Tetrahedron Letters 54 (2013) 695–698

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Lewis acid-catalyzed Csp^3–H functionalization of methyl azaarenes with α-trifluoromethyl carbonyl compounds

Vincent B. Graves, Abid Shaikh *

Department of Chemistry, Georgia Southern University, Statesboro, GA 30460-8064, USA

ARTICLE INFO

Article history:
Received 26 October 2012
Revised 3 December 2012
Accepted 5 December 2012
Available online 12 December 2012

Keywords:
Azaarenes
C–H functionalization
Trifluoromethyl ketone
Catalysis
Lewis acid

ABSTRACT

A Lewis acid promoted Csp^3–H bond functionalization of methyl azaarenes with α-trifluoromethylated carbonyl compounds is described. Catalytic amounts of $Yb(OTf)_3$ provided a straightforward access to the corresponding trifluoromethylated alcohols in excellent yields up to 94% under mild reaction conditions.

Published by Elsevier Ltd.

Introduction

Csp^2-H functionalization using transition metal catalysts proved a valuable tool in C–C bond formation.[1] In contrast; Csp^3–H functionalization of alkyl group directly attached to aromatic ring is less explored. A few known methods involve the use of Pd and Cu based catalysts for the C–H activation of substituted azines and azarenes.[2] Recent investigations demonstrated the role of Lewis acid catalysts in Csp^3–H functionalization of 2-methylazaarenes with α,β-unsaturated carbonyls,[3] aldimines,[4] carbonyls,[5] and azodicarboxylates.[6] However, the coupling of 2-methylazaarenes with α-trifluoromethylated carbonyl compounds to provide trifluoromethylated tertiary alcohols has not yet been explored. Our investigations revealed the Lewis acid-catalyzed C–H functionalization of 2-alkylazaarene with α-trifluoromethylated carbonyl compounds can be achieved under mild reaction conditions.

Design and synthesis of fluorine-based drugs have gained significant attention[7] and numerous studies proved the role of fluorine atom in facilitating drug delivery and improving binding to the target sites.[8] Currently, more than 20% of the top selling drugs have at least one fluorine atom in them. Trifluoromethylated ($-CF_3$) compounds are particularly interesting due to their strong electron withdrawing effect that can create exceptional properties.[9] Various independent studies have also shown the presence of CF_3-group is essential for the biological activity of many compounds.[10] Also, trifluoromethyl hydroxy compounds have recently been investigated for their anti-fibrillogenesis properties in Alzheimer's disease.[11]

Results and discussion

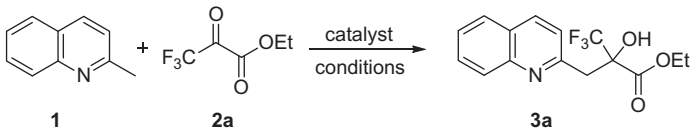
Continuing our interest in the synthesis of trifluoromethylated alcohols, herein, we report a simple protocol for Lewis acid promoted addition of substituted 2-methylquinoline and 2-methylpyridine with α-trifluoromethyl carbonyl compounds, producing corresponding trifluoromethyl alcohols. In order to validate this idea, quinaldine **1** and ethyl 3,3,3-trifluoropyruvate **2a** were chosen as model substrates and were screened in the presence of various Lewis acid as well as Brønsted acid catalysts. The optimization studies are summarized in Table 1.

Initial trials with $Sc(OTf)_3$ and AgOTf (Table 1, entries 1 and 2) did not provide the expected product at all. $Cu(OAc)_2$ under various solvents, molar ratios, and temperature conditions promoted the reaction only up to a 45% conversion (Table 1, entries 3–5). In contrast, the results using $Yb(OTf)_3$ were inspiring. The conversion jumped to 94% with only 5 mol % of catalyst at relatively lower reaction temperature of 90 °C (Table 1, entry 6). Increasing the catalyst amount to 10 mol % did not affect the conversion; on the other hand increasing temperature to 110 °C gave a lower conversion of 88% (Table 1, entries 7 and 8). Trials with Brønsted acid such as TfOH (10 mol %) also promoted the reaction with 84% conversion, although a higher temperature of 120 °C was required (Table 1, entries 9–11). CF_3COOH (Table 1, entry 12) and PTSA (Table 1, entry 13) were also examined but the conversion was not satisfactory.

* Corresponding author. Tel.: +1 912 478 0973; fax: +1 912 478 0699.
E-mail address: malnu@georgiasouthern.edu (A. Shaikh).

