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New *gem*-difluoromethylene-containing isocyanide as a useful building block for the synthesis of difluorinated pseudopeptides via Ugi reaction

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ABSTRACT

A new and efficient method was developed for the synthesis of novel *gem*-difluoromethylene-containing isocyanide, which can be used as a building block for the synthesis of difluorinated pseudopeptides via Ugi reaction.

Recently, fluorinated amino acids have received extensive attention and played important roles in peptidomimetic and medicinal chemistry.[1] They exhibit interesting pharmacological effects and, therefore, are frequently used to construct various biologically active peptides with enhanced enzymatic stability compared with these non-fluorinated amino acids. Among them, α,α-difluoro-β-amino acids have been one of the most attractive unusual amino acids.[2] For example, (*S*)-methyl 3-acetamido-2,2-difluoro-4-phenylbutanoate was found to be slow-binding or reversible competitive inhibitors of α-chymotrypsin, showing the most potent inhibitory activity (Fig. 1).[3] The replacement of the methylene group with the difluoromethylene in β-amino acids has been recognized as an important method in the blockage of metabolic processes. The combination of fluorinated β-amino acid moieties with naturally occurring pharmacophores can alter both molecule metabolism and enzyme substrate recognition. For example, the CH_2 to CF_2 transposition in the β-amino acid fragment of Rhodopeptin, a natural cyclic tetrapeptide with antifungal activities, resulted in an improved toxicity profile.[4]

The general methods for introducing fluorine atoms into organic molecules involve either direct fluorination (using fluorine gas, hydrogen fluoride, and fluorinating agents) or the use of fluorinated building blocks.[5] The use of fluorinated building blocks as a strategy for the construction of fluorinated organic molecules is becoming more popular. Nowadays, fluorinated amino acids are increasingly used as valuable building blocks for the incorporation of fluorine into peptides and proteins.[6] Despite their promising applications in peptide chemistry, there are a very limited number of versatile fluorinated amino acid building blocks to be used. Thus, finding or designing efficient and practical fluorinated amino acid building blocks seems to be important.

In recent years, multicomponent reactions have become one of the most productive areas in organic synthesis and drug discovery.[7] However, up to now there were only a few reports on the use of fluoro-containing building blocks as one of the components in the multicomponent reactions.[8] Therefore, the strategy we proposed previously,[9] multicomponent reactions including fluoro-containing building blocks (MCRs-FBB), will be a powerful tool for one-pot construction of complex and diverse fluoro-containing molecules with high efficiency. Isocyanide is an extremely versatile component in multicomponent reactions due to their exceptional reactivity. The most unique character of isocyanide is that they can react readily with both nucleophiles and electrophiles at the same carbon atom to give expected or unexpected products. Therefore, isocyanide-based multicomponent reactions have attracted much attention as useful strategy for the discovery and development of novel MCRs.[10] In this Letter, firstly we synthesized a novel fluoro-containing building block, α,α-difluoro-β-amino amide bearing the isocyanide functionality, and then utilized the MCRs-FBB strategy for the synthesis of several difluorinated pseudopeptides via Ugi reaction under solvent-free conditions.

3-Amino-*N*-cyclohexyl-2,2-difluoro-3-phenylpropanamide **6** is the key intermediate for preparation of the novel difluorinated isocyanide, *N*-cyclohexyl-2,2-difluoro-3-isocyano-3-phenylpropanamide **8**. However, very few methods were reported for the preparation of this kind of amide **6**. Welch reported a method of preparing this amide by using a new fluorinated building block, 1,1-difluoro-2-trimethylsilyl-2-trimethylsilyloxyethene, as starting material.[11] It is obvious that this method is not very practical due to its unavailability. Although there are several reports on the synthesis of 3-amino-2,2-difluoro-3-substituted propyl acid and ester,[12] the precursors of amide, there are several shortcomings of these methods such as expensive starting materials,[13] too many steps.[14] Here, we describe an efficient route to prepare **6** from commercially available fluoro-containing building block, ethyl bromodifluoro acetate **1** (Scheme 1).

