Metal triflates combined with caffeine based imidazolium salts: A new family of highly efficient and reusable catalysts

Rui M.A. Pinto [a], Jorge A.R. Salvador [a], Christophe Le Roux [b,*]

[a] *Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, 3000-295 Coimbra, Portugal*
[b] *Laboratoire Hétérochimie Fondamentale et Appliquée (UMR-CNRS 5069), Université Paul-Sabatier, 118, Route de Narbonne, 31062 Toulouse Cedex 09, France*

Abstract

The direct alkylation of caffeine (**1**), by ethyl triflate gave 1,3,7-trimethyl-9-ethylxanthinium triflate (**2**) which led to 1,3,7-trimethyl-9-ethylxanthinium bis(trifluoromethanesulfonyl)amide (**3**) after methathesis with LiNTf$_2$; **3** proved to be an ionic solid which can be used for the recovery of metal triflates (M(OTf)$_n$ with M = Sc, La, Yb, Cu, Hf, Bi). These reusable catalysts proved to be efficient Lewis acids for Diels–Alder reactions leading to very little or no polymerisation of the diene. In the case of bismuth (III) triflate, the catalyst can be recovered and reused at least 10 times without loss of activity.
© 2007 Elsevier B.V. All rights reserved.

Keywords: Imidazolium salts; Metal triflates; Catalysis; Diels–Alder reaction; Caffeine

1. Introduction

The catalyst separation from products is a key problem within the development of a sustainable commercial process. It is of great interest to recover and reuse costly and/or toxic catalysts for economical and environmental reasons as well as to reduce the amounts of catalysts or its components in many products in order to respect defined specifications [1].

The use of bio-available, cheap and non-toxic sources of compounds is highly desirable for the design of any green synthesis or process. Caffeine (**1**) is a natural product which can be found in more than 60 plant species whose biosynthesis results from the purine nucleotide pool [2]. Our approach was based on caffeine (**1**), a cheap source of *N*-methyl imidazole resulting from the decaffeination of coffee. Use of caffeine has been recently reported for the synthesis and structural characterization of *N*-heterocyclic carbenes [3,4] but, to our knowledge, caffeine has not yet been used in the preparation of reusable catalysts. Alkyl triflates are commercially available compounds known for their high alkylating power [5,6]. Moreover, the replacement by anion exchange of triflate by bis-trifluoromethanesulfonyl amide anion (Tf$_2$N$^-$) is known to confer hydrophobicity and a lower melting point [7]. We now wish to report our first results related to the synthesis and the uses of 1,3,7-trimethyl-9-ethylxanthinium bis(trifluoromethanesulfonyl)amide (**3**).

2. Experimental

2.1. Preparation of 1,3,7-trimethyl-9-ethylxanthinium triflate (2)

Into a 250 mL round bottomed flask was placed **1** (4.54 g, 23.4 mmol) in 60 mL of anhydrous nitrobenzene. The suspension was heated to 100 °C in an oil bath for 15 min until all **1** dissolved. Then, ethyl triflate (5.0 g,

* Corresponding author. Tel.: +33 (0)5 61 55 65 57; fax: +33 (0)5 61 55 82 04.
E-mail address: leroux@chimie.ups-tlse.fr (C. Le Roux).

28.07 mmol) was added via syringe as one portion and the solution was stirred for 16 h. After this time, the cooled brown solution was subjected to reduced pressure distillation to remove nitrobenzene and unreacted EtOTf (the distillate can be kept and reused for another reaction) to give pure **2** as a deep brown viscous oil. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.70 (t, $J = 7.3$ Hz, 3H, Me), 3.34 (s, 3H, Me), 3.89 (s, 3H, Me), 4.22 (s, 3H, Me), 4.79 (q, $J = 7.3$ Hz, 2H, CH$_2$), 9.23 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 14.9, 27.9, 31.4, 35.6, 45.6, 108.7, 121.0 (q, $J(^{13}$C/^{19}F) = 320.9 Hz), 138.4, 139.6, 150.7, 153.7; ^{19}F NMR (188 MHz, acetone-d_6) δ −79.1.

