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First one-pot stereoselective synthesis of *cis*-2,3-dihydro-4-perfluoroalkyl-1*H*-1,5-benzodiazepines *via* a catalyst-free three-component reaction†

Jiechao Xu,[a] Jiamei Wei,[a] Linglin Bian,[a] Jiaping Zhang,[a] Jie Chen,[a] Hongmei Deng,[a] Xiaoyu Wu,*[a] Hui Zhang*[a] and Weiguo Cao*[abc]

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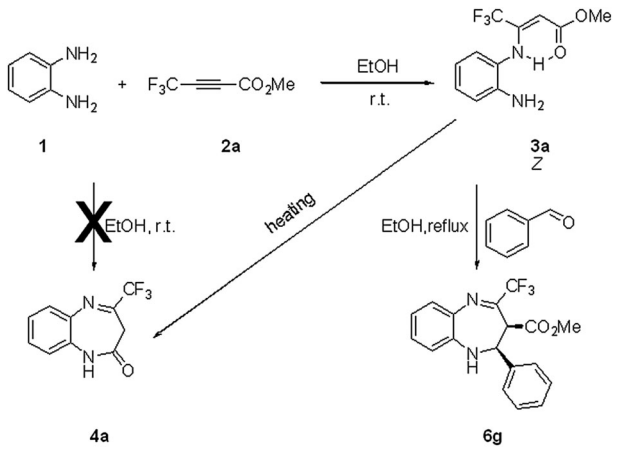
***cis*-2,3-Dihydro-4-perfluoroalkyl-1*H*-1,5-benzodiazepines were stereoselectively synthesized using a one-pot, catalyst-free, three-component reaction. This novel, efficient and convenient approach was used to synthesize 22 related products in moderate to excellent yields, demonstrating the scope and potential economic impact of the reaction.**

1,5-Benzodiazepines occupy an important place in the area of heterocyclic chemistry because they are important precursors of a variety of fused ring compounds[1,2] and also possess significant pharmaceutical properties.[3,4] They are also commercially important dyes for acrylic fibers.[5] These pharmacological and industrial applications have made their synthesis considerably important in the field of synthetic organic chemistry.

Typically, 1,5-benzodiazepines are prepared by cyclo-condensation of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds,[6] β-haloketones,[7] or ketones in the presence of Lewis acids and transition-metal salts as catalysts.[8–10] Unfortunately, many of the synthetic methods also catalyze the formation of side products, involve long reaction times, give low yields, or use expensive reagents. Furthermore, the use of such catalysts gives rise to tedious work-up procedures for their separation for recycling or disposal. Therefore, the search continues for better methods for the synthesis of 1,5-benzodiazepines in terms of mild reaction conditions, operational simplicity, economic viability and selectivity.

Though it is well known that the introduction of poly-fluoroalkyl groups into organic molecules can bring about some remarkable changes in the physical properties, chemical reactivity and biological activity of the derived fluorinated compounds,[11] there are few reports about the synthesis of perfluoroalkylated 1,5-benzodiazepines which can serve as synthons for developing new drugs.[12] Moreover, to the best of our knowledge, there have been no reports of stereoselective synthesis of *cis*-2,3-dihydro-4-perfluoroalkyl-1*H*-1,5-benzo-diazepines. Thus, in continuing our endeavor to find novel synthetic methodologies to develop new drugs,[13] in this communication, we describe a novel and efficient method for one-pot catalyst-free three-component synthesis of perfluoro-alkylated 1,5-benzodiazepines with high stereoselectivity.

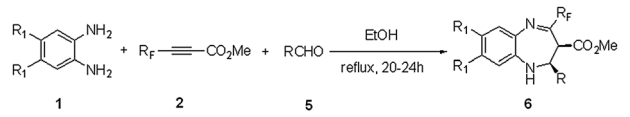
Initially, due to the powerful electron-withdrawing ability of R_F groups and thus the enhancement of electrophilicity of the carbonyl group of acetylenic ester, we tried to obtain 4-perfluoroalkylated 1,5-benzodiazepine-2-ones **4**[14] by reacting *o*-phenylenediamine **1** (1.0 equiv.) with methyl 4,4,4-trifluorobut-2-ynoate **2a**[15] (1.0 equiv.) in ethanol without any catalyst at room temperature (Scheme 1). However, no desired product, 4-(trifluoromethyl)-1*H*-benzo[*b*][1,4] diazepin-2(5*H*)-one **4a**, was obtained. Only (*Z*)-methyl 3-(2-aminophenylamino)-4,4,4-trifluorobut-2-enoate **3a** was isolated as the major product. When the reaction was performed under reflux, both compounds **4a** and **3a** could be obtained, but the yield of **4a** was very low (23%). One broadened one-proton singlet at 9.25 ppm (N–H atom involved in the formation of the