N-Benzylidene-4-methoxyaniline **2** was easily prepared in good yield by condensation of benzaldehyde with 4-methoxyaniline in methanol and used without further purification. 4-Methoxyaniline

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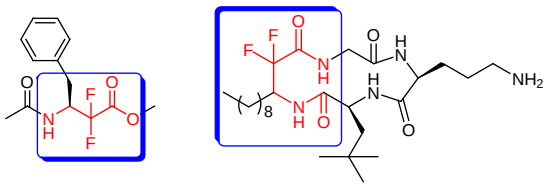
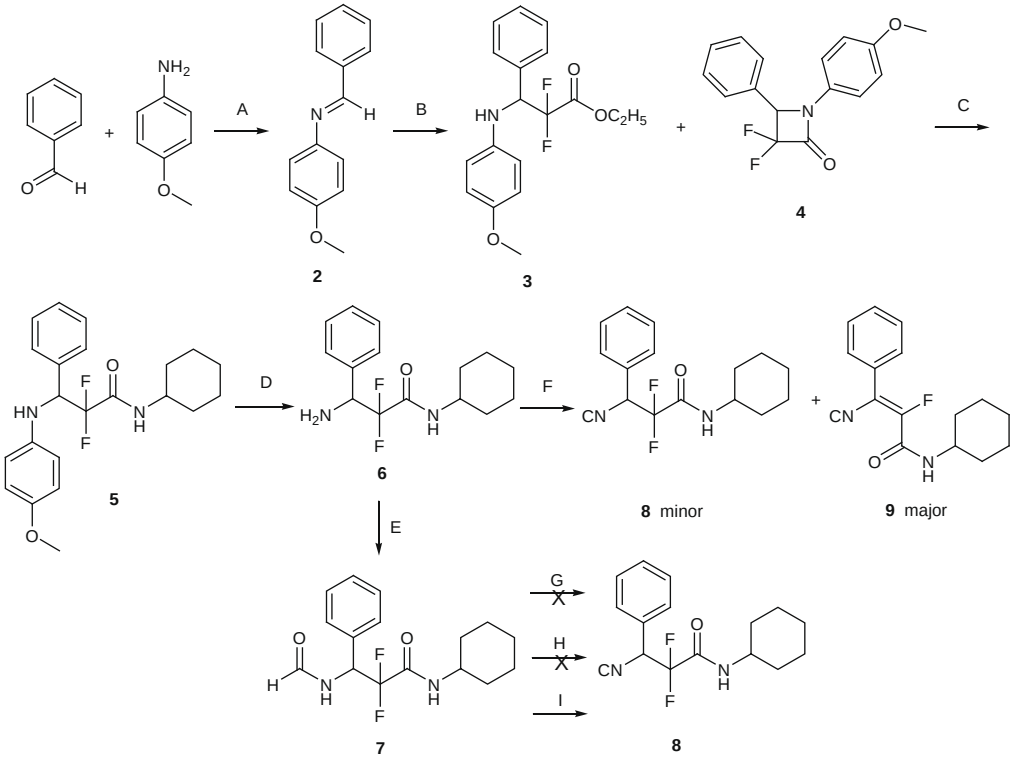


Figure 1. Difluorinated phenylalanine and Rhodopeptin.

