Tetrahedron Letters 55 (2014) 5908–5910

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Operationally convenient method for preparation of sulfonamides containing α,α-difluoro-β-amino carbonyl moiety

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ARTICLE INFO

Article history:
Received 1 June 2014
Revised 26 July 2014
Accepted 1 September 2014
Available online 6 September 2014

Keywords:
N-Sulfonyl imines
α,α-Difluoroenolates
Pentafluoro-β-di-ketone hydrate
C—C bond cleavage
Mannich reaction

ABSTRACT

We report here that the reactions of in situ generated unprotected α,α-difluoroenolates with various *N*-sulfonyl imines take place under operationally convenient conditions affording a novel type of fluorinated sulfonamides of high pharmaceutical potential. The reactions feature structural generality, excellent yields and can be easily scaled up for practical preparation of the target fluorine-containing sulfonamides.

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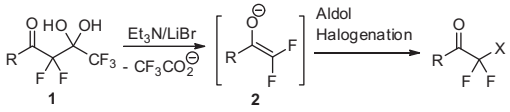
Sulfonamide functionality is commonly used in the design of biologically active compounds. Of particular interest are sulfonamide derivatives containing fluorine atoms, allowing for an additional enhancing and modulating target biological properties.[1] For example, fluorine-containing Crestor and Celebrex[2] are currently among the most successful drugs in the pharmaceutical market. Thus far, numerous types of fluorine-containing sulfonamides have been synthesized and biologically tested.[3] However, one potentially interesting structural type of derivatives possessing pharmacophoric fluorinated β-amino carbonyl fragment is still hitherto unknown. Consistent with our longstanding interest in the synthesis of biologically relevant fluorinated compounds,[4] here we report exceptionally useful reactions between Colby α,α-difluoroenolates and *N*-(*p*-tolylsulfonyl)imines providing reliable and practical access to this novel class of fluorine-containing sulfonamides.

β-Amino-α,α-difluoro carbonyl compounds generally show a potent inhibitory activity towards hydrolytic enzymes[5] and their syntheses have received a significant attention. The established preparation of these compounds involves application of α,α-difluoroenol silyl ethers (or α,α-difluorovinyl methyl ethers) which must be separately prepared and purified before the corresponding reactions with imines.[6] This step is obviously a methodological bottleneck rendering the target compounds expensive and not available on even relatively large scale. Recently the Colby group made a significant discovery in this area demonstrating that unprotected α,α-difluoroenolates **2** can be easily generated in situ by treatment of hydrates **1** (Scheme 1) with organic bases.[7]



Scheme 1. Generation of enolates **2** and their reactions with some electrophiles.

Reactivity of thus generated α,α-difluoroenolates **2** is still virtually unexplored though their aldol additions[8] and reactions with halogens[9] have been reported. Drawing inspiration from these results and our experience in the chemistry of *N*-sulfinyl imines,[10,11] we envisioned that studying the Mannich-type additions of α,α-difluoroenolates **2** with imines might offer a general approach for preparation of various β-amino-α,α-difluoro ketone derivatives of high pharmaceutical potential.[12]

First we conducted reactions of unsubstituted ketone/hydrate **3** with a series of benzaldehyde derived *N*-sulfonyl imines **4** (Table 1).

We found that 1:1.5 ratio of triethylamine/LiBr is optimal for the reactions to proceed with excellent rates and chemical yields.

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http://dx.doi.org/10.1016/j.tetlet.2014.09.001
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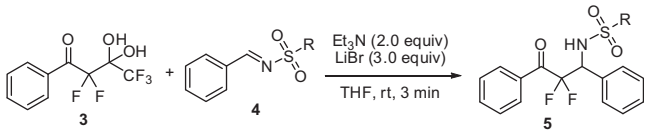
Table 1
Reactions of ketone/hydrate **3** with imines **4**[a]



Entry	R	Product	Yield[b] (%)
1	Me	**5a**	97
2	C_6H_5	**5b**	97
3	4-ClC_6H_4	**5c**	97
4	4-MeC_6H_4	**5d**	97
5	4-$NO_2C_6H_4$	**5e**	97
6	4-MeC_6H_4	**5d**	92[c]

[a] Reaction conditions: hydrate of di-ketone **3** (0.5 mmol), imine **4** (0.6 mmol, 1.2 equiv), LiBr (1.5 mmol, 3.0 equiv), Et_3N (1.0 mmol, 2.0 equiv), THF (10 mL).
[b] Isolated yields of analytically pure **5**.
[c] The reaction was performed on 25 mmol scale (~10 g).