0040-4039/$ - see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2012.12.013

Table 1
Evaluation of various Lewis acid and Brønsted acid catalysts[a]

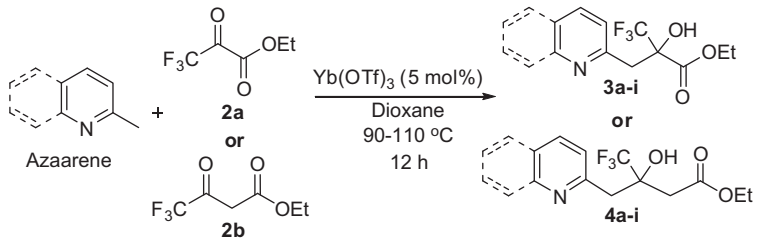


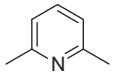
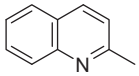
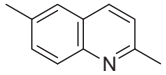
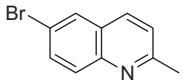
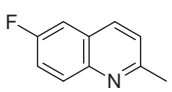
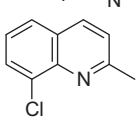
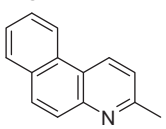
1 2a 3a

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Conv.[b] (%)
1	$Sc(OTf)_3$ (10)	THF	80	24	0
2	AgOTf (10)	THF	80	24	0
3	$Cu(OAc)_2$ (5)	THF	80	24	21
4	$Cu(OAc)_2$ (5)	Dioxane	110	12	40
5	$Cu(OAc)_2$ (10)	Dioxane	110	12	45
6	$Yb(OTf)_3$ (5)	Dioxane	90	12	94
7	$Yb(OTf)_3$ (10)	Dioxane	90	12	94
8	$Yb(OTf)_3$ (5)	Dioxane	110	12	88
9	TfOH (5)	Dioxane	90	12	79
10	TfOH (10)	Dioxane	90	12	82
11	TfOH (10)	Dioxane	110	12	84
12	CF_3COOH (10)	Dioxane	110	12	25
13	PTSA (10)	Dioxane	110	12	51

[a] Reaction conditions: quinaldine **1** (0.70 mmol), ethyl trifluoropyruvate **2a** (0.35 mmol), catalyst (5–10 mol %).
[b] Determined by GCMS.

Table 2
Substrate scope of 2-methyl azaarenes[a]



Entry	Azaarene	Reactant	Product	*T* (°C)	Yield[b] (%)
1		**2a**	**3b**	90	89
		2b	**4b**	110	91
2		**2a**	**3c**	90	94
		2b	**4c**	110	70
3		**2a**	**3d**	90	91
		2b	**4d**	110	87
4		**2a**	**3a**	90	78
		2b	**4a**	110	83
5		**2a**	**3e**	90	86
		2b	**4e**	110	91
6		**2a**	**3f**	90	94
		2b	**4f**	110	93
7		**2a**	**3g**	90	88
		2b	**4g**	110	79
8		**2a**	**3h**	90	81
		2b	**4h**	110	72
9		**2a**	**3i**	90	85
		2b	**4i**	110	87

[a] Reaction conditions: quinaldine **1** (0.70 mmol), ethyl trifluoropyruvate **2a** and ethyl trifluoroacetoacetate **2b** (0.35 mmol), $Yb(OTf)_3$ (5 mol %), dioxane (2 mL).
[b] Isolated yields after flash chromatography.

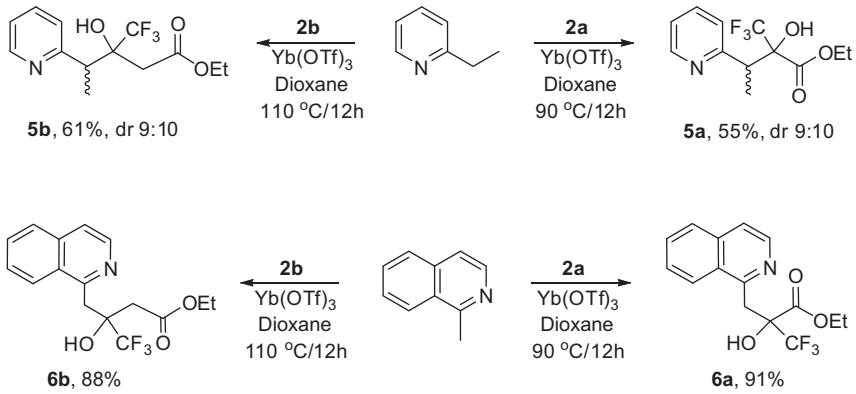
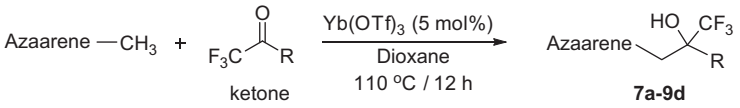
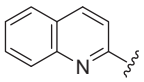
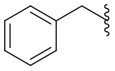
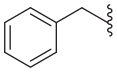
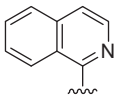
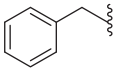


Figure 1. $Yb(OTf)_3$ promoted Csp^3–H functionalization of 2-ethyl pyridine and 1-methyl isoquinoline with **2a** and **2b**.

