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Short communication

FSG-Hf(NPf_2)$_4$ catalyzed, environmentally benign synthesis of 1,8-dioxo-decahydroaridines in water–ethanol

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ABSTRACT

An efficient, eco-friendly and simple work-up procedure for the synthesis of 1,8-dioxo-decahydroacridines has been developed through one-pot condensation reaction of aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedion and different aromatic amine or ammonium acetate in the presence of a catalytic amount of FSG supported Hf(NPf_2)$_4$ as a stable and recyclable catalyst under water–ethanol (1:1, v/v). This protocol was found to be applicable to obtain a diverse range of 1,8-dioxo-9-aryl-decahydroacridine derivatives in 49–83% isolated yields and the catalyst was recycled for three cycles.

1. Introduction

Acridines derivatives, constituting a 1,4-dihydropyridine (DHP) ring skeleton are reported to possess a multiplicity of pharmacological properties including antimalarials and in cancer chemotherapy [1–5]. Also, these derivatives are used for the production of dyes in the industry [6]. Another role of acridines is to synthesize labeled conjugates with medicinals, peptides, proteins and nucleic acids that exhibit antitumor and DNA-binding properties [7–9]. Due to the broad utility of acridines, there has been growing interest in the development of a number of efficient synthetic protocols for the preparation of these molecules. One of the commonly used methods reported for the synthesis of acridine derivatives involved the condensation of aldehydes, 5,5-dimethyl-1,3-cyclohexanedione and different anilines, ammonium acetate or ammonium bicarbonate via one-pot multicomponent reaction in the presence of different catalysts such as *p*-dodecylbenezensulfonic acid (DBSA) [10], praline [11], amberlyst-15 [12], [Hmim]TFA [13], MCM-41-SO_3H [14] and Brønsted acidic imidazolium salts containing perfluoroalkyl tails [15], *etc*. Although these methods are effective, some of them often involve the use of expensive and non-recyclable catalysts, hazardous organic solvents and tedious conditions. Furthermore, the substrate amine was specialized in *p*-toluidine. Consequently, the development of more convenient, economical and eco-friendly methodology and expand of substrate for the synthesis of acridines is highly desired.

In recent decades, the catalytic application of metal bis(perfluorooctanesulfonyl)imides in FBS has undergone rapid growth [16–18]. But perfluorinated solvents are expensive and environmentally persistent. Yamamoto synthesized fluorous phenylboronic [19], super Brønsted acid [20] and polystyrene-bound super Brønsted acid [21] as recyclable fluorous acid catalysts to catalyze reaction without fluorous solvent. Nishikido and co-workers have already reported the immobilization of fluorous Lewis acids using β-cyclodextrin epichlorohydrin copolymer as a support to catalyze Diels–Alder and Mukaiyama-aldol reactions in water [22]. They also reported that FSG-supported fluorous Lewis acids act as effective catalysts of Baeyer–Villiger and Diels–Alder reactions in water [23]. Furthermore, the use of water as a promising solvent for organic reactions has received considerable attention in the arena of organic synthesis owing to its green credentials [24]. Due to our continuing interest in the use of fluorous silica gel supported Hf(NPf_2)$_4$ (FSG-Hf(NPf_2)$_4$) as catalyst for the synthesis of fine chemicals and heterocyclic compounds of biological importance we observed that 5,5-dimethyl-1,3-cyclohexanedione undergoes smooth condensation with aromatic aldehydes and anilines or ammonium acetate to give 1,8-dioxo-9-aryl-decahydroacridines in aqueous media (Scheme 1).

2. Results and discussion

Reactivities of several FSG-supported Lewis acids were investigated in the reaction of benzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione and ammonium acetate in water–ethanol (1:1, v/v) at reflux for 6 h. The results are summarized in Table 1. FSG-supported Hf(NPf_2)$_4$ catalyzed the reaction to give

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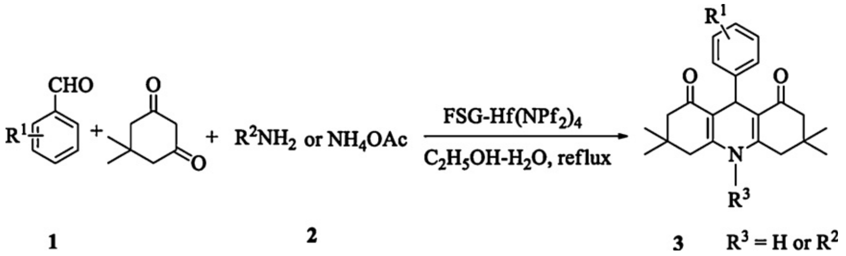

