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ARTICLE

Synthesis of Tetrazines from *gem*-Difluoroalkenes under Aerobic Condition at Room Temperature

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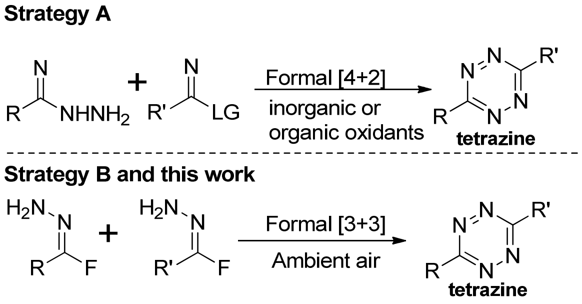
Zheng, Fang,[a] Wen-Li Hu,[a] De-Yong Liu,[a] Chu-Yi Yu,[ab] Xiang-Guo Hu*[a]

An efficient and green procedure for the synthesis of tetrazines has been developed based on an old chemistry reported by Carboni in 1958. Both symmetric and asymmetric 3,6-disubstituted 1,2,4,5-tetrazines can be obtained in moderate to high yields from corresponding *gem*-difluoroalkenes under aerobic condition at room temperature. This work represents a rare example that ambient air is utilized as oxidant for the synthesis of tetrazines.

The 1,2,4,5-tetrazine heterocyclic ring system is one of the most unique and versatile aromatic heterocycles.[1] The 1,2,4,5-tetrazines are applied extensively in life science for different purposes such as intracellular small molecule imaging, post synthetic DNA labelling, in-vivo imaging, and among others.[2] In addition, the 1,2,4,5-tetrazines are also useful for the development of explosive, propellant materials due to the property of high energy density.[3] Furthermore, They are also used in organic chemistry as synthetic intermediates, which have been elegantly utilized for the synthesis of many natural products.[4]

Owning to the immense usefulness of 1,2,4,5-tetrazine derivatives, many routes has been developed for the efficient synthesis of such compounds. As there is no direct way for the construction of tetrazine ring system, 1,2,4,5-tetrazines are always obtained from their dihydro-precursors.[1,5] Consequently, almost all of these methods need stoichiometrical or excess oxidants(for example: NO_2, HNO_2, CrO_3, $NaBO_3$, powdered sulphur and hypervalent iodine reagents[6]) , which inevitably lead to the generation of huge amounts of waste. From a sustainable and green chemistry viewpoint, it is more preferable to use oxygen as oxidant owing to its inexpensive, inexhaustible and environmentally benign features. Although there are nearly 300 papers describing the synthesis of 1,2,4,5-tetrazines,[1] oxygen has been barely explored for this purpose.[7] Here, we report a green and efficient synthesis of 1,2,4,5-tetrazine from *gem*-difluoroalkenes under aerobic condition at room temperature.[7]



Scheme 1 Strategies for the synthesis of 1,2,4,5-tetrazine

Strategically and mechanistically, most of the reported methods for the synthesis of tetrazines proceed from a formal [4+2] addition(strategy A). We, however, envisioned that tetrazines could be prepared through a formal [3+3] addition of a hydrazone bearing a leaving group(strategy B). Based on the continuing interest of one of the authors in organofluorine chemistry,[8] fluoride was selected as the leaving group.[9] Literature survey shows that this strategy has been explored by Carboni and co-workers early in 1958.[10] Unfortunately, Carboni's method has received little attention probably because it suffers from low overall yields(27%-33%) and limited substrate scope(3 substrates bearing a fluoroalkyl chain were tested).

In this work, we have addressed the limitations of Carboni's chemistry[10] and demonstrated that ordinary *gem*-difluoroalkenes can be used for the synthesis of both symmetric and asymmetric 3, 6-dialkyl-1,2,4,5-tetrazines. The yields are generally high, ranging from 61% to 91%.

