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Convenient synthesis of perfluoroalkyl substituted 2-oxopyridine-fused 1,3-diazaheterocycles via a one-pot three-component reaction

Zewei Wang [a], Tianqi Sun [a], Jie Chen [a], Hongmei Deng [d], Min Shao [d], Hui Zhang [a,*], Weiguo Cao [a,b,c,*]

[a] Department of Chemistry, Shanghai University, Shanghai 200444, PR China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China
[c] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China
[d] Instrumental Analysis and Research Center of Shanghai University, Shanghai 200444, PR China

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ABSTRACT

An efficient one-pot synthesis of perfluoroalkylated ring-fused 2-pyridones by three-component reaction of diamine, ketene dithioacetal, and methyl 2-perfluoroalkynoate in EtOH is reported. This protocol has the advantages of easiness, higher yields, and shorter reaction time. A plausible mechanism for this type of cyclization is proposed.

1. Introduction

Many ring-fused 2-pyridones show biological activities.[1] Among these compounds, 2-oxopyridine-fused 1,3-diazaheterocycle moieties are of general interest as a basis for analgesics and antiinflammatory agents in medicinal chemistry.[2] Although a variety of methods for the synthesis of such ring-fused 2-pyridinones are available,[2–6] a survey of literatures shows that the preparation of fluorinated 2-oxopyridine-fused 1,3-diazaheterocycles is challenging because of the paucity of synthetic access.

Multicomponent reactions (MCRs) are powerful tools in creating fused heterocycles because of the inherent molecular diversity, efficiency, and atom-economy.[7]

The ketene dithioacetals of the type **2** are well known as two-carbon synthons and for their push–pull electronic nature.[8] The Michael acceptor characteristics of the ethylene portion of **2** and the possibility of substitution of the two alkylsulfanyl groups with nucleophiles have been well exploited for the synthesis of a variety of heterocycles.[9]

On considering the importance of the introduction of trifluoromethyl or the perfluoroalkyl groups in many biologically active pharmaceutical and agrochemical compounds,[10] and in continuation of our interest in exploiting methyl 2-perfluoroalkynoate as fluorinated building block for the synthesis of perfluoroalkylated heterocycles,[11] herein, we describe an efficient synthesis of perfluoroalkylated 2-oxopyridine-fused 1,3-diazaheterocycles via a new and one-pot three-component reaction between ketene dithioacetal,[12] various diamines and methyl 2-perfluoroalkynoates.[13]

2. Results and discussion

Initially, the three-component reaction of 1,3-propyldiamine **1a** and 1,1-bis(methylthio)-2-nitroethylene **2a** in the presence of methyl 4,4,4-trifluorobut-2-ynoate **3a** as a simple model reaction was investigated to establish the feasibility of the strategy and to optimize the reaction conditions. The reaction was performed in a one-pot two-step process. A mixture of **1a** (1.0 mmol) and 1,1-bis(methylthio)-2-nitroethylene **2a** (1.5 mmol) was stirred in refluxing solvent (5 mL) for 0.5 h, then methyl 4,4,4-trifluorobut-2-ynoate **3a** (1.1 mmol) was added and continued to be stirred for the rest of the designated time. Since the choice of an appropriate reaction medium is of crucial importance for successful synthesis, different solvents, such as methanol, ethanol, acetonitrile,

* Corresponding authors. Fax: +86 21 66134856; e-mail addresses: wgcao@staff.shu.edu.cn, yehao7171@shu.edu.cn (W. Cao).

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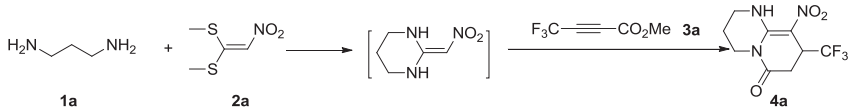
tetrahydrofuran (THF), toluene, and dichloromethane (DCM) were explored. The results are summarized in Table 1. As can be seen from the table, the best results were obtained by refluxing the reaction mixture in EtOH to yield product **4a** in excellent yield (Table 1, entry 7).