Table 3
Scope of methyl azaarenes with various trifluoromethyl ketones



Entry	Azaarene	R	Product	Yield[a] (%)
1		CH_3CH_2-	**7a**	79
2			**7b**	90
3			**7c**	88
4			**7d**	93
5		CH_3CH_2-	**8a**	83
6			**8b**	94
7			**8c**	91
8			**8d**	89
9		CH_3CH_2-	**9a**	83
10			**9b**	94
11			**9c**	91
12			**9d**	89

[a] Isolated yields after flash chromatography.

The substrate scope of this reaction was investigated by treating various substituted 2-methyl pyridines and 2-methyl quinolines with ethyl trifluoropyruvate (**2a**). The results are summarized in Table 2. All the reactions proceeded in good to excellent yields (78–94%) and no by-product formation was observed. Based on the excellent results obtained in case of **2a**, a similar sequence of substrates was tried with ethyl trifluoroacetoacetate **2b**. After optimizing the reaction conditions, it was observed that a slight in-

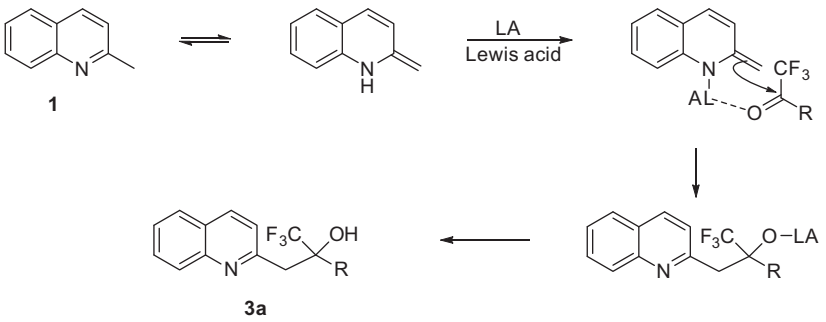


Figure 2. Proposed hypothesis on Lewis acid promoted Csp^3–H functionalization of methyl azaarenes.

crease in reaction temperature (110 °C) was necessary due to the fact that **2b** is comparatively less electrophilic than **2a**. In all the cases, reactions provided good to excellent yields (70–93%). An important observation worth mentioning is that the reactions with halogenated azaarenes (Table 2, entries 6–8) provided the expected products without the loss of halogens.

The reactivity of 2-ethyl pyridine and 1-methyl isoquinoline was also investigated (Fig. 1). The reaction of 2-ethyl pyridine with **2a** and **2b** provided the expected product **5a** and **5b** as a mixture of diastereomers in 55% and 61% yields, respectively. 1-Methyl isoquinoline with **2a** and **2b** proceeded exclusively at the Csp^3–H position and provided the addition products in excellent yields.

To investigate the generality of this method, furthermore, the substrate scope with regard to various trifluoromethyl ketones was examined. The first set of reactions was carried out with quinaldine and α-trifluoromethylated 2-butanone, acetophenone, 3-phenyl-2-propanone, and 2-acetyl thiophene. The reactions proceeded smoothly at 110 °C providing the corresponding addition products **7a**–**7d** in good to excellent yields (79–93%). Similarly, 2-picoline and 1-methyl isoquinoline were allowed to react with α-trifluoromethylated ketones to afford the corresponding Csp^3–H functionalized products **8a**–**9d** in yields ranging from 83% to 94%. The results are summarized in Table 3.

Lewis acid promoted Csp^3–H activation of 2-methyl azaarenes occurs under the proton-transfer condition.[3a] Coordination of a Lewis acid significantly increases the acidity of Csp^3–H bond that leads to the cleavage of C–H bond to generate a metal enamide species. The addition of metal enamide to the electrophilic carbonyl carbon would afford a metal enolate intermediate, which on further protonation would give the expected product. We envision that the coordination of metal with carbonyl oxygen would also promote the reaction by facilitating the attack on electron deficient carbon. The hypothesis is shown in Figure 2.