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[a] National Engineering Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022 (P. R. China). E-mail: huxiangg@iccas.ac.cn
[b] Beijing National Laboratory for Molecular Science (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190

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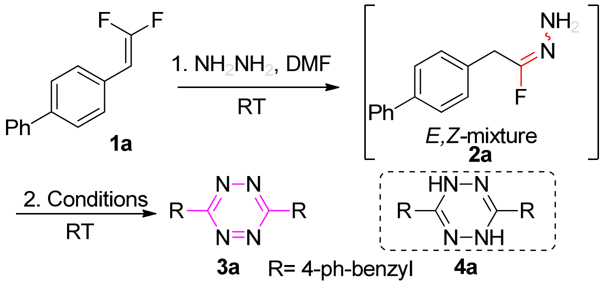
More importantly, ambient air is used as green oxidant instead of toxic nitrous acid used in Carboni's method. [10]

At the onset of our work, we attempted to synthesize the fluorohydrazone by the reaction of *gem*-difluoroalkene **1a** with hydrazine.[11] Two products were observed by thing layer chromatograph (TLC) after the reaction mixture was stirred in *N*, *N*-Dimethylformamide(DMF) for 8 hours(for a screen of solvents, see the Supporting information). This phenomenon was expected as two *E, Z* isomers of fluorohydrazone **2a** would be formed. In contrast to Carboni's observation that fluorohydrazone with a fluoroalkyl substituent is stable, [10] efforts for the isolation **2a** proved to be unsuccessful. The difference of chemical stability between the aforementioned two fluorohydrazones might be due to the unique stabilizing effect of the fluoroalkyl group.[12]

Table 1 Optimization of the reaction conditions

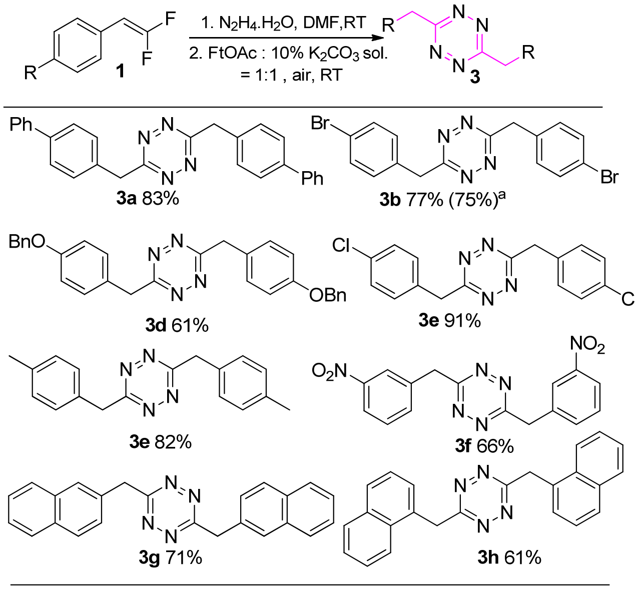


Entry	Oxidants	Solvent and additive	Yields(X%)
1	NaClO	H_2O	0
2	$NaNO_2$	1 M HCl sol.	7
3	$NaNO_2$	0.5 M H_2SO_4 sol.	56
4	$NaNO_2$	HOAc	88
5	$NaNO_2$	10% K_2CO_3 sol.	51
6	*m*-CPBA	10% K_2CO_3 sol.	14
7	*m*-CPBA	$CHCl_3$/HOAc(3equvi.)	37
8	*m*-CPBA	$CHCl_3$	56
9	*m*-CPBA	$CHCl_3$/aq. 0.5 M H_2SO_4	52
10	O_2	THF/KOH(5equiv.)	trace
11	O_2	THF/K_2CO_3(5equiv.)	trace
12[a]	O_2	EtOAc/10% KOH sol.[c]	75
13[b]	O_2	EtOAc/10% K_2CO_3 sol.[c]	89
14[a]	air	EtOAc/10% K_2CO_3 sol.[c]	64
15[b]	**air**	**EtOAc/10% K_2CO_3 sol.[c]**	**83**

[a]Yield after 8h; [b] Yield after 24h; [c] Volume(EtOAc) : Volume(base solution) = 1:1

