Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500150

Nucleophilic Difluoroalkylation of Isocyanates with Difluoromethyl 2-Pyridyl Sulfone

Shan Li,[+a] Peng Peng,[+a] Jun Wei,[a] Yongzhou Hu,[a] Jinbo Hu,[b] and Rong Sheng[a,*]

[a] Zhejiang Province Key Laboratory of Anti-Cancer Drug Research, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, People's Republic of China
E-mail: shengrong1973@163.com

[b] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China

[+] These authors contribute equally to this work.

Received: February 13, 2015; Revised: August 18, 2015; Published online: November 12, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500150.

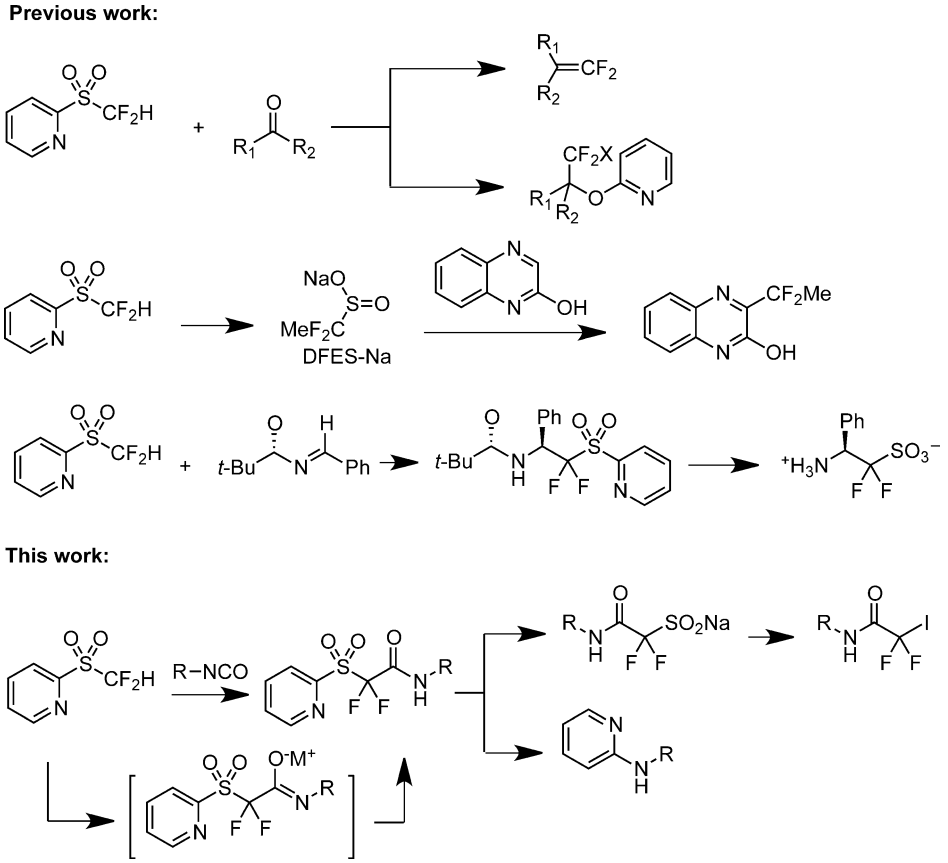
Abstract: The nucleophilic difluoroalkylation of isocyanates with difluoromethyl 2-pyridyl sulfone furnished 2,2-difluoro-2-pyridinylsulfonylacetamides with good to excellent yield. These products can be converted to 2,2-difluoroacetamide sulfinate, iodo-difluoroacetamide and 2-aminopyridine derivatives easily.