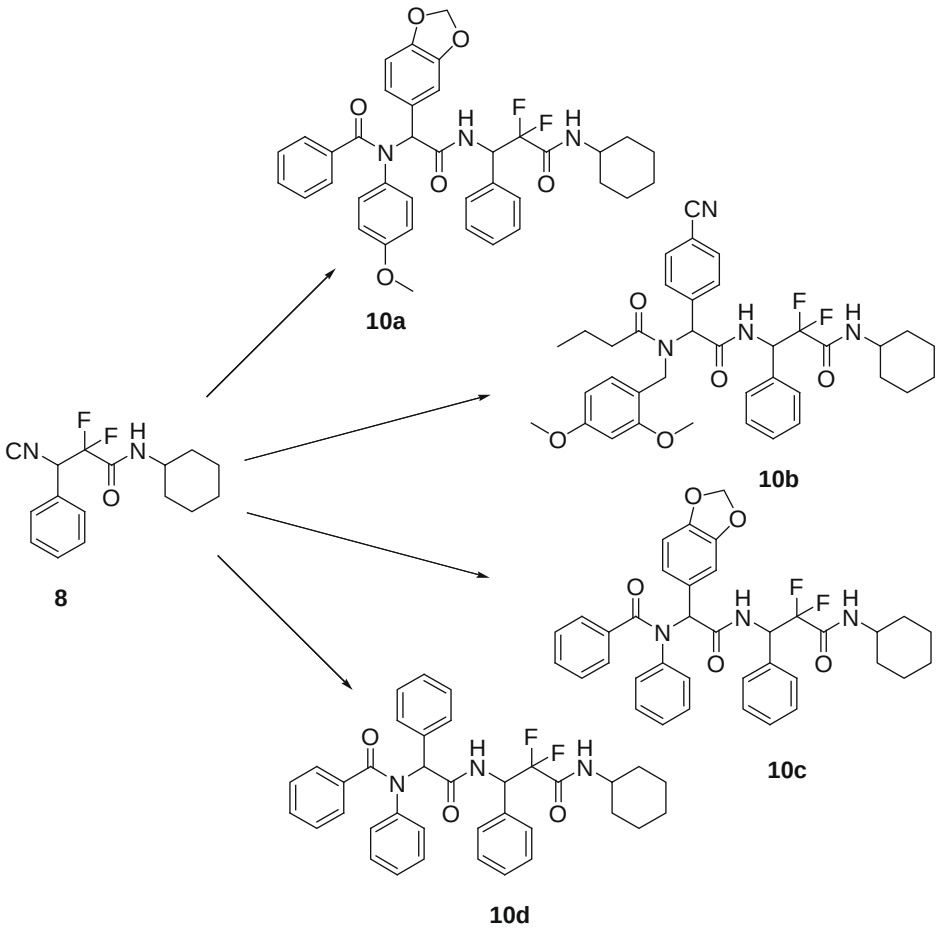
was used as a nitrogen source, so as to have a substituent on the nitrogen which makes its cleavage possible under mild conditions. The reaction of Schiff base **2** with **1** in the presence of Zn dust in THF via Reformatsky-type reaction afforded two products, difluorinated β-aminoester **3** and β-lactam **4** in nearly 1:1 ratio in excellent yield. It is easy to obtain amide **5** by the reaction of ester **3** with cyclohexanamine. However, to the best of our knowledge, no direct aminolysis from 3,3-difluoro-1-(4-methoxyphenyl)-4-phenylazetidin-2-one **4** to the corresponding amide **5** has been reported. The only method to aminolyze the nonfluoro-substituted β-lactam was reported by Park in 1994 who used various amino acid esters to open β-lactam ring.[15] In 2000, Ohta described the ring-opening reaction of difluorinated β-lactam with sodium methoxide, followed by treatment with primary amine (glycine *tert*-butyl ester hydrochloride) to give aminolysis products.[4] In order to improve reaction efficiency and avoid the separation of the mixture of **3** and **4**, herein, we tried to obtain difluorinated amide **5** by the reaction of cyclohexanamine with the mixture of **3** and **4** directly. To our delight, both of them could react with cyclohexanamine in methanol at room temperature to afford the same product **5** in almost quantitative yield. The deprotection of **5** was effectively realized by classical treatment with 3 equiv of ceric(IV) ammonium nitrate (CAN) in a mixture of acetonitrile and water in a 9:1 ratio,[16] obtaining the key intermediate, 3-amino-*N*-cyclohexyl-2,2-difluoro-3-phenylpropanamide **6**, in 45% yield.

