Tetrahedron Letters 52 (2011) 2076-2079

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Facile Cu(OTf)₂-catalyzed preparation of 9-tosylaminofluorene derivatives from