Scheme 1. FSG-Hf(NPf$_2$)$_4$ catalyzed synthesis of 1,8-dioxo-9-aryl-decahydroacridines.

the corresponding product in the yield of 82% and FSG-supported HNPf$_2$, Yb(NPf$_2$)$_3$ and Sc(NPf$_2$)$_3$ showed less catalytic than the above catalyst. The reaction catalyzed by Hf(NPf$_2$)$_4$ without support afforded the desired product in 69% yield and the reaction in the presence of FSG without Lewis acid gave poor yield. When the reaction was performed in the absence of catalyst under the same reaction conditions, it did not produce the desired product even after 24 h (Table 1, entry 10), demonstrating the catalytic role of FSG-Hf(NPf$_2$)$_4$ in the success of the reaction in terms of the yields. Encouraged by these results and to optimize the reaction conditions, the effect of load of the catalyst on the reaction yields was studied. It was observed that 1 mol% of FSG-Hf(NPf$_2$)$_4$ was as effective as higher loads of the catalyst to efficiently catalyze the reaction (Table 1, entries 5 and 9) and hence, the optimal reaction conditions for the model reaction were found to be 1 mol% FSG-Hf(NPf$_2$)$_4$ in water–ethanol (1:1, v/v) at reflux.

Under the optimized reaction conditions, the scope and limitations of this synthetic protocol were investigated by treating 5,5-dimethyl-1,3-cyclohexanedione with a wide range of aromatic aldehydes and anilines or ammonium acetate to afford the corresponding 1,8-dioxo-9-aryl-decahydroacridines (**3a**–**v**) in good yields in the presence of 1 mol% FSG-Hf(NPf$_2$)$_4$ (Table 2). The effect of electron and the nature of substituents on the aromatic ring of the aldehydes did not show expected strong effects in terms of yields under these reaction conditions. Benzaldehyde and other aromatic aldehydes containing electro-withdrawing groups (such as nitro, halide groups) or electron-donating groups (hydroxyl, alkoxyl groups) were employed and they were found to react well to give the corresponding 1,8-dioxo-9-aryl-decahydroacridines. We also observed that ammonium acetate and various aromatic amines such as aniline, *p*-toluidine, *p*-methoxyaniline reacted smoothly under the conditions. However, anilines used as the ammonium source gave **3** in lower yield than ammonium acetate as the ammonium source. The reason may be that ammonia released from ammonium acetate is more nucleophilic than aromatic amines like aniline. Aromatic amines substituted with electron-donating group gave the expected molecules in 49–67% yield, while aromatic amine substituted with electro-withdrawing such as Cl gave no product.

Additionally, we also investigated the recyclability of FSG-Hf(NPf$_2$)$_4$ for four consecutive cycles (fresh + 3 cycles) for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (**3o**). The mixture of 5,5-dimethyl-1,3-cyclohexanedion, benzaldehyde and ammonium acetate was heated in the presence of 1 mol% FSG-Hf(NPf$_2$)$_4$ in water–ethanol (1:1, v/v) at reflux for 6 h. After completion of the reaction, FSG-Hf(NPf$_2$)$_4$ could be easily recovered by centrifugation and decantation and showed good reusability with slight decrease in its activity after three runs (Table 1, entry 5). The Hf(IV) leaching in the crude mixture of each recycling process was less than 8 ppm as determined by ICP analysis. There was marginal decrease in yield after three reuses which might be due to the small amount of catalyst lost during handling.

Table 1
Optimization of the reaction conditions for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine.[a]

Entry	Catalyst	Catalyst load (mol%)	Yields (%)[b]
1	FSG-HNPf$_2$	1	41
2	FSG-HNPf$_2$	4	54
3	FSG-Yb(NPf$_2$)$_3$	1	51
4	FSG-Sc(NPf$_2$)$_3$	1	59
5	FSG-Hf(NPf$_2$)$_4$	1	82, 79, 77, 76[c]
6	Hf(NPf$_2$)$_4$	1	69
7	FSG	–	25
8	FSG-Hf(NPf$_2$)$_4$	0.5	53
9	FSG-Hf(NPf$_2$)$_4$	1.5	85
10	–	–	Trace

[a] Reaction conditions: 1 mmol benzaldehyde, 2 mmol 5,5-dimethyl-1,3-cyclohexanedione, 1.2 mmol ammonium acetate, 8 mL water–ethanol (1:1, v/v), reflux, 6 h.