As one can see from Table 1, the reactions show exceptional practicality and substrate generality being completed in just a few minutes and affording the target products **5** in virtually quantitative yields. Considering operationally convenient conditions of this process, such as ambient temperature, commercial grade solvent and reagents,[13] we decided to test this reaction for a large-scale preparation of fluorinated sulfonamides **5**. To this end, we repeated the addition between ketone/hydrate **3** and *N*-sulfonyl imine **4d** (Table 1, entry 6) on 25 mmol scale. Delightfully, the reaction was completed in 3 min and the target product **5d** was isolated in chemically pure form in 92% yield. These results clearly underscored the synthetic value of the described process for practical preparations of novel fluorine-containing sulfonamides **5**.

With these truly exciting results in hand, we focused the rest of this preliminary study on structural generality of both starting keto/hydrates and *N*-sulfonyl imines. To test the substituent effect on the imines side, we chose *N*-tosyl derivatives **6** (Table 2) which were reacted with unsubstituted keto/hydrate **3** under the standard conditions. It should be noted that all reactions were stopped just after 3 min and yields of products **7** were not optimized.

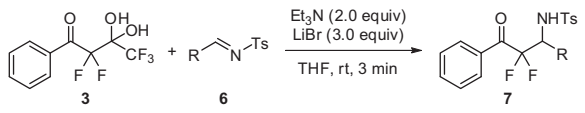
As usual, for structural study we selected aromatic *o*-, *m*-, *p*-substituted derivatives **6** as well as examples featuring electron-donating and -withdrawing groups, heterocyclic and aliphatic moieties. Inspection of the results collected in Table 2 clearly suggests that substituent effect plays a relatively minor role in the outcome of these addition reactions. Thus, the electron-withdrawing substituents tend to slow the reaction rates, which is a bit surprising as the electrophilicity of the C=N should be increased in these cases. Furthermore, the reaction of *o*-Cl-substituted *N*-(tosyl)imine **6a** (Table 2, entry 1) gave rather low yield of product **7**, suggesting some steric/electrostatic effect of the chlorine atom. On the other hand 2-naphthyl derivative **6g** (Table 2, entry 7) gave the corresponding product **7** in virtually quantitative yield. Excellent yield was also observed in the reaction of heterocyclic substrate **6h** (Table 2, entry 8), while cinnamyl derived **6i** (Table 2, entry 9) gave sulfonamide **7** in a bit lower yield. Overall, these preliminary results clearly demonstrate that nature and electronic properties of the substituents on the *N*-(tosyl)imines **6** do not play any detrimental role in the reaction outcome.

To complete the structural generality study, we examined next the role of substituents on the starting ketone/hydrate. In this case we also selected substrates featuring diverse substitution type including aromatic *o*-, *m*-, *p*-substituted derivatives **8** (Table 3) as well as examples featuring electron-donating/withdrawing groups and heterocyclic rings. Also in this case, the reactions were conducted under the standard conditions and yields were not optimized.

Considering the data presented in Table 3, one may assume that substituent effect on the starting ketone/hydrates **8** is even less pronounced as compared with the results discussed above (Table 2). However, *o*-Cl-substituted **8a** (Table 3, entry 1) also gave the lowest yield of the corresponding product **9**, while in the case of *m*- and *p*-Cl-derivatives **8b**,**c** the reaction rates and yields were noticeably higher (Table 3, entries 2 and 3). For the rest of substrates **8** containing electron-donating (Table 3, entries 4 and 5), 2-naphthyl (Table 3, entry 6) and heterocyclic moiety (Table 3, entry 7) the yields of the target sulfonamides **9** were agreeably excellent. On the whole, one may assume that the nature of the substitution on the starting ketone/hydrates **8** has an insignificant effect on the successful outcome of these Mannich-type addition reactions.