Scheme 1

[a] *Department of Chemistry, Shanghai University, 99 Shangda Rd, Shanghai 200444, People's Republic of China. E-mail: wgcao@staff.shu.edu.cn, yehao7171@shu.edu.cn, wuxy@shu.edu.cn; Fax: +86 21-66134856*
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China*
[c] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China*

† Electronic supplementary information (ESI) available: Synthesis and characterization of compounds. CCDC 762456 (**6f**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc05039c.



Scheme 2

intramolecular hydrogen bond) in ^{1}H NMR ($CDCl_3$) spectra confirmed the double-bond configuration of **3a**.

By heating the reaction mixture of **3a** (1.0 equiv.) and benzaldehyde (1.0 equiv.) in ethanol under reflux, the α-addition product methyl 2-phenyl-4-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine-3-carboxylate **6g** was produced in moderate yield (72%). In view of the utility of multi-component reactions (MCRs) in the process of drug discovery and the total synthesis of complex natural products,[16] we examined the reaction in detail using *o*-phenylenediamine **1**, methyl 2-perfluoroalkynoates **2** and aldehydes **5** as starting materials, including aromatic and aliphatic aldehydes (Scheme 2). When all substrates were simultaneously mixed in one pot and heated to reflux in ethanol for 20–24 h, the desired products **6** were obtained in moderate to excellent yield (Table 1).

The results indicate the scope and the generality of the reaction with respect to the examples described. As shown in Table 1, both aromatic and aliphatic aldehydes reacted readily with *o*-phenylenediamine and methyl 2-perfluoroalkynoates to afford the corresponding 4-perfluoroalkylated 1,5-benzodiazepines. Benzaldehydes with electron-donating groups at the *para* position gave much better results than those with electron-withdrawing groups, which is probably due to the push-pull type electron-effect (entries 2–7). The result of using *o*-bromobenzaldehyde indicated that this reaction was influenced by steric effects (entry 1). Furthermore, 1-naphthaldehyde, 2-furancarboxaldehyde and 1*H*-indole-3-carbaldehyde were all applicable for this reaction (entries 8, 10, 11). The yields and the time of reaction slightly depended on the chain length of the polyfluoroalkyl group (the smaller the substituent, the higher the yield), but were very sensitive to the temperature. The reactions were completed upon refluxing within 24 h. While at room temperature, it took about two to three days, in the latter case yields being lower than 10%. We also found that 4,5-disubstituted *o*-benzodiamines could also be applicable to the reaction (entries 13 and 14). However, when 3-methyl-benzene-1,2-diamine was used as a substrate, two main products, which were proved to be a pair of isomers in the ratio of 3 : 1—methyl 2-(4-methoxyphenyl)-6-methyl-4-(trifluoro-methyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine-3-carboxylate **6u** and methyl 2-(4-methoxyphenyl)-9-methyl-4-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine-3-carboxylate **6u′**, were obtained in 64% yield. They couldn't be separated from each other by column chromatography, so the ratio and the structures of compounds **6u** and **6u′** were determined by ^{1}H NMR and NOSEY techniques.

Table 1 One-pot synthesis of 4-perfluoroalkylated-1,5-benzodiazepines[a]