[b] Isolated yields.

[c] Catalytic system was reused for three times.

3. Experimental

3.1. General

The progress of the reactions was monitored by thin layer chromatography (TLC). Melting points were obtained with Shimadzu DSC-50 thermal analyzer and are uncorrected. Mass spectra were obtained with automated FININIGAN TSQ Advantage mass spectrometer. ^{1}H NMR spectra were measured on Bruke Advance RX500. FTIR were conducted on a Bruker VERTEX70 spectrophotometer. Inductively coupled plasma (ICP) spectra were measured on an Ultima2C apparatus. Fluorous silica gel was purchased from Fluorous Technologies Inc. All chemicals (AR grade) were commercially available and used without further purification.

3.2. Preparation of catalyst

The synthesis of FSG-Hf(NPf$_2$)$_4$ was carried out as reported in literature [20]. Into a solution of hafnium (IV) bis(perfluorooctanesulfonyl)imide complex (200 mg) in ethanol (10 mL), fluorous silica gel (2 g) was added and the resulting mixture was stirred for 1 h at room temperature. After removal of the solvent under reduced pressure, residual FSG-supported hafnium (IV) bis(perfluorooctanesulfonyl)imide complex was dried under vacuum at 80 °C for 6 h.

3.3. General procedure for the synthesis of 1,8-dioxo-9-aryl-decahydroacridines

A mixture of an aromatic aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), aromatic amine or ammonium acetate (1.2 mmol) and FSG-Hf(NPf$_2$)$_4$ (1 mol%) in water–ethanol (1:1, v/v, 8 mL) was stirred at reflux. The progress of the reaction was monitored by TLC. After completion of the reactions, the mixture was cooled to r.t. and filtered. The filtrate was concentrated to obtained the crude product. The supported

Table 2
FSG-Hf(NPf_2)$_4$ catalyzed synthesis of 1,8-dioxo-decahydroacridines via one-pot condensation reaction.[a]

Entry	R^1	R^2 or NH_4OAc	Product	Reaction time (h)	Yields (%)[b]
1	H	Ph	**3a**	6	49
2	4-CH_3	Ph	**3b**	6	58
3	4-CH_3O	Ph	**3c**	6	59
4	3-NO_2	Ph	**3d**	5.5	57
5	4-Cl	Ph	**3e**	6	58
6	H	4-$CH_3C_6H_4$	**3f**	7	66
7	4-CH_3	4-$CH_3C_6H_4$	**3g**	5.5	67
8	4-Cl	4-$CH_3C_6H_4$	**3h**	6.5	66
9	H	4-$CH_3OC_6H_4$	**3i**	6	61
10	4-CH_3	4-$CH_3OC_6H_4$	**3j**	5.5	67
11	4-Cl	4-$CH_3OC_6H_4$	**3k**	6.5	65
12	H	4-ClC_6H_4	**3l**	7	Trace
13	4-CH_3	4-ClC_6H_4	**3m**	7	Trace
14	4-Cl	4-ClC_6H_4	**3n**	7	Trace
15	H	NH_4OAc	**3o**	4	82
16	4-CH_3	NH_4OAc	**3p**	5	75
17	4-CH_3O	NH_4OAc	**3q**	5	80
18	4-$(CH_3)_2N$	NH_4OAc	**3r**	6	80
19	4-OH	NH_4OAc	**3s**	5	77
20	4-Cl	NH_4OAc	**3t**	3	82
21	4-Br	NH_4OAc	**3u**	3	83
22	2,4-Cl_2	NH_4OAc	**3v**	4	83

[a] Reaction conditions: 1 mmol aromatic aldehydes, 2 mmol 5,5-dimethyl-1,3-cyclohexanedione, 1.2 mmol anilines or NH_4OAc, 1 mol% FSG Hf(NPf_2)$_4$, reflux.
[b] Isolated yields after recrystallization.

catalyst was washed with ethanol and dried under vacuum, then reused in the next cycle. The crude products were purified by recrystallization from EtOH (95%).