Keywords: difluoromethyl 2-pyridyl sulfone; 2,2-difluoro-2-pyridylsulfonylacetamide; isocyanates; Julia–Kocienski reaction

Incorporation of fluorine atoms into organic molecules has become a powerful strategy to modulate their biological properties due to the high electronegativity and small size of fluorine as well as its very different chemical reactivity with respect to hydrogen.[1] Fluorinated drugs have constituted approximately 5–12% of the total number of launched drugs all over the world and with a noticeable increase in the past few years.[2] As the bioisostere of methylene (CH_2), the difluoromethyl moiety (CF_2) has attracted much attention in the field of medicinal chemistry and it was incorporated into the structure of the PDE-4 inhibitor Roflumilast.[3] Among all the difluoromethylation reagents,[4] difluoromethyl 2-pyridyl sulfone (2-PySO_2CF_2H, Scheme 1) has aroused much interest due to its wide use in the construction of various difluoromethyl derivatives.[5] For example, 2-PySO_2CF_2H could act as a novel and efficient *gem*-difluoroolefination reagent for both aldehydes and ketones through the Julia–Kocienski reaction,[5] the *in situ* halogenation of Julia–Kocienski intermediates yielded a wide range of iodo- and bromodifluoromethyl derivatives.[6] In addition, it also can react with alkyl halides to yield alkyl 2,2-difluorinated 2-pyridyl sulfones, which undergo dearylation with EtSNa to produce alkyl 2,2-difluorosulfinates, such as sodium difluoroethylsulfinate (DFES-Na), which acts as an efficient difluoroethylation agents for a variety of heterocycles, including quinoxaline, indole, pyridine and pyrimidine derivatives.[7,8] Besides that, 2-PySO_2CF_2H also can realize a highly stereoselective nucleophilic difluoro-(sulfinato) methylation of *N-tert*-butanesulfinylimine to yield optically active α,α-difluoro-β-amino sulfonic acids as well as fluorinated peptidosulfonamides.[9]

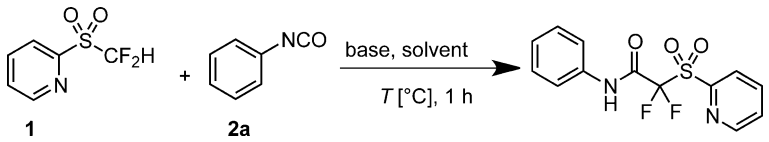
Up to date, the substrate scope of 2-PySO_2CF_2H is still limited to the above reported carbonyl, alkyl halide and imine derivatives. Isocyanates are highly potent electrophilic substrates for a variety of nucleophilic agents, including Grignard reagents, amines and alcohols, resulting in the production of numerous biologically active compounds, including ureas, carbamates and amides.[10] Therefore, the reactions between 2-PySO_2CF_2H and isocyanates were carried out to explore the novel usage of this difluromethylation agent.

We first attempted the reaction of 2-PySO_2CF_2H (**1**) with phenyl isocyanate **2a** by applying lithium hexamethyldisilazide (LiHMDS) as the base with THF as the solvent at −78 °C. After simple work-up, we isolated the desired 2,2-difluoro-2-pyridylsulfonylacetamide **3a** in 29% yield. The addition of hexamethylphosphoramide (HMPA) to the system had no beneficial effect to improve the yield (Table 1, entries 1 and 2). With the use of sodium hydride as the base, no sulfonylacetamide was found and the diphenylurea was the main product. (Table 1, entry 3) We



Scheme 1. The reactions of difluoromethyl 2-pyridyl sulfone.

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



1 2a

Entry	**1** (equiv.)	**2** (equiv.)	Base (equiv.)	Solvent	Temperature [°C]	Yield [%][b]
1	1.0	1.2	LiHMDS (1.8)	THF	−78	29
2	1.0	1.2	LiHMDS (1.8)	THF:HMPA = 10:1	−78	31
3	1.0	1.2	NaH (1.8)	DMF	−45	0
4	1.0	1.2	*t*-BuOK (1.8)	DMF	−45	41
5	1.0	1.2	*t*-BuONa (1.8)	DMF	−45	52
6	1.0	1.0	*t*-BuONa (1.8)	DMF	−45	32
7	1.0	1.2	*t*-BuONa (2.5)	DMF	−45	67
8	1.0	1.5	*t*-BuONa (1.8)	DMF	−45	61
9	1.0	1.2	*t*-BuONa (1.8)	DMF	−55	58
10	1.0	1.2	*t*-BuONa (1.8)	DMF	−35	55