2.2. Preparation of 1,3,7-trimethyl-9-ethylxanthinium bis(trifluoromethanesulfonyl)amide (3)

To the amount of **2** prepared above was added distilled water (30 mL). Then, under good stirring, a solution of LiNTf$_2$ (6.72 g, 23.4 mmol) in distilled water (10 mL) was gradually added at room temperature to the solution of **2** which led to the instantaneous formation of **3**. Then water (60 mL) was added and after 20 min under stirring, the brown solution was filtered to give **3** (11.66 g, 91% overall yield starting from **1**) as a white solid. Mp: 111–112 °C; IR (compressing cell with diamond windows) 3166, 3102, 2963, 1724, 1678, 1633, 1582, 1548, 1467, 1417, 1336, 1198, 1139, 1052, 762 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 1.72 (t, $J = 7.3$ Hz, 3H, Me), 3.35 (s, 3H, Me), 3.90 (s, 3H, Me), 4.24 (s, 3H, Me), 4.81 (q, $J = 7.3$ Hz, 2H, CH$_2$), 9.19 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 14.9, 27.9, 31.4, 35.7, 45.7, 108.8, 120.0 (q, $J(^{13}$C/^{19}F) = 321.3 Hz), 138.0, 139.5, 150.6, 153.5; ^{19}F NMR (188 MHz, acetone-d_6) δ −79.8; MS/DCI: 521 [C$_{12}$H$_{15}$F$_6$N$_5$O$_6$S$_2$ + NH$_4$]$^+$, 242 [C$_{10}$H$_{15}$N$_4$O$_2$ + NH$_4$]$^+$, 223 [C$_{10}$H$_{15}$N$_4$O$_2$]$^+$, 280 [C$_2$NO$_4$F$_6$S$_2$]$^-$; TGA analysis revealed that **3** starts to decompose around 280 °C (TGA plot not shown). X-ray diffraction study carried out on monocrystals of **3** obtained from cold acetone showed the nitrogen in the NTf$_2$ anion to be located in the center of the imidazolium ring (structure not shown).

2.3. Preparation of the catalytic systems metal triflates/3

For Bi(OTf)$_3$ · 4H$_2$O/**3** system (1/10 molar ratio): a mixture of **3** (1.062 g, 2.1 mmol) and bismuth(III) triflate (0.153 g. 0.21 mmol) was dissolved in acetone (6 mL); the addition of heptane (18 mL) precipitated the salts which were dried under vacuum. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.68 (t, $J = 7.3$ Hz, 3H, Me), 3.22 (s, 3H, Me), 3.87 (s, 3H, Me), 4.21 (s, 3H, Me), 4.77 (q, $J = 7.3$ Hz, 2H, CH$_2$), 9.17 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 16.3, 29.3, 32.8, 37.1, 47.1, 110.2, 121.4 (q, $J(^{13}$C/^{19}F) = 321.3 Hz, N(SO$_2$CF$_3$)$_2$), 121.9 (q, $J(^{13}$C/^{19}F) = 320.0 Hz, OSO$_2$CF$_3$), 139.5, 140.9, 155.0, 155.3; ^{19}F NMR (188 MHz, acetone-d_6) δ −79.8 (s; N(SO$_2$CF$_3$)$_2$), −79.0 (s, OSO$_2$CF$_3$), the ratio between these two signal was respectively 6.7:1.

2.4. Typical procedure for Diels–Alder reaction

Into a 50 mL flask at room temperature were successively added the system Bi(OTf)$_3$ · 4H$_2$O/**3** (0.256 g, which corresponds to 0.044 mmol of Bi(OTf)$_3$ · 4H$_2$O) and dichloromethane (4.5 mL). Then, with magnetic stirring, ethyl vinyl ketone (0.363 g, 4.4 mmol) and 2,3-dimethylbuta-1,3-diene (0.363 g, 4.4 mmol) were added and the mixture was stirred for 3 h. After this time of reaction heptane was added (9 mL). The suspension was filtered and the filtrate was concentrated under vaccum to afford 1-(3,4-dimethylcyclohex-3-enyl)propan-1-one (0.722 g, 99% yield) as a pale yellow liquid characterized by NMR and GC/MS [8].

