selectfluor (eq.)	*T*/°C	Time	Product	Yield[b]/%
1	H_2O	1.1	25	30 h	**2j**	51[c]
2	H_2O	1.1	60	8 h	**2j**	52[d]
3	PEG-400	1.1	25	30 h	**2j**	87[e]
4	**PEG-400**	**1.1**	**60**	**8 h**	**2j**	**95**
5	PEG-400	1.1	60	8 h	**2j**	97[f]
6	PEG-400	1.1	60	8 h	**2j**	94[g]
7	$[BMIM]BF_4$	1.1	60	8 h	**2j**	86[h]
8	$[BMIM]PF_6$	1.1	60	8 h	**2j**	69[i]
9	PEG-400	2.2	60	19 h	**3j**	97

[a] All reactions were carried out with acetoacetarylamide **1j** (1.0 mmol), Selectfluor as the fluorine source, unless otherwise indicated. [b] Isolated yield and trace **3j** (≤3%) was detected by HPLC in all reactions. [c] 48% **3j** was found. [d] 40% **1j** was recovered. [e] 9% **1j** was recovered. [f] Microwave irradiation with power range was up to 800 W. [g] Ultrasound was used. [h] 12% **1j** was recovered. [i] 28% **1j** was recovered.

in 8 h, and also 40% **1j** was recovered (entry 2 *vs.* 4). Under other green conditions, microwave irradiation was as good as heating method during the process (entry 5 *vs.* 4) and ultrasound was inefficient (entry 6 *vs.* 4). In hydrophilic ionic liquids, $[BMIM]BF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate), and hydrophobic ionic liquids, $[BMIM]PF_6$ (1-butyl-3-methyl-imidazolium hexafluorophosphate), the reactions gave **2j** 86% and 69% yield after 8 h at 60 °C and 12% and 28% **1j** was recovered, respectively. It is noteworthy that the reaction was fast in hydrophilic ionic liquid than in hydrophobic ionic liquid (entries 7 and 8). From the ^1H NMR and ^{13}C NMR we did not find 2,2-difluoro acetoacetamide **3j**.[37] In order to confirm whether or not the reaction generates di-fluorinated products in the end, we analyzed the HPLC spectrum of all attempts in Table 1. The HPLC data showed that not more than 3% di-fluori-nated product **3j** was produced in all surveys. When using 2.2 equiv. of Selectfluor for α-fluorination of acetoacetamides **1j**, in PEG-400, the di-fluorinated product **3j** could be obtained with a yield of 97% at 60 °C (Table 1, entry 9). So we determined entry 4 as the final optimal conditions for the preparation of mono-fluorinated products, considering the factors of price, ease to get and industrialization.

Having concluded from the above results that the optimal reac-tion solvent system was PEG-400 for mono-fluorination, the effect of various β-keto amides were then further evaluated using similar reaction conditions (Table 2). It was apparent that all reactions could finish in 27 h at 60 °C or slightly higher tempera-ture with a yield of 90–100% (Table 2, compounds **2j–2y**). The diverse substituents on the aryl, whether electron-donating groups (EDG) or electron-withdrawing groups (EWG), had no significant effect on the yield of α-mono-fluorinated acetoaceta-mides (Table 2, compounds **2j–2t**). In the case of β-keto amide **1g**, 2-fluoro-β-keto amide **2g** could be isolated in yield of 84% which HPLC yield was 93%.[36] The yield of mono-fluorinated products of aliphatic β-keto amide **2h**, **2i** and **2u** were also satis-factory.[20] Acyl changes are permitted too, isobutyryl and benzoyl substituted amides can smoothly slide into the products

Table 2 The preparation of α-mono-fluorinated acetoacetamides[a,b]



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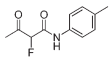
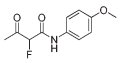
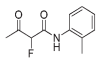
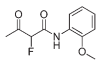
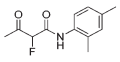
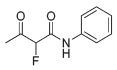

2j, 8 h, 95%

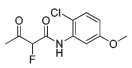

2k, 12 h, 94%

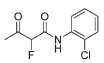

2l, 10 h, 92%

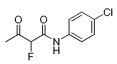

2m, 14 h, 97%

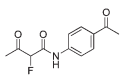

2n, 5 h, 99%

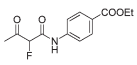

2o, 6 h, 92%

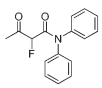

2p, 20 h, 91%[c]


2q, 8 h, 98%[c]


2r, 5 h, 96%

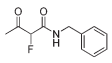

2s, 8 h, 94%

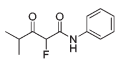

2t, 24 h, 90%[d]

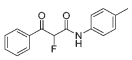

2g, 10 h, 84%, (93%)[e]

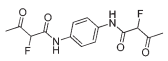

2h, 11 h, 98%

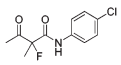

2i, 8 h, 94%


2u, 27 h, 76%,[c] (96%)[e]


2v, 17 h, 96%


2w, 2 h, 97%


2x, 6 h, 81%, (98%)[e]


2y, 14 h, 100%

[a] Unless otherwise indicated, all reactions were carried out with acetoacetamide **1** (1.0 mmol), Selectfluor (1.1 mmol), PEG-400 (3.0 mL) at 60 °C. [b] Isolated yield and trace **3** (≤3%) was detected by HPLC in all reactions. [c] 80 °C was used. [d] 9% **1t** was recovered and prolonged reaction time did not improve the yield of **2t**. [e] HPLC yield.

in the yield of 96% and 97%, respectively (Table 2, compounds **2v–2w**). To our delight, the reaction could also be conducted successfully when *N*,*N*′-(1,4-phenylene)bis(acetoacetamide) **1x** was employed, despite its poor solubility in PEG-400, 81% yield of **2x** was isolated which HPLC yield was 98%. We also explored the possibility of the reaction by using α-methyl-substituted β-keto amide **1y** in a single case; as a result, quantitative yield of **2y** was obtained in 14 h. A significant amount of mono-fluorinated of acetoacetamides was found in the water during work-up, which account for the low isolated yields of compound **2g**, **2u** and **2x**. It must be mentioned that traces of difluorinated compounds **3** (≤3%) were detected by HPLC in all reactions.

Conclusions

In conclusion, a highly efficient approach to α-mono-fluoro acetoacetamides has been developed *via* selective α-electrophilic mono-fluorination of acetoacetamides using industrialized Selectfluor as the F^+ source in green solvent PEG-400. The ratio of mono- and di-fluorinated products was more than 30 : 1 and the approach avoided the use of base or metal catalyst, and most cases proceeded in nearly quantitative conversions regardless of the electronic nature of the diversity substituent. At the same time, this efficient procedure avoided complicated separation, just recrystallization or evaporating the extraction solvent. The electrophilic fluorination of other 1,3-dicarbonyl derivatives to form 2-monofluoro-l,3-dicarbonyl analogues under green conditions are in progress.

Experimental

General procedure for synthesis of 2-fluoro-acetoacetamides 2 (see ESI† for more details)

The mixture of 3-oxo-*N*-*p*-tolylbutanamide **1j** (191 mg, 1.0 mmol) and Selectfluor (390 mg, 1.1 mmol) in PEG-400 (3.0 mL) was well stirred for 8 h at 60 °C oil bath, then to the mixture was added water (10 mL), then extracted with diethyl ether (15 mL × 4). The solvent was removed under reduced pressure, and the residue was purified by a short flash silica gel column chromatography to give compound **2j** (199 mg, 95%) as a yellow solid (eluent: petroleum ether–ethyl acetate = 5 : 1).

Acknowledgements

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