[a] This reaction was run on a 1.0 mmol scale.
[b] Yields of isolated products.

surmised that it was produced *via* the condensation of phenyl isocyanate with *in situ* formed aniline (reduction of phenyl isocyanate with H_2 in the system). To avoid this severe side reaction, potassium *tert*-butoxide and sodium *tert*-butoxide were employed in the reaction, and we were pleased to find that the yield increased to 41% and 52%, respectively.

The obvious difference between the two *tert*-butoxide bases indicated that the counterion ($M^+ = Na^+$, K^+) would significantly influence the stability of the

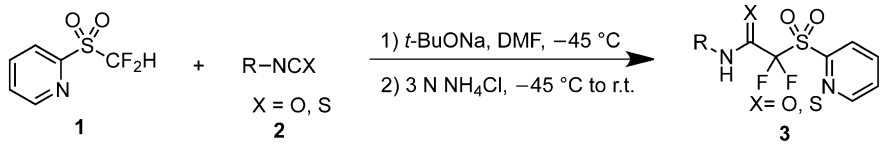
imine intermediate as a result of the different M–O bond strengths. With exhaustive optimization of the proportions of the substrates, the best reaction conditions were established as 1.0 equivalent of 2-Py-SO_2CF_2H reacting with 1.2 equivalents of phenyl isocyanate and 2.5 equivalents of *t*-BuONa in DMF at −45 °C for 2 h (Table 1, entry 7). An additional investigation on the influence of the reaction temperature also confirmed that −45 °C was the optimal one (Table 1, entries 8 and 9).

With the optimized reaction conditions in hand, we examined the substrate scope of this novel nucleophilic difluoromethylation reaction. As shown in Table 2, the reaction tolerates various substituents on the phenyl isocyanate as well as in different positions, including alkyl (**3f**, **3g**), methoxy (**3j**, **3k**, **3l**), halides (**3b**, **3c**, **3d**, **3i**). Interestingly, condensation of 2-Py-SO_2CF_2H with 4-cyano- and 4-acetylphenyl isocyanate also produced the anticipated products with moderate yield (**3n**, 41%; **3o**, 68%), which revealed that the isocynate moiety is a more favorable substrate than the cyano and acetyl moieties in this reaction. In addition, the reaction is also amenable to phenyl thioisocyanates with good yields (**3r**, 81%; **3s**, 84%). Especially for aliphatic isocyanates, good to excellent yields were achieved, indicating the extensive application of this reaction. However, when 4-nitrophenyl isocyanate was used as the substrate, no desired product **3t** was detected even using LC-MS analysis of the reaction mixture, probably due to the weak electrophilic activity of **2t** and its poor solubility in DMF.