According to the related literatures, three strategies for the synthesis of isocyanide **8** were tested. Initially, the reaction of **6** with chloroform and 50% NaOH by using tetra-butylammonium bromide as phase transfer catalyst at room temperature yielded little product after a long reaction time (over 72 h). Although the reaction proceeded smoothly in a much shorter time at elevated temperature, unexpectedly, another isocyanide, *N*-cyclohexyl-2-fluoro-3-isocyano-3-phenylacrylamide **9**, was formed as the major product, only 15% of the desired isocyanide **8** being obtained. The structure of compound **9** was also identified by ^{1}H, ^{13}C, ^{19}F NMR and HRMS. In the second attempt, compound **7**, *N*-cyclohexyl-2,2-difluoro-3-formamido-3-phenylpropanamide, was successfully prepared first by the treatment of **6** with ethyl formate. And then, transformation of **7** to **8** under different reaction conditions was investigated. Treatment of **7** with phosphorus oxychloride ($POCl_3$) in the presence of triethylamine (NEt_3) gave a poor yield of **8**. The alternative approach to **8** by reaction of **7** with carbon tetrachloride (CCl_4) and triphenylphosphine (PPh_3) in the presence of NEt_3 in refluxing dichloromethane proved unsuccessful. To accomplish this task, other reaction conditions were screened including solvent, time, and temperature. Finally, the reaction of **7** with CCl_4, NEt_3, and PPh_3 in a 1:2:2:2 ratio by using 1,2-dichloroethane as solvent at 60 °C afforded the desired novel isocyanide **8** in 70% yield.[17]

Recently, we have reported a mild and efficient organic solvent-free Ugi four-component condensation for the synthesis of pseudopeptides.[18] In this Letter, after the successful synthesis of this novel difluorinated isocyanide, we next wished to use this new fluorine-containing building block to synthesize several difluorinated pseudopeptides via Ugi reaction. Thus, **10a–d** were obtained in moderate to high yields at 60 °C under solvent-free conditions for about 0.8 h (Scheme 2).[19]



Scheme 1. Synthesis of *N*-cyclohexyl-2,2-difluoro-3-isocyano-3-phenylpropanamide **8**. Reagents and conditions: (A) CH_3OH, reflux, 95%; (B) $BrCF_2COOEt$ **1**, Zn, THF, reflux, 90%; (C) cyclohexanamine, CH_3OH, rt, 95%; (D) CAN, CH_3CN, H_2O, 0 °C → rt, 45%; (E) $HCOOC_2H_5$, rt, 95%; (F) 50% NaOH, $CHCl_3$, Bu_4NBr, rt or 50 °C, for **8**, 15%, for **9**, 53%; (G) $POCl_3$, NEt_3, CH_2Cl_2; (H) PPh_3, CCl_4, NEt_3, CH_2Cl_2, reflux; (I) PPh_3, CCl_4, NEt_3, $ClCH_2CH_2Cl$, 60 °C, 70%.



Scheme 2. Several examples of α,α-difluoromethylene analogs of β-amino acid synthesized via Ugi reaction.

In summary, we have developed an efficient method to synthesize novel *gem*-difluoromethylene-containing isocyanide, and then utilized multicomponent reactions including fluoro-containing building blocks (MCRs-FBB) strategy to prepare several difluorinated pseudopeptides via Ugi reaction under solvent-free conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.056.