Table 1
Optimization of reaction conditions

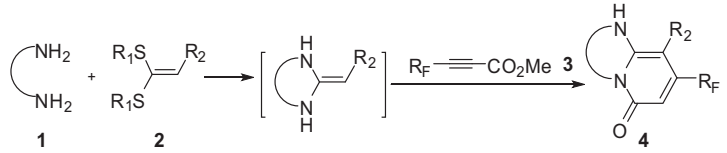


Entry	Solvent	Temperature	Time (h)	Yield[a] (%)
1	DCM	rt	12	34
2	DCM	Reflux	12	39
3	Acetonitrile	Reflux	12	14[b]
4	Toluene	Reflux	12	Trace
5	THF	Reflux	12	40
6	MeOH	Reflux	4	60
7	**EtOH**	**Reflux**	**4**	**95**

Bold entry signifies best result for the reaction condition optimization.
[a] Isolated yield.
[b] The unreacted starting material was recovered.

To test the generality of the conversion, ketene dithioacetal **2** was subjected to reaction with a variety of diamines **1** and methyl 2-perfluoroalkynoates **3**. Using the combinations of **2a** with **3a** and a variety of diamines **1a**–**j**, as shown in Table 2, almost all of the tested combinations successfully produced the desired 2-oxopyridine-fused 1,3-diazaheterocycles with good to excellent yields. However, to synthesize 2-oxopyridine-fused eight-membered 1,3-diazaheterocycle **4e**, only a trace amount of conversion with respect to **1e** was observed even when the reaction was conducted for 48 h. The results also suggested that the cis or trans configuration of the corresponding diamine had some influence on this cascade process. For example, ring-closure to compound **4f** was accomplished with *cis*-cyclohexanediamine **1f** while the use of its trans-isomer **1g** gave no product. Aliphatic diamines were proven to be more reactive than aryl diamines. Moreover, these studies clearly reveal that aryl diamines having electron-withdrawing groups on benzene ring are not compatible

Table 2
Synthesis of perfluoroalkylated 2-oxopyridine-fused 1,3-diazaheterocycles[a]



1a 1,3-propyldiamine **1b** 1,2-ethyldiamine **1c** 2,2-dimethy-1,3-propyldiamine
1d 1,4-butyldiamine **1e** 1,5-pentanediamine **1f** *cis*-1,2-cyclohexanediamine
1g *trans*-1,2-cyclohexanediamine **1h** 1,2-benzenediamine
1i 4,5-dichloro-1,2-benzenediamine **1j** 4,5-dimethyl-1,2-benzenediamine
2a R_1 = Me, R_2 = NO_2 **2b** R_1 = Et, R_2 = COPh
3a R_F = CF_3 **3b** R_F = C_2F_5 **3c** R_F = *n*- C_3F_7

Entry	Diamine **1**	Ketene dithioacetal **2**	2-Perfluoroalkynoate **3**	Time (h)	Product **4**	Yield[b] (%)
1	**1a**	**2a**	**3a**	4	**4a**	91
2	**1b**	**2a**	**3a**	4	**4b**	95
3	**1c**	**2a**	**3a**	4	**4c**	90
4	**1d**	**2a**	**3a**	4	**4d**	87
5	**1e**	**2a**	**3a**	48	**4e**	Trace
6	**1f**	**2a**	**3a**	4	**4f**	92
7	**1g**	**2a**	**3a**	48	**4g**	0
8	**1h**	**2a**	**3a**	4	**4h**	76
9	**1i**	**2a**	**3a**	48	**4i**	0
10	**1j**	**2a**	**3a**	48	**4j**	53
11	**1a**	**2b**	**3a**	8	**4k**	78
12	**1b**	**2b**	**3a**	8	**4l**	85
13	**1c**	**2b**	**3a**	8	**4m**	81
14	**1a**	**2a**	**3b**	4	**4n**	80
15	**1b**	**2a**	**3b**	4	**4o**	85
16	**1c**	**2a**	**3b**	4	**4p**	80
17	**1a**	**2a**	**3c**	4	**4q**	67
18	**1b**	**2a**	**3c**	4	**4r**	75
19	**1c**	**2a**	**3c**	4	**4s**	70
20	**1f**	**2a**	**3c**	4	**4t**	63

[a] Reaction conditions: a mixture of **1** (1.0 mmol) and ketene dithioacetal **2** (1.5 equiv) was stirred in refluxing solvent (5 mL) for 0.5 h, then methyl 2-perfluoroalkynoate **3** (1.1 equiv) was added and continued to be stirred for the rest of the designated time.
[b] Isolated yield.