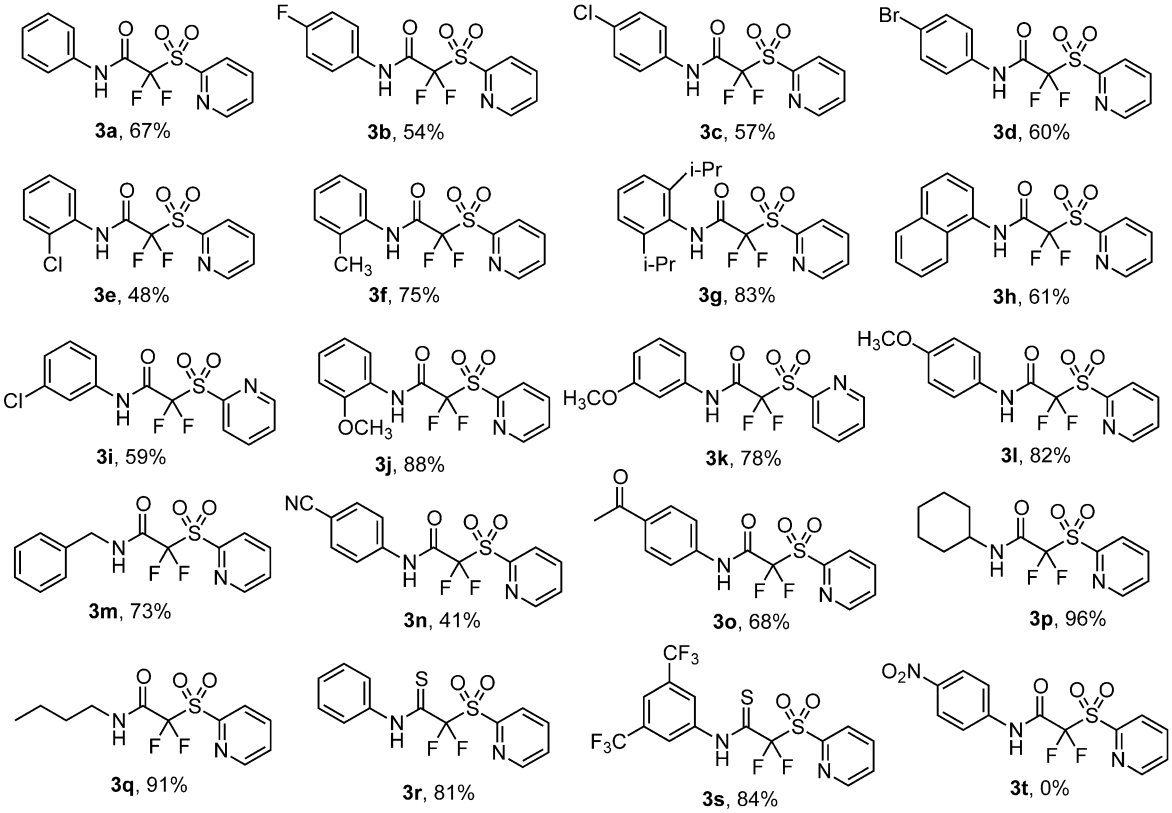
To explore the potential synthetic application of these novel 2,2-difluoro-2-pyridylsulfonylacetamides, compound **3p** was used as a model compound to be treated with EtSH/EtSNa and KI/I_2, as expected, iododifluoroacetamide **4p** was obtained in moderate yield (Scheme 2), which has been revealed as an important intermediate for a variety of Cu-mediated fluoroalkylation reaction reported by our lab.[11]

In an attempt to treat compound **3a** with NaH and *i*-PrBr to get tertiary amide **5a**, to our surprise, **3a** was easily transformed to *N*-phenylpyridin-2-amine **6a** in

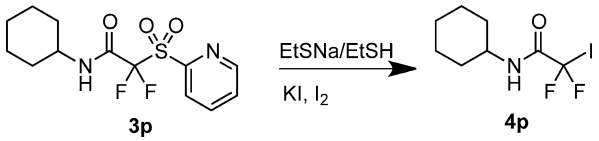
Table 2. Preparation of substituted 2,2-difluoro-2-pyridylsulfonylacetamides from isocyanates.[a]



