Tetrahedron 74 (2018) 3904–3911

Contents lists available at ScienceDirect

Tetrahedron

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

AcOH-catalyzed aza-Michael addition/*N*-nitrosation: An efficient approach to CF_2HCH_2-containing *N*-nitrosoamines

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ARTICLE INFO

Article history:
Received 23 March 2018
Received in revised form
23 May 2018
Accepted 25 May 2018
Available online 26 May 2018

Keywords:
Cascade reaction
tert-Butyl nitrite
Difluoroethyl group
Three-component reaction
CF_2HCH_2-Containing *N*-nitrosoamines

ABSTRACT

A simple and highly efficient protocol for the AcOH-catalyzed three-component reaction among nitroalkenes, difluoroethylamine and *tert*-butyl nitrite through cascade aza-Michael addition/*N*-nitrosation has been developed. A range of CF_2HCH_2-containing *N*-nitrosoamines were obtained in good to excellent yields. This approach features easily available cheap materials, without using additional organic solvents, simple operation under room temperature, gram scalable preparation and functionally diverse products.

1. Introduction

The development of new methods for the introduction of fluorine atom into organic molecules is a hot topic in modern organic chemistry, which is attributed to the improved lipophilicity, metabolic stability and bioavailability compared to their parent compounds.[1] Among the various synthetic strategies, fluorination,[2] difluoromethylation,[3] trifluoromethylation,[4] and trifluoromethylthiolation[5] by nucleophilic, electrophilic, radical or transition metal-mediated pathways are straightforward approaches that have been widely investigated, leading to the production of a broad range of fluorinated molecules. However, introduction of a 2,2-difluoroethyl group ($-CH_2CF_2H$) is rare. On the basis of an inspection into the literature data, it was found that the general strategies for the syntheses of organic molecules bearing a 2,2-difluoroethyl group include: (1) direct fluorination of styrene derivatives,[6] (2) fluorination of *gem*-bistriflates and *gem*-dihalides,[7] (3) fluorodecarboxylation of dicarboxylic acids,[8] (4) chlorodifluoromethylation followed by an elimination and a migration process,[9] (5) reactions of organozinc reagents with potassium bromodifluoroacetate,[10] (6) arylation of difluoroethylamine,[11] (7) difluoroethylation of arylboronic acids,[12] and (8) esterification of carboxylic acids with difluoromethyl diazomethane.[13] Despite the elegance of the above approaches, most of the approaches are mainly limited to the use of either relatively complex reagents or harsh reaction conditions, which reduces the synthetic efficiency. Accordingly, the development of facile and practical methods with easily accessible precursors for the synthesis of CF_2HCH_2-containing compounds is desirable and valuable.

In recent years, multi-component reactions have been recognized as a powerful strategy in organic synthesis because of their applications in the construction of diversified and complex molecules in a one-pot fashion.[14,15] Three-component reactions involving fluorine-containing building blocks, in particular, have also been investigated to access versatile fluorine-based products.[16] In our recent studies, we have shown that *in situ* generated difluoromethyl diazomethane (CF_2HCHN_2) from difluoroethylamine and *tert*-butyl nitrite is an effective building block in the construction of CF_2H-containing 3,3′-spirooxindoles.[17] During our ongoing studies on the synthesis of CF_2H-containing heterocycles, we hypothesized that *in situ* generated CF_2HCHN_2 and nitroalkenes would undergo a [3 + 2] cycloaddition/1,3-H shift/dehydrogenation cascade process to deliver 3-(difluoromethyl)-1*H*-pyrazoles (Scheme 1a).[18] However, to our surprise, an unexpected three-

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https://doi.org/10.1016/j.tet.2018.05.073
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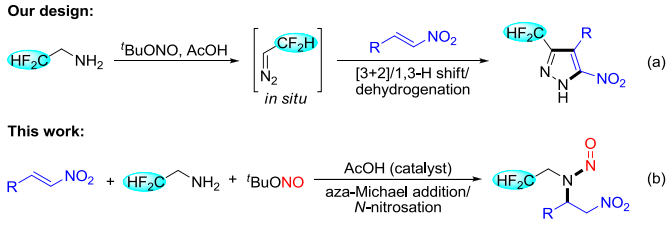