The analytical data for other Diels–Alder adducts were in agreement with those reported in the literature: Table 3, entries 1 [9], 2 [8], 3 [10], 4 [11], 5 [8], 6 [10]; for entry 7, Mp: 51 °C; IR (compressing cell with diamond windows) 3141, 2978, 2920, 2856, 1710, 1567, 1456, 1424, 1381, 1114, 1018, 809 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.09 (t, $J = 7.3$ Hz, 3H), 2.47 (q, $J = 7.3$ Hz, 2H), 2.73 (m, 2H), 2.87 (m, 2H), 5.86 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 7.8, 22.3, 36.0, 40.5, 105.6, 153.1, 210.1; MS (EI) m/z 236 [C$_{14}$H$_{20}$O$_3$]$^+$, 165, 107, 57.

2.5. Reusability of the catalyst

At the end of the reaction Bi(OTf)$_3$ · 4H$_2$O/**3** was recovered by simple filtration and washed with a 1:2 CH$_2$Cl$_2$:heptane solution (15 mL). The recovered Bi(OTf)$_3$ · 4H$_2$O/**3** (0.254 g, 99.2%) was used for subsequent experiments.

3. Results and discussion

The synthesis of **3** started by the direct alkylation of **1** by EtOTf which was quantitatively carried out in nitrobenzene, as previously reported for other such type of reactions [4] (see Scheme 1). After removal of the solvent under reduced pressure, a viscous brown oil of 1,3,7-trimethyl-9-ethylxanthinium triflate (**2**) was obtained which was dissolved in pure water. The addition of LiNTf$_2$, a salt developed for lithium batteries [12], to this solution led instantaneously to the quantitative precipitation of **3** as a white powder in not optimized 91% overall yield starting from **1**.

We then decided to study the catalytic efficiency of **3** in Diels–Alder reactions since other catalysts such as LiNTf$_2$ in acetone [13] or Sc(OTf)$_3$ in [BMIM][PF$_6$] [14] proved to be active for this reaction. For this study we chose the reaction of 1,3-dimethylbutadiene with ethyl vinyl ketone as a model reaction since these two compounds do not react spontaneously without any catalyst. Our results are summarized in Table 1.

While under our conditions **3** proved to be inactive (Table 1, entries 1 and 8), metal triflates (1% towards the reactants) combined with **3** (see Sections 2.3 and
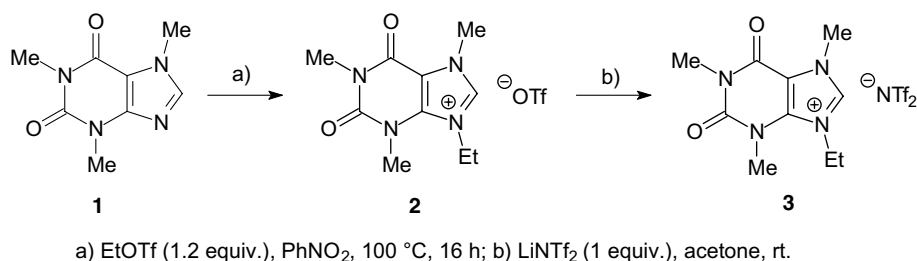
a) EtOTf (1.2 equiv.), PhNO$_2$, 100 °C, 16 h; b) LiNTf$_2$ (1 equiv.), acetone, rt.

Scheme 1. Reagents and conditions: (a) EtOTf (1.2 equiv.), PhNO$_2$, 100 °C, 16 h and (b) LiNTf$_2$ (1 equiv.), acetone, rt.

Table 1
Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene and ethyl vinyl ketone catalyzed by metal triflates/3

Entry	M(OTf)$_n$/3[a] (mol%)	Time (h)	Yield[b,c] (%)
1	–[d]	3	–
2	Sc(OTf)$_3$ (1)	3	83 (77)
3	Bi(OTf)$_3$ · 4H$_2$O (1)	3	99 (98)
4	La(OTf)$_3$ (1)	3	5 (4)
5	Hf(OTf)$_4$ (1)	3	98 (98)
6	Cu(OTf)$_2$ (1)	3	61 (58)
7	Yb(OTf)$_3$ (1)	3	24 (15)
8	–[d]	14	3
9	Sc(OTf)$_3$ (0.1)	14	86 (94)
10	Bi(OTf)$_3$ · 4H$_2$O (0.1)	14	81 (80)

[a] M(OTf)$_n$: x mol% with respect to reactants; 3: 10 mol% with respect to reactants.
[b] Isolated yield, purity determined by GC and ^{1}H NMR.
[c] In brackets is shown the yield of the second experiment using the recovered catalytic system.
[d] Reaction performed using only 3 as catalyst (10 mol% with respect to reactants).