1 2 3

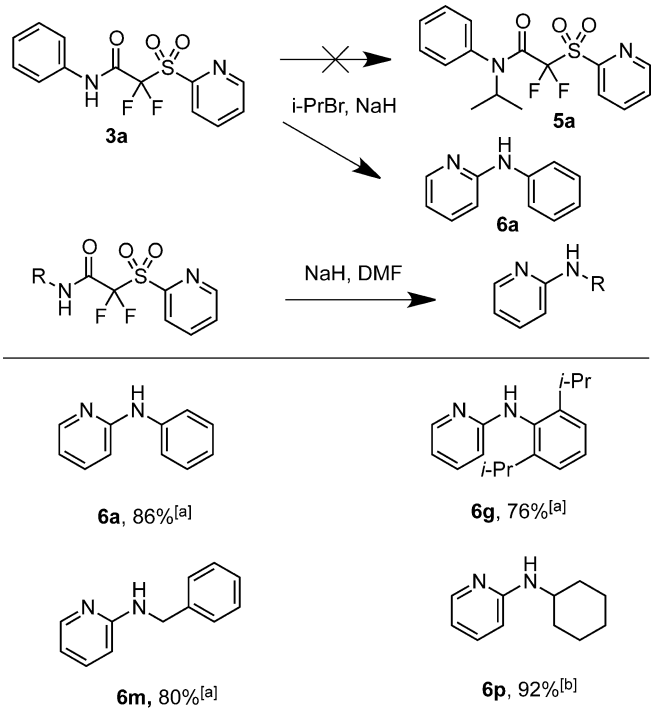


[a] *Reaction conditions:* **1** (0.5 mmol), **2** (0.6 mmol), *t*-BuONa (1.25 mmol), DMF, −45 °C, 1–3 h.



Scheme 2. Preparation of iododifluoroacetamide from 2,2-difluoro-2-sulfonylacetamide.

excellent yield. This transformation was also suitable for other 2,2-difluoro-2-sulfonylacetamide compounds including **3g**, **3m** and **3p**, which result in the production of corresponding **6g**, **6m** and **6p** with good yields (Scheme 3). Based on these results, we deduce that



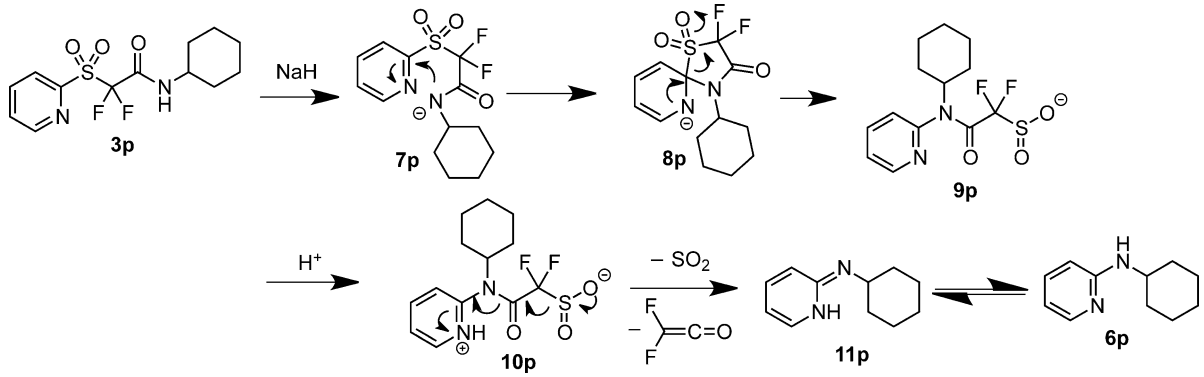
Scheme 3. Unexpected Julia–Kocienski reaction.

these difluoro-2-sulfonylacetamides experienced an intramolecular Julia–Kocienski reaction.[5,6,12]

We speculate that the driving force of this new Julia–Kocienski reaction is based on the weak acidity of the amide moiety of **3p**. The reaction mechanism was proposed as shown in Scheme 4. First, **3p** is deprotonated under basic conditions to obtain amide anion **8p**, which was cyclized to a five-membered ring to obtain intermediate **9p**, then the C–S bond was broken to form sulfinate salt **10p**, which can be easily protonated in the presence of H^+, followed by removal of 2,2-difluoroethenone and sulfur dioxide to get *N*-cyclohexylpyridin-2-amine **6p**.