In conclusion, we have developed an efficient and simple protocol for the Csp^3–H functionalization of 2-alkyl azaarenes with α-trifluoromethyl carbonyl compounds.[12] $Yb(OTf)_3$ promoted the reaction to provide the corresponding trifluoromethyl hydroxy compounds in good to excellent yields. In all the cases, exclusively only one product was observed which eliminates the possibility of the formation of Friedel–Crafts alkylation product. The products were obtained as a racemic mixture and our current efforts are directed toward developing enantioselective synthesis.

Acknowledgments

Financial support provided by Georgia Southern University and Faculty Research Grant (FRC-GSU) to A.S. is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.013.

References and notes

1. (a) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964; (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (c) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200; (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173; (e) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35; (f) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013.
2. (a) Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266; (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155; (c) Haslam, E. *Shikimic Acid Metabolism and Metabolites*; John Wiley & Sons: New York, 1993; (d) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650; (e) Jiang, H.; Chen, H.; Wang, A.; Liu, X. *Chem. Commun.* **2010**, 7259.
3. (a) Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706; (b) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. *Org. Lett.* **2012**, *14*, 957.
4. (a) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650; (b) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. *J. Org. Chem.* **2011**, *76*, 6849; (c) Qian, B.; Xie, P.; Xie, Y.; Huang, H. *Org. Lett.* **2011**, *13*, 2580; (d) Rueping, A.; Tolstoluzhsky, N. *Org. Lett.* **2011**, *1095*, 13; (e) Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195.
5. Niu, R.; Xiao, J.; Liang, T.; Li, X. *Org. Lett.* **2012**, *14*, 676.
6. Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304.
7. (a) Fried, J.; Sabo, E. T. *J. Am. Chem. Soc.* **1954**, *76*, 1455; (b) Ramachandran, P. V. *Asymmetric Fluoroorganic Chemistry*; ACS Symp. Series, ACS: Washington, DC, 2000; (c) Himaya, T. *Organofluorine Compounds*; Springer-Verlag: Berlin, Heidelberg, 2001; (d) Török, B.; Prakash, G. K. S. *Adv. Synth. Catal.* **2003**, *345*, 165; (e) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: New York, Heidelberg, 2004.
8. Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996.
9. Filler, R. In *Asymmetric Fluoroorganic Chemistry*; Ramachandran, P. V., Ed.; Springer: New York, 2000; p 1. Chapter 1.
10. (a) Pappolla, M.; Bozner, P.; Soto, C.; Shao, H.; Robakis, N. K.; Zagorski, M.; Frangiones, B.; Ghiso, J. *J. Biol. Chem.* **1998**, *273*, 7185; (b) Chyan, Y.-J.; Poeggeller, B.; Omar, R. A.; Chain, D. G.; Frangione, B.; Chiso, J.; Pappolla, M. A. *J. Biol. Chem.* **1999**, *274*, 21937; (c) Poeggeller, B.; Miravalle, L.; Zagorski, M. G.; Wisniewski, T.; Chyan, Y.-J.; Zhang, Y.; Shao, H.; Bryant-Thomas, T.; Vidal, R.; Frangione, B.; Ghiso, J.; Pappolla, M. A. *Biochemistry* **2001**, *40*, 14995; (d) Bendheim, P. E.; Poeggeler, B.; Neria, E.; Ziv, V.; Pappola, M. A.; Chain, D. G. *J. Mol. Neurosci.* **2002**, *19*, 213; (e) Kato, K.; Fujii, S.; Gong, Y. F.; Tanaka, S.; Katayama, M.; Kimoto, H. *J. Fluorine Chem.* **1999**, *99*, 5; (f) Karbwang, J.; White, N. J. *Clin. Pharmacokinet.* **1990**, *19*, 264.
11. (a) Torok, M.; Abid, M.; Mhadgut, S. C.; Torok, B. *Biochemistry* **2006**, *45*, 5377; (b) Sood, A.; Abid, M.; Hailemichael, S.; Foster, M.; Torok, B.; Torok, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6931.
12. *General procedure:* Quinaldine **1** (100 mg, 0.70 mmol) and ethyl trifluoropyruvate **2a** (47 μL, 0.35 mol) were placed in a screw cap pressure tube along with 2 mL of 1,4-dioxane. Ytterbium triflate (21 mg, 5 mol %) was added with constant stirring. The closed tube was then stirred at 90 °C for 12 h. Inert reaction atmosphere is not necessary. After the reaction was completed, as indicated by TLC, the resulting reaction mixture was directly subjected to column chromatography (hexane/ethyl acetate 90:10–80:20) to get a white solid with 78% isolated yield.