We reasoned that the instability of **2a** was the result of the condensation of two molecules to form dihydrotetrazine **4a**. We then tried to convert **2a** directly to the corresponding stable tetrazine **3a** with the aid of an oxidant. As shown in table 1, Different oxidants, such as sodium hypochlorite, sodium nitrite and *meta*-Chloroperoxybenzoic acid, under different conditions were tested(Entry 1-9), and sodium nitrite in acetic acid gave the best result(entry 4). During the workup of this reaction with base solution, we had always observed a small amount of deep purple compound, which was thought to be the color of the desired tetrazine product. Based on this observation, we then tried to carry out the reaction under oxygen atmosphere. However, Conducting the reaction in tetrafuran under an oxygen atmosphere gave only trace of the desired product(Entry 10-11). Solvent screen also proved that this reaction didn't work in any other organic mediums(not shown). In sharp contrast, oxygen was indeed found to be an effective oxidant under a biphasic condition{volume(EtOAc) : volume(base solution) = 1:1}, and the desired **3a** was obtained in comparable yields(Entry 12-13) to that with sodium nitrite. Further optimization showed that the desired product could be obtained even under air atmosphere(Entry 14-15). The procedure in Entry 15 was thus selected as the optimized condition not only because of the operational simplicity(no purification of the intermediate) but also the green nature when compared to the Carboni's method.[10]

Table 2 Synthesis of symmetric 3,6-diakyl- 1,2,4,5-tetrazines



[a]yield on gram scale

With the optimized condition in hand, we next proceeded to explore the reaction scope with various *gem*-difluoroalkenes. As shown in Table 2, This reaction tolerates different substitution pattern and substituents on the phenyl ring. Substrates bearing Halides, aryloxy, phenyl and alkyl on the para-position and nitro group at the meta position gave the desired products in moderate to excellent yields(**3a-3f**). The structure of **3b** was proved by means of X-ray crystallographic analysis(Figure 1).[13] It is interesting to note that the reaction of **3d** and **3f** proceeded at a slower reaction rate and gave lower yields than other substrates, which is possibly due to their lower solubility in the reaction

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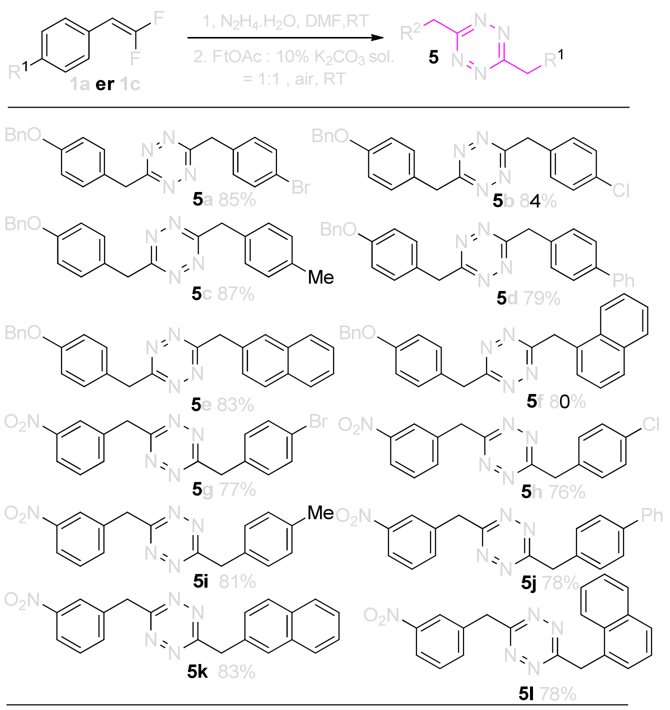
media. Polycyclic aromatic substrates are also viable for this reaction and **3g** and **3h** were obtained in 71% and 61% yield, respectively. To demonstrate the practicability of this method, we have conducted the reaction on gram scale with **1b**, and the product **3b** was obtained in 75% yield.

Table 3 Synthesis of asymmetric 3,6-diakyl-1,2,4,5-tetrazines [a]



[a] All the reactions were conducted employing **1b** and **1d-l** in large excess(**1b, 1d-l** : **1a** or **1c** = 10 : 1). Yields were calculated based on the amounts of **1a** or **1c**.

We next directed our efforts to the synthesis of asymmetric 3,6-disubstituted 1,2,4,5-tetrazines. Due to the consideration of ease of purification, we chose **1a** and **1c** to react with other *gem*-difluoroalkenes(**1b, 1d-l**) which were in large excess.[14] As shown in Table **3**, this reaction again tolerates different substitution pattern and substituents on the phenyl ring, and all of the desired products were obtained in good yields, ranging from 76%-87%. the structure of **5c** was proved by means of X-ray crystallographic analysis(Figure 1). As noted by Devej and co-workers, dialkyl asymmetric tetrazines with bulkier substituents are very challenging targets.[6b] Our method provides an easy access to a small library of this kind of compounds.