To get some solid support for the proposed mechanism, we attempted to separate the intermediate **9p** but failed, probabaly due to its high reactivity and instability. Therefore, we performed an LC-MS analysis on the the reaction mixture to trap the intermediate **9p**.[13] To a solution of **3p** (0.15 mmol) in DMF was added NaH (0.23 mmol) in one portion and the mixture was stirred at room temperature for 10 min, then 10 μL of the solution were taken out for LC-MS analysis (Figure 1 and Supporting Information). The HPLC chromatogram shows that there are three peaks (**A**, **B** and **C**) with retention times of 4.75 min, 7.00 min and 10.63 min, respectively. The positive ESI-MS of the peak **A** ($m/z = 177.25$) indicates the production of target compound **6p** (calcd. for $C_{11}H_{17}N_2^+$: $m/z = 177.14$ $[M+H]^+$). The positive ESI-MS of peak **B** ($m/z = 319.20$) is consistent with the compound **3p** (calcd. for $C_{13}H_{17}F_2N_2O_3S^+$: $m/z = 319.35$ $[M+H]^+$). The negative ESI-MS of peak **C** ($m/z = 317.10$) proved the presence of intermediate **9p** (calcd. for $C_{13}H_{15}F_2N_2O_3S^-$: $m/z = 317.08$ $[M-H]^-$). Therefore, these LC-MS analysis results provide the solid proof for our proposed mechanism.

In conclusion, the first nucleophilic difluoroalkylation of isocyanates with difluoromethyl 2-pyridyl sulfone has been reported. The produced 2,2-difluoro-2-pyridinylsulfonylacetamides can be converted to difluoroacetamide sulfinate and iododifluoroacetamide easily. More interestingly, the unusual Julia–Kocienski



Scheme 4. Proposed mechanism for the Julia-Kocienski reaction.

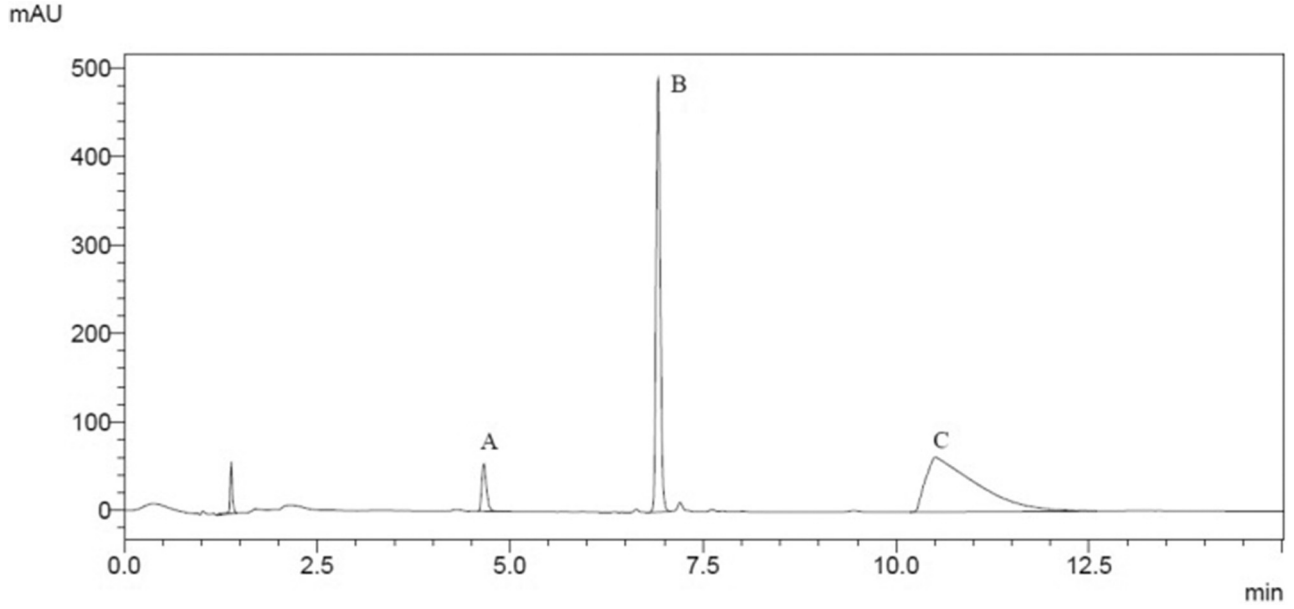


Figure 1. The HPLC chromatograms from the HPLC-MS analysis of the Julia–Kocienski reaction.

reaction results in the production of pyridine-2-amines under basic conditions.