As the final objective of this preliminary study, we would like to propose a plausible mechanism to account for the results obtained. Among possible transition states (TSs) for these reactions, we believe that TSs A and B (Fig. 1) are the most reasonable. First of all, they both have the most bulky R and R′ groups away from each other and have additional stabilization via coordination of Li ion to the *N*-sulfone imine moiety. However, TS A seems to be more plausible as it can account for the lower reactivity of the substrates with electron-withdrawing groups as well as the negative effect of the *o*-Cl-substitution (Table 2). Presumably, the additional

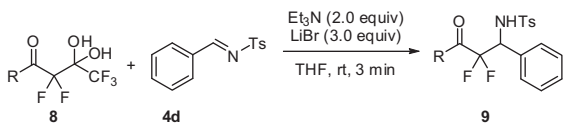
Table 2
Reaction scope of ketone/hydrate **3** with *N*-(tosyl)imine **6**[a]



Entry	R	Product	Yield[b] (%)
1	2-ClC_6H_4	**7a**	81
2	3-ClC_6H_4	**7b**	88
3	4-ClC_6H_4	**7c**	93
4	4-$MeOC_6H_4$	**7d**	96
5	4-CNC_6H_4	**7e**	91
6	4-$NO_2C_6H_4$	**7f**	88
7	2-Naphthyl	**7g**	97
8	2-Thienyl	**7h**	95
9	(*E*)-Ph—CH=CH–	**7i**	88

[a] Reaction conditions: hydrate of di-ketone **3** (0.5 mmol), imine **6** (0.6 mmol, 1.2 equiv), LiBr (1.5 mmol, 3.0 equiv), Et_3N (1.0 mmol, 2.0 equiv), THF (10 mL).
[b] Isolated yields of analytically pure products **7**.

Table 3
Reaction scope of ketone/hydrates **8** with *N*-(tosyl)imine **4d**[a]



Entry	R	Product	Yield[b] (%)
1	2-ClC_6H_4	**9a**	84
2	3-ClC_6H_4	**9b**	92
3	4-ClC_6H_4	**9c**	94
4	4-MeC_6H_4	**9d**	97
5	4-$MeOC_6H_4$	**9e**	98
6	2-Naphthyl	**9f**	98
7	2-Thienyl	**9h**	96

[a] Reaction conditions: hydrate of di-ketone **8** (0.5 mmol), imine **4d** (0.6 mmol, 1.2 equiv), LiBr (1.5 mmol, 3.0 equiv), Et_3N (1.0 mmol, 2.0 equiv), THF (10 mL).
[b] Isolated yields of analytically pure sulfonamides **9**.

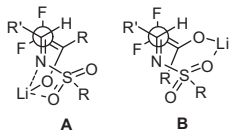


Figure 1. Plausible transition states in the reactions under study.

coordination of the Li ion to the imine nitrogen will be less effective in the case of electron-withdrawing groups on the starting imine. On the other hand, the *o*-Cl atom of the imine R′ group might be involved in destabilizing electrostatic interactions with the fluorine atoms[14] of the enolate part.

In conclusion, we disclose here the reactions between in situ generated unprotected α,α-difluoroenolates with various *N*-sulfonyl imines as a very practical and generalized approach for preparation of novel type of fluorinated sulfonamides. The reactions can be conducted under operationally convenient conditions and feature exceptional reaction rates and chemical yields of the target sulfonamide products. Full scope of these synthetically useful reactions is currently under study and will be reported in a due course.

Acknowledgments

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21102071) and the Fundamental Research Funds for the Central Universities (Nos. 1107020522 and 1082020502). The Jiangsu 333 Program (for Pan) and Changzhou Jin-Feng-Huang Program (for Han) are also acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.001.

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