2.4) proved to be highly active. In contrast to other work with scandium triflate [14], the presence of 3 had no detectable influence on the catalytic activity (results not shown of experiments carried out without 3). Notably our catalytic systems are still active even at 0.1% of Bi(OTf)$_3$ · 4H$_2$O or Sc(OTf)$_3$ (Table 1, entries 9 and 10). From a practical point of view the major advantage of adding only 10 mol% of 3 is that it can be fully recovered (>99%) after precipitation and filtration at the end of the reaction by simple addition of heptane (or any mixture of alkanes) which induces the co-precipitation of the metal triflate. We believe that such systems can be classified between classical organic Lewis acids such as trityl triflate (non-recyclable and decomposed by water), metal triflates (recyclable after extraction from water) and ionic liquids (recyclable and moisture insensitive for those derived from NTf$_2^-$) [15,16]. A similar use of triflimide salts as been recently reported for dehydrative esterification reactions [17].

Since bismuth(III) triflate [18] combined with 3 emerged as the cheapest and most active catalytic system, we decided to study its recovery. As shown in Table 2, this catalytic system can be recovered and reused at least 10 times without any appreciable loss of activity. Only a slight erosion of the yield was observed in the subsequent runs which indicate that some loss of the metal triflate occurred. Such loss can be determined by ^{19}F NMR and was estimated to be around 19% which is in agreement with our observations. The integration of the two ^{19}F NMR signals at −79.8 and −79.0 was respectively 8.2:1 which gives an estimation of the loss of bismuth triflate (19% in this case).

This new reusable Bi(OTf)$_3$ · 4H$_2$O/3 catalytic system was then tested in other typical Diels–Alder reaction (Table 3). In all cases high yields were achieved, very little or no polymerisation of the diene was observed and the catalytic system was recovered (>99%) in all reactions. Interestingly, 3 is compatible with furan, an acid sensitive compound (Table 1, entry 7) [19]. Thus, the reaction of furan with ethyl vinyl ketone (Table 3, entry 7) did not gave the expected adduct, but a Michael-type addition product which was previously reported [20] from the room temperature reaction of furan with methyl vinyl ketone.
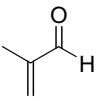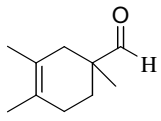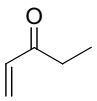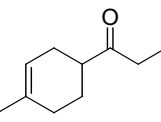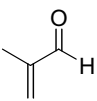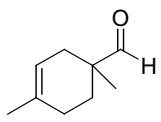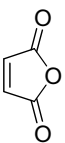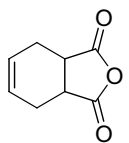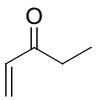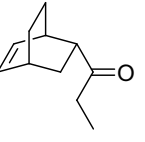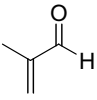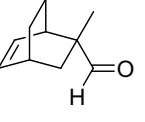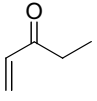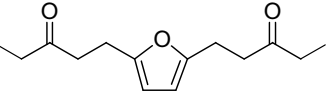
Table 2
Recover and reuse of the system Bi(OTf)$_3$ · 4H$_2$O/3 in the Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene and ethyl vinyl ketone[a]

Run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Yield[b] (%)	96	95	98	93	94	90	92	92	93	91	90	86	84	84	75

[a] Conditions: see typical procedure.
[b] Isolated yield. Purity determined by GC and ^{1}H NMR.