The physical and spectral data of known compounds (**3a**–**v**) were found to be in agreement with the reported data.

4. Conclusion

In summary, FSG-Hf(NPf_2)$_4$ has been successfully applied as an efficient and environmentally benign supported catalyst for the synthesis of a series of 1,8-dioxo-9-aryl-decahydroacridines through one-pot condensation of 5,5-dimethyl-1,3-cyclohexanedione, aromatic aldehydes and different anilines or ammonium acetate in water–ethanol at reflux. This synthetic protocol offers several advantages including recyclability of the catalyst, operational simplicity, cleaner reaction and minimal environmental impact which makes it a useful and attractive process for the synthesis of these compounds.

References

[1] S. Girault, P. Grellier, A. Berecibar, L. Maes, E. Mouray, P. Lemiere, M. Debreu, E. Davioud-Charvet, C. Sergheraet, Journal of Medicinal Chemistry 43 (2000) 2646–2654.
[2] W. Cholody, B. Horowska, J. Paradziej-Lukowicz, S. Martelli, J. Konopa, Journal of Medicinal Chemistry 39 (1996) 1028–1032.
[3] T. Chen, R. Fico, E.S. Cancellakis, Journal of Medicinal Chemistry 21 (1978) 868–874.
[4] W. Denny, G.J. Atwell, B.C. Baguley, L.P.G. Wakelin, Journal of Medicinal Chemistry 28 (1985) 1568–1574.
[5] G. Rewcastle, G.J. Atwell, D. Chambers, B.C. Baguley, W.A. Denny, Journal of Medicinal Chemistry 29 (1986) 472–477.
[6] A. Albert, The Acridines, Edward Arnold, London, 1966.
[7] E. Delfourne, C. Roubin, J. Bastide, Journal of Organic Chemistry 65 (2000) 5476–5479.
[8] J. Antonini, P. Polucci, A. Magnano, S. Martelli, Journal of Medicinal Chemistry 44 (2001) 3329–3333.
[9] M.G. Ferlin, C. Marzano, G. Chiarelotto, F. Baccichetti, F. Bordin, European Journal of Medical Chemistry 35 (2000) 827–837.
[10] T.S. Jin, J.S. Zhang, T.T. Guo, A.Q. Wang, T.S. Li, Synthesis (2004) 2001–2005.
[11] K. Venkatesan, S.S. Pujari, K.V. Srinivasan, Synthetic Communications 39 (2009) 228–241.
[12] B. Das, P. Thirupathi, I. Mahender, V.S. Reddy, Y.K. Rao, Journal of Molecular Catalysis A: Chemical 247 (2006) 233–239.
[13] M. Dabiri, M. Baghbanzadeh, E. Arzroomchilar, Catalysis Communications 9 (2008) 939–942.
[14] S. Rostamizadeh, A. Amirahmadi, N. Shadjou, A.M. Amani, Journal of Heterocyclic Chemistry 49 (2012) 111–115.
[15] W. Shen, L.M. Wang, H. Tian, J. Tang, J.J. Yu, Journal of Fluorine Chemistry 130 (2009) 522–527.
[16] X.H. Hao, O. Yamazaki, A. Yoshida, J. Nishikido, Green Chemistry 5 (2003) 524–528.
[17] X.H. Hao, A. Yoshida, J. Nishikido, Green Chemistry 6 (2004) 566–569.
[18] X.H. Hao, A. Yoshida, J. Nishikido, Tetrahedron Letters 46 (2005) 2697–2700.
[19] K. Ishihara, S. Kondo, H. Yamamoto, Synlett (2001) 1371–1374.
[20] K. Ishihara, A. Hasegawa, H. Yamamoto, Synlett (2002) 1299–1301.
[21] K. Ishihara, A. Hasegawa, H. Yamamoto, Synlett (2002) 1296–1298.
[22] J. Nishikido, M. Nanbo, A. Yoshida, H. Nakajima, Y. Matsumoto, K. Mikami, Synlett (2002) 1613–1616.
[23] O. Yamazaki, X.H. Hao, A. Yoshida, J. Nishikido, Tetrahedron Letters 44 (2003) 8791–8795.
[24] C.I. Herreras, X. Yao, Z. Li, C.J. Li, Chemical Reviews 107 (2007) 2546–2562.