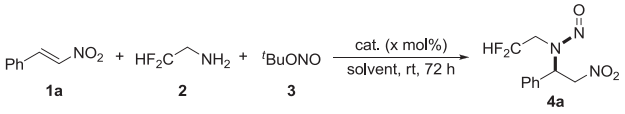
Scheme 1. Design for the construction of 3-(difluoromethyl)-1*H*-pyrazoles and the unexpected chemistry for the synthesis of CF_2HCH_2-containing *N*-nitrosoamines.

component reaction of nitroalkenes, difluoroethylamine and *tert*-butyl nitrite was observed, in which aza-Michael addition occurred followed by *N*-nitrosation of adducts, delivering *N*-(2,2-difluoroethyl)-*N*-[2-nitro-1-(hetero)arylethyl]nitrous amides (Scheme 1b).[19] It is to note that *N*-nitroso compounds are attractive targets in organic synthesis because of their presentation in a wide range of natural products, as well as highly pronounced biological activities.[20,21] Consequently, *N*-(2,2-difluoroethyl)-*N*-[2-nitro-1-(hetero)arylethyl]nitrous amides, which contains both difluoroethyl group and *N*-nitrosoamine moiety, can be conceived as probable drug leads in pharmaceutical chemistry. Herein, we report our preliminary studies on this subject.

2. Results and discussion

Initially, the optimization of reaction conditions was carried out with (*E*)-(2-nitrovinyl)benzene (**1a**), difluoroethylamine (**2**) and *tert*-butyl nitrite (**3**) in a 1:5:5 ratio in CH_2Cl_2 at room temperature in the presence of 150 mol% AcOH, giving *N*-(2,2-difluoroethyl)-*N*-(2-nitro-1-phenylethyl)nitrous amide (**4a**) in 61% yield (Table 1, entry 1).[22] To our delight, the yield of **4a** could be improved to 66% with only 5 mol% AcOH (Table 1, entry 2).[23] After examination to some other kinds of catalysts, including Brønsted acid and Lewis acid, which revealed that the yield of **4a** wasn't further improved (Table 1, entries 3–7). To promote the efficacy of the transformation, other kinds of solvents was further investigated, revealing that $CHCl_3$, CH_2ClCH_2Cl, THF, CH_3CN, PhMe, DMF and DMSO were inferior to CH_2Cl_2 for the conversion (Table 1, entry 2 *vs* entries 8–14). Interestingly, in the absence of other organic solvents, the yield was rapidly improved to 95% with **1a**, **2** and **3** in a 1:5:16 ratio (Table 1, entry 15). Increasing temperature from room temperature to 60 °C led to a lowered yield (89%) (Table 1, entry 16). In addition, no improvement in the reaction performance by decreasing the *tert*-butyl nitrite amount (8.0 equiv.) and slightly increasing the reaction temperature (45 °C) (Table 1, entry 17). Moreover, only trace amount of desired compound **4a** was obtained when the reaction was carried out in the absence of catalyst (Table 1, entry 18), suggesting that the catalyst is important for the synthesis of **4a** under the reaction conditions.

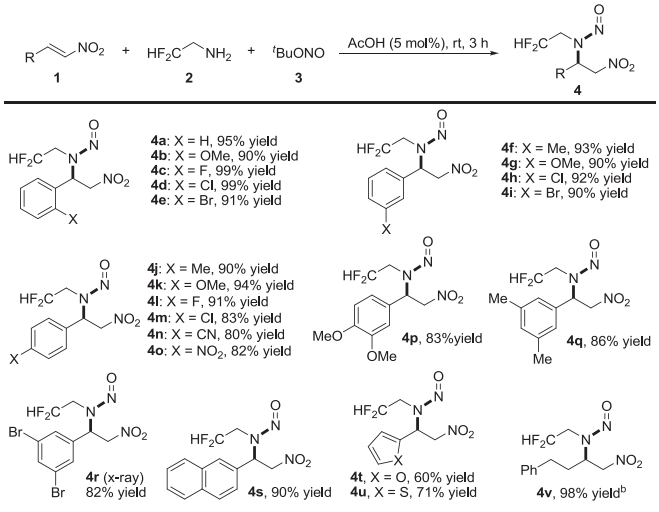
Table 1
Optimization of reaction conditions.[a]