Experimental Section

N-Phenyl-2,2-difluoro-2-(pyridin-2-ylsulfonyl)-acetamide (3a)

To a mixture of isocyanatobenzene (**2a**) (65 μL, 0.6 mmol), 2-(difluoromethylsulfonyl)pyridine **1** (96 mg, 0.5 mmol) in 5 mL DMF, *t*-BuONa (120 mg, 1.25 mmol) was added at −45 °C under an N_2 atmosphere. The mixture was continuously stirred until the TLC indicated the disappearence of **2a**. Then, aqueous saturated ammonium chloride (1 mL) was added to the mixture and the resulting mixture was warmed up to room temperature. After extraction with EtOAc (15 mL × 3), the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the residue was purified with silica gel column chromatography to give **3a** as a white solid; yield: 105 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.85$ (d, $J = 4.0$ Hz, 1H), 8.54 (s, 1H), 8.24 (d, $J = 8.0$ Hz, 1H), 8.10 (dt, $J = 8.0$ Hz, $J = 1.6$ Hz, 1H), 7.73–7.71 (m, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.40 (t, $J = 8.0$ Hz, 2H), 7.24 (m, 1H); ^{19}F NMR: $\delta = -108.48$ (s, 2F); ^{13}C NMR: $\delta = 155.06$ (t, $J =$ 24.7 Hz), 151.84, 150.99, 138.75, 135.65, 129.37, 129.32, 126.53, 126.25, 120.54, 117.48 (t, $J = 298.5$ Hz); HR-MS (CI): $m/z = 313.0459$, calcd. for $C_{13}H_{10}F_2N_2O_3S$ $[M]^+$: 313.0453.

N-Cyclohexyl-2,2-difluoro-2-iodoacetamide (5p)

EtSH (6 mL) was slowly added into a sealed tube containing NaH (80 mg, 2.0 mmol) and THF (8 mL) at 0 °C under an N_2 atmosphere. After stirring for 5 min, a solution of **3p** (318 mg, 1.0 mmol) in THF was added to this EtSNa suspension. Then, the tube was closed with a PTFE-lined screw cap and the mixture was stirred at 0 °C for about 2 h, then at room temperature overnight. After removal of the solvent in vacuum, the residue was equilibrated with 10 mL water and 15 mL Et_2O. The ether layer was discarded, and KI (249 mg, 1.5 mmol) and I_2 (477 mg, 1.75 mmol) were added to the aqueous solution in one portion. The mixture was stirred at 80 °C for 3 h. After cooling to room temperature, the mixture was extracted with EtOAc (15 mL × 3) and the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was purified with silica gel column chromatography to give product **5p** as a white solid; yield: 175 mg (58%). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 8.77$ (d, $J = 9.0$ Hz, 1H), 3.61–3.46 (m, 1H), 1.79–1.63 (m, 4H), 1.60–1.52 (m, 1H), 1.33–1.20 (m, 4H), 1.12–1.06 (m, 1H); ^{19}F NMR: $\delta = -59.88$ (s, 2F); ^{13}C NMR: $\delta = 161.72$ (t, $J =$ 24.3 Hz), 95.90 (t, $J = 318.4$ Hz), 49.27, 31.90, 25.43, 25.12; MS (ESI): $m/z = 304.3$ $(M + H^+)$.