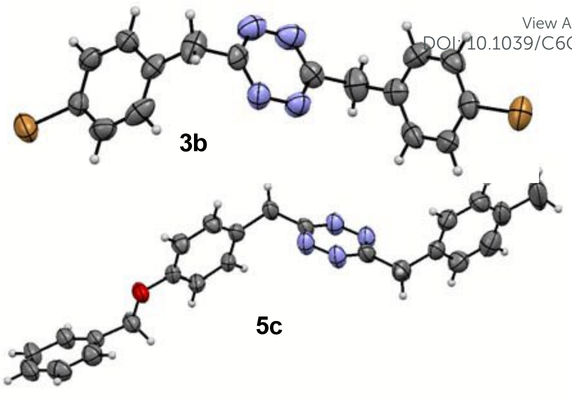
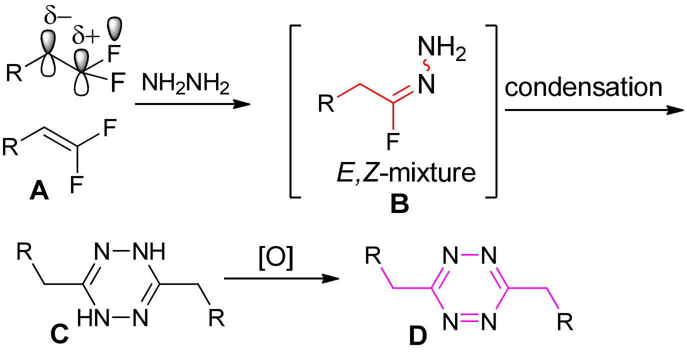


Figure 1: X-ray structures of **3b** and **5c**

Although fluorohydrazone **B** was proposed as the key intermediate in Carboni's synthesis of tetrazine(Scheme 2),[10] no spectra data were provided. Due to the unstable nature, we were unable to isolate **B**. We have, however, proved its existence by running the reaction of **1a** in deuterated acetonitrile (Section 7, Supporting Information). Two groups of doublet at 3.83ppm (J = 16.1 Hz) and 3.65ppm (J = 13.1 Hz) corresponding to the benzylic protons in ^{1}H-NMR and two groups of triplet at -65.9ppm (J = 13.1 Hz) and -71.5ppm (J = 16.1 Hz) corresponding to the fluorine attached to the C=N bond in ^{19}F-NMR indicated the presence of *E,Z*-isomers of **B** (ratio, 4:1),[15] which corroborated well with aforementioned TLC results. It should be note that our work here provides the first set of NMR spectra of a fluorohydrazone without aryl or alkyl group on the NH_2.[16] The mechanism of formation of tetrazine **D** next involves condensation of fluorohydrazone **B**, followed by oxidation of the resulting 1,2-dihydrotetrazine **C** by the oxygen.



Scheme 2 A plausible mechanism of the reaction

In conclusion, We have extended Carboni's method[10] to an efficient and green procedure for the synthesis of tetrazines under aerobic condition at room temperature. This work represents a rare example that ambient air is utilized as oxidant for the synthesis of tetrazines.[7] Both symmetric and asymmetric 3,6-disubstituted 1,2,4,5-tetrazines can be obtained in moderate to good yields from corresponding *gem*-difluoroalkenes. The practicability of this method is demonstrated by scaling up the reaction of **1b** to gram scale. The NMR study carried out in this work provides solid proof

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that fluorohydrazone is the key intermediate to the tetrazine from the *gem*-difluoroalkene.

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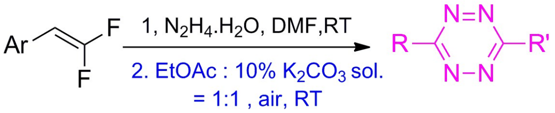
A procedure for the synthesis of tetrazines from *gem*-difluoroalkenes under aerobic condition has been developed.



● 20 exmples ● 61-91% Yields

● air as green oxidant

● symmetric and asymmetric products