entry	solvent	cat. (x mol%)	yield[b]
1	CH_2Cl_2	AcOH (150)	61
2	CH_2Cl_2	AcOH (5)	66
3	CH_2Cl_2	PivOH (5)	40
4	CH_2Cl_2	TFA (5)	21
5	CH_2Cl_2	*p*-TsOH (5)	<10
6	CH_2Cl_2	$Sc(OTf)_3$ (5)	49
7	CH_2Cl_2	$Zn(OTf)_2$ (5)	trace
8	$CHCl_3$	AcOH (5)	27
9	CH_2ClCH_2Cl	AcOH (5)	60
10	THF	AcOH (5)	14
11	CH_3CN	AcOH (5)	trace
12	PhMe	AcOH (5)	41
13	DMF	AcOH (5)	11
14	DMSO	AcOH (5)	trace
15[c]	–	AcOH (5)	95
16[c,d]	–	AcOH (5)	89
17[e]	–	AcOH (5)	83
18[c]	–	–	trace

[a] Unless otherwise noted, all reactions were carried out with (*E*)-(2-nitrovinyl) benzene (**1a**, 1.0 mmol, 1.0 equiv.), difluoroethylamine (**2**, 5.0 mmol, 5.0 equiv.), *tert*-butyl nitrite (**3**, 5.0 mmol, 5.0 equiv.), and catalyst (x mol%) in 20.0 mL of solvent at room temperature for 72 h.
[b] Isolated yield of product **4a** based on **1a**.
[c] The reaction was carried out with tBuONO (**3**, 16.0 mmol, 16.0 equiv.) for 3 h.
[d] The reaction was performed at 60 °C.
[e] The reaction was performed with tBuONO (**3**, 8.0 mmol, 8.0 equiv.) at 45 °C for 24 h.

With the optimal reaction conditions in hand (Table 1, entry 15), the generality of this reaction was subsequently examined. As shown in Scheme 2, the nitroolefins with both electron-donating and electron-withdrawing group at the *ortho* position on the aromatic ring reacted smoothly with difluoroethylamine and *tert*-butyl nitrite to give the desired products **4b**–**e** in 90–99% yields. Whether substituent group is electron–rich or –deficient at the *meta* position, the corresponding products **4f**–**i** were also obtained in high yields (90–93%). For the *para* position, this methodology was also compatible with the nitroolefins bearing various groups, such as –Me, –OMe, –F, –Cl, –CN, and $-NO_2$, affording the corresponding products **4j**–**o** in 80–94% yields. This reaction can be extended to disubstituted nitroolefins on the aromatic ring, leading to **4p**–**r** in 82–86% yields (the X-ray of **4r** is shown in Fig. 1).[24,25] To our delight, 2-(2-nitrovinyl)naphthalene also underwent the cascade reaction, affording the expected product **4s** in 90% yield. In addition, further extension of this protocol to heteroaryl nitroalkenes revealed that 2-(2-nitrovinyl)furan and 2-(2-nitrovinyl) thiophene were also tolerated, giving the corresponding products



[a] Unless otherwise noted, all reactions were carried out with nitroalkenes (**1**, 1.0 mmol, 1.0 equiv.), $CF_2HCH_2NH_2$ (**2**, 5.0 mmol, 5.0 equiv.), tBuONO (**3**, 16.0 mmol, 16.0 equiv.), and AcOH (0.05 mmol, 5 mol%) at room temperature for 3 h. Isolated yields of **4** based on **1** were given.
[b] The reaction was allowed to run for 36 h.

Scheme 2. Substrate scope.[a]