Table 3
Diels–Alder reaction catalysed by Bi(OTf)$_3$ · 4H$_2$O/**3**[a]

Entry	Diene	Dienophile	Time (h)	Major product[b]	Yield[c] (%)	Isomeric ratio
1			3		99	–
2			5		92	95:5[d]
3			20		99	98:2[d]
4			15		55[e]	–
5			18		95	95:5[f]
6			18		95[g]	80:20[f]
7			1		88	–

[a] Reactions performed at room temperature, using CH$_2$Cl$_2$ as solvent (1 M solutions) and diene and dienophile in equimolar amounts, except for entry 7 (2 equiv. of dienophile were used).

[b] The identity of the products was determined by ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and GC/MS.

[c] Isolated yields.

[d] Isomeric ratio of 1:4/1:3 adducts was determined by ^{1}H NMR.

[e] Reaction performed at −8 °C, non-optimized yield.

[f] Isomeric ratio of endo/exo adducts was determined by ^{1}H NMR.

[g] Traces of polymerization were observed in the crude product.

4. Conclusion

In conclusion, we have shown that the direct alkylation of caffeine leads to a new imidazolium compound which can be used, combined with metal triflates, as catalytic systems. Due to their very low solubility in solvents of low polarity, these new catalytic systems can be easily, quantitatively recovered and reused at least 10 times in the case of Diels–Alder reactions. The catalysis of other reactions with these new catalytic systems, the use of other metal salts such as rare earth triflates as well as the synthesis of other alkyl derivatives of caffeine are currently under investigation in our laboratory and will be reported in due course.

Acknowledgements

References

[1] R.T. Baker, S. Kobayashi, W. Leitner, Adv. Synth. Catal. 348 (2006) 1337.
[2] H. Ashihara, A.M. Monteiro, F.M. Gillies, A. Crozier, Plant Physiol. 111 (1996) 747.
[3] J. Schutz, W.A. Herrmann, J. Organomet. Chem. 689 (2004) 2995.
[4] A. Kascatan-Nebioglu, M.J. Panzner, J.C. Garrison, C.A. Tessier, W.J. Youngs, Organometallics 23 (2004) 1928, and references cited.
[5] R.D. Howells, J.D. Mc Cown, Chem. Rev. 77 (1977) 69.
[6] R.L. Hansen, J. Org. Chem. 30 (1965) 4322.
[7] P. Bonhôte, A.P. Dias, N. Papageorgiou, K. Kalyanasundaram, M. Grätzel, Inorg. Chem. 35 (1996) 1168.
[8] D. Nakashima, H. Yamamoto, Org. Lett. 7 (2005) 1251.
[9] J.E. Baldwin, M.J. Lusch, J. Org. Chem. 44 (1979) 1923.
[10] E.J. Corey, T. Shibata, T.W. Lee, J. Am. Chem. Soc. 124 (2002) 3808.
[11] H.K. Hall Jr., P. Nogues, J.W. Rhoades, R.C. Sentman, M. Detar, J. Org. Chem. 47 (1982) 1451.
[12] M. Liu, S.J. Visco, L.C. De Jonghe, J. Electrochem. Soc. 138 (1991) 1891.
[13] S.T. Handy, P.A. Grieco, C. Mineur, L. Ghosez, Synlett (1995) 565.
[14] C.E. Song, W.H. Shim, E.J. Roh, S.G. Lee, J.H. Choi, Chem. Commun. (2001) 1122.
[15] S. Gmouh, H. Yang, M. Vaultier, Org. Lett. 5 (2003) 2219.
[16] T. Ollevier, V. Desyroy, B. Debailleul, S. Vaur, Eur. J. Org. Chem. 70 (2005) 4971.
[17] Y. Nakamura, T. Maki, X. Wang, K. Ishihara, H. Yamamoto, Adv. Synth. Catal. 348 (2006) 1505.
[18] B. Garrigues, F. Gonzaga, H. Robert, J. Dubac, J. Org. Chem. 62 (1997) 4880.
[19] C. Le Roux, M. Maraval, M.E. Borredon, H. Gaspard-Iloughmane, J. Dubac, Tetrahedron Lett. 33 (1992) 1053.
[20] M. Avalos, R. Babiano, L.B. Bravo, P. Cintas, J.L. Jiménez, J.C. Palácios, Tetrahedron Lett. 39 (1998) 9301.