N-Phenylpyridin-2-amine (6a)

To a solution of 2,2-difluoro-*N*-phenyl-2-(pyridin-2-ylsulfonyl)acetamide (**3a**) (78 mg, 0.25 mmol) in DMF (10 mL) was added NaH (15 mg, 0.37 mmol) in one portion at 0 °C, the reaction mixture was stirred at 60 °C for 3 h. After being quenched with water at room temperature, the mixture was extracted with EtOAc (30 mL × 3) and the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was subjected to silica gel column chromatography to provide **6a** as a white solid; yield: 40 mg (92%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 5.0$ Hz, 1H), 7.51 (dt, $J = 8.0$ Hz, $J =$ 2.0 Hz, 1H), 7.34–7.32 (m, 4H), 7.07–7.04 (m, 1H), 6.90 (d, $J = 8.5$ Hz, 1H), 6.87 (s, 1H), 6.74–6.72 (m, 1H); ^{13}C NMR: $\delta = 156.10$, 148.31, 140.51, 137.76, 129.32, 122.86, 120.44, 114.98, 108.24; MS (ESI): $m/z = 171.2$ $(M + H^+)$.

Acknowledgements

This work was financially supported by the Science and Technology Department of Zhejiang Province (2014C33181). We thank Mrs. Jianyang Pan (Pharmaceutical Informatics Institute, Zhejiang University) for performing the NMR and mass spectrometry.

References

[1] W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369.
[2] a) W. K. Hagmann *J. Med. Chem.* **2008**, *14*, 4359–4369; b) E. Parisini, P. Metrangolo, T. Pilati, G. Resnati, G. Terraneo, *Chem. Soc. Rev.* **2011**, *40*, 2267- 2278.
[3] S. A. Antoniu, *Int. J. Chron. Obstruct. Pulmon. Dis.* **2011**, *6*, 147–155.
[4] a) B. E. Smart, *Chem. Rev.* **1996**, *96*, 1555–1556; b) G. K. Prakash, J. Hu, *Acc. Chem. Res.* **2007**, *40*, 921–930.
[5] Y. Zhao, W. Huang, L. Zhu, J. Hu, *Org. Lett.* **2010**, *12*, 1444–1447.
[6] Y. Zhao, B. Gao, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 5790–5793.
[7] G. K. Prakash, C. Ni, F. Wang, J. Hu, G. A. Olah, *Angew. Chem.* **2011**, *123*, 2607–2611; *Angew. Chem. Int. Ed.* **2011**, *50*, 2559–2563.
[8] a) Q. Zhou, J. Gui, C. M. Pan, E. Albone, X. Cheng, E. M. Suh, L. Grasso, Y. Ishihara, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12994–12997; b) Q. Zhou, A. Ruffoni, R. Gianatassio, Y. Fujiwara, E. Sella, D. Shabat, P. S. Baran, *Angew. Chem.* **2013**, *125*, 4041–4044; *Angew. Chem. Int. Ed.* **2013**, *52*, 3949–3952.
[9] G. K. Prakash, C. Ni, F. Wang, Z. Zhang, R. Haiges, G. A. Olah, *Angew. Chem.* **2013**, *125*, 11035–11039; *Angew. Chem. Int. Ed.* **2013**, *52*, 10835–10839.
[10] a) Z. Wang, S. M. Cohen, *Chem. Soc. Rev.* **2009**, *38*, 1315–1329; b) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814–825; c) M. Moniruzzaman, Y. Tahara, M. Tamura, N. Kamiya, M. Goto, *Chem. Commun.* **2010**, *46*, 1452–1454.
[11] J. Zhu, W. Zhang, L. Zhang, J. Liu, J. Zheng, J. Hu, *J. Org. Chem.* **2010**, *75*, 5505–5512.
[12] a) C. Aissa, *Eur. J. Org. Chem.* **2009**, 1831–1844; b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585; c) B. Gao, Y. Zhao, M. Hu, C. Ni, J. Hu, *Chem. Eur. J.* **2014**, *20*, 7803–7810.
[13] a) W. Cheng, Y. Yuan, N. Qiu, P. Peng, R. Sheng, Y. Hu, *Bioorg. Med. Chem.* **2014**, *22*, 6796–6805; b) W. Cheng, S. Zhu, X. Ma, N. Qiu, P. Peng, R. Sheng, Y. Hu, *Eur. J. Med. Chem.* **2015**, *89*, 826–834.