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17. *Preparation of N-cyclohexyl-2,2-difluoro-3-isocyano-3-phenylpropanamide* (**8**): *N*-Cyclohexyl-2,2-difluoro-3-formamido-3-phenylpropanamide **7** (1.55 g, 5 mmol), PPh_3 (2.60 g, 10 mmol), CCl_4 (1.54 g, 10 mmol), NEt_3 (1.01 g, 10 mmol), and 1, 2-dichloroethane (15 mL) were added into a 50 mL round-bottomed flask, and the mixture was stirred at 60 °C for about 2 h (GC–MS). Then, the dark brown reaction mixture was cooled to room temperature. Subsequently, white triethylamine hydrochloride salt was removed by filtration and the solid was washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the resultant crude residue was purified by chromatography (AcOEt/heptane = 1:8), and white isocyanide **8** was obtained. Yield, 70%; mp: 95–97 °C. IR (KBr, film): 3314, 2932, 2858, 2112, 1668, 1527, 1446, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.36 (m, 5H), 6.08 (s, 1H), 5.50 (t, J_{HF} = 12.0 Hz, 1H), 3.80–3.71 (m, 1H), 1.96–0.93 (m, 10H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.3, 159.8 (t, $^2J_{CF}$ = 26.7 Hz), 130.3, 129.3, 128.9, 128.7, 113.7 (dd, $^1J_{CF}$ = 260.8, 260.5 Hz), 59.6 (dd, $^2J_{CF}$ = 24.1, 25.8 Hz), 49.0, 32.0, 31.8, 25.4, 25.2, 25.1 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ −110.0 (dd, J = 9.5, 256.5 Hz, 1F), −114.1 ppm (dd, J = 9.5, 256.5 Hz, 1F); HRMS (ESI): *m/z*: 293.1468 $[M+H]^+$; calcd for $C_{16}H_{18}F_2N_2O$ + H: 293.1465.
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19. *N-(1-(Benzo[d][1,3]dioxol-5-yl)-2-(3-(cyclohexylamino)-2,2-difluoro-3-oxo-1-phenylpropylamino)-2-oxoethyl)-N-phenylbenzamide* (**10c**): To a stirred aniline (32 mg, 0.34 mmol), benzo[*d*][1,3]dioxole-5-carbaldehyde (51 mg, 0.34 mmol) was added in portions for about 5 min. The mixture was stirred for 25 min again at room temperature. Then, the reaction mixture was heated to 60 °C. Benzoic acid (42 mg, 0.34 mmol) and **8** (100 mg, 0.34 mmol) were added in portions for 10 min. Stirring was continued at 60 °C for 0.8 h (TLC). The crude residue was purified by chromatography (AcOEt/heptane = 1:5) to give the desired product **10c**.Yield: 76%; white solid, mp: 221–223 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 9.2 Hz, 1H), 7.41–7.11 (m, 10H), 7.06–7.05 (m, 3H), 6.97 (s, 2H), 6.82–6.79 (m, 2H), 6.69 (d, J = 7.6 Hz, 1H), 6.26 (s, 1H), 5.94 (s, 2H), 5.88 (d, J = 7.6 Hz, 1H), 5.82–5.74 (m, 1H), 3.66–3.58 (m, 1H), 1.60 (s, 5H), 1.32–0.83 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 169.3, 161.8 (t, $^2J_{CF}$ = 27.4 Hz), 147.7, 147.6, 141.1, 135.9, 135.8, 133.6, 130.2, 129.5, 128.8, 128.7, 128.6, 128.5, 127.7, 127.6, 127.3, 124.1, 117.3 (dd, $^1J_{CF}$ = 258.0, 274.8 Hz), 110.5, 108.1, 101.2, 66.3, 56.3 (dd, $^2J_{CF}$ = 24.8, 27.1 Hz), 48.3, 32.2, 25.2, 24.5, 24.4 ppm; ^{19}F NMR (470 MHz, $CDCl_3$): δ −111.6, −112.1 (d, J = 4.8 Hz), −113.0 (d, J = 9.5 Hz), −113.5 (d, J = 9.5 Hz) ppm; HRMS (ESI): *m/z*: 662.2424 $[M+Na]^+$; calcd for $C_{37}H_{35}F_2N_3O_5$+Na: 662.2442.