Entry	R_1	R_1	R_F	R	Product	(*cis*)Yield[b] (%)
1	H	H	CF_3	*o*-Bromophenyl	**6a**	57
2	H	H	CF_3	*p*-Bromophenyl	**6b**	73
3	H	H	CF_3	*p*-Methylphenyl	**6c**	90
4	H	H	CF_3	*p*-Fluorophenyl	**6d**	54
5	H	H	CF_3	*p*-Methoxyphenyl	**6e**	80
6	H	H	CF_3	*p*-Nitrophenyl	**6f**	50
7	H	H	CF_3	Phenyl	**6g**	72
8	H	H	CF_3	3-1*H*-Indolyl	**6h**	56
9	H	H	CF_3	*n*-Heptyl	**6i**	56
10	H	H	CF_3	Cyclohexyl	**6j**	68
11	H	H	CF_3	1-Naphthalenyl	**6k**	85
12	H	H	CF_3	2-Furanyl	**6l**	81
13	CH_3	CH_3	CF_3	*p*-Methoxyphenyl	**6m**	62
14	Cl	Cl	CF_3	*p*-Methoxyphenyl	**6n**	60
15	H	H	C_2F_5	*p*-Nitrophenyl	**6o**	31
16	H	H	C_2F_5	*p*-Methylphenyl	**6p**	61
17	H	H	C_2F_5	*p*-Methoxyphenyl	**6q**	51
18	H	H	C_2F_5	*p*-Bromophenyl	**6r**	71
19	H	H	*n*-C_3F_7	1-Naphthalenyl	**6s**	74
20	H	H	*n*-C_3F_7	*p*-Bromophenyl	**6t**	70

[a] Conditions: *o*-phenylenediamine **1** (0.5 mmol), methyl 2-perfluoro-alkynoates **2** (0.5 mmol), aldehyde **5** (0.5 mmol) in ethanol (5 mL), reflux for 20–24 h. [b] Isolated yield.

The ^{1}H NMR spectra of compounds **6** manifested themselves in a similar manner. The coupling constant of the two vicinal protons was in the range of 5.0–5.5 Hz, which is a distinctive clue for deducing a *cis* relationship between two vicinal protons at 2 and 3 positions of the seven-membered ring. A 3D perspective view of the crystal structure of **6f** proved unequivocally to be the *cis*-isomer by X-ray crystallographic analysis, that is, the ester group and R are on the same side of the bicyclic system (Fig. 1).‡ Thus, the ring closure occurred stereoselectively to afford the single product *cis*-2,3-dihydrogen-4-perfluoroalkyl-1,5-benzodiazepines.

On the basis of previous reports,[10,17] the proposed mechanism is shown in Scheme 3. Michael addition first occurred between *o*-phenylenediamine **1** and methyl 2-perfluoroalkynoate **2** to give intermediate enamine **3**, which was stabilized by an intramolecular hydrogen bond. Then, **3** was condensed with aldehyde **5** to form **A**. To convert **A** to dihydrobenzodiazepines, the transformation from the most stable conformer **A** to the

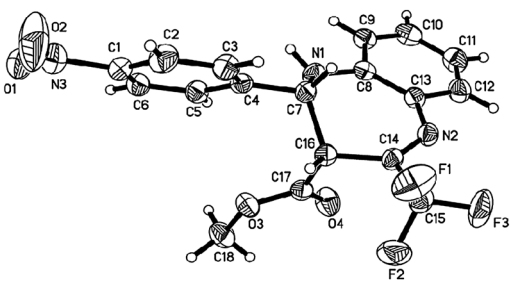
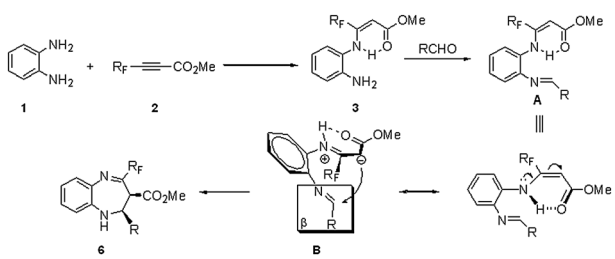


Fig. 1 X-Ray structure of compound **6f**.



Scheme 3

twisted **B** suitable for subsequent cyclization would be necessary.[17a] The anionic carbon α to the ester group in **B** attacked the carbon of the imine intramolecularly from the back side of the plane β to afford the sole α-addition product *cis*-2,3-dihydrogen-4-perfluoroalkyl-1,5-benzodiazepines.

In conclusion, we have developed a novel one-pot three-component reaction of aldehydes, *o*-phenylenediamines, and methyl 2-perfluoroalkynoates in the absence of a catalyst. The main feature of this reaction is the formation of *cis*-α-addition perfluoroalkylated products. The easy work-up, mild reaction conditions, good yields and high stereoselectivity of the reaction make the present methodology attractive for the preparation of a wide variety of biologically relevant 1,5-benzodiazepines.

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Notes and references

‡ Unit cell parameters: *a*: 8.825(6) Å; *b*: 9.598(7) Å; *c*: 12.295(9) Å; α: 88.156(10)°; β: 70.934(9)°; γ: 63.004(8)°; space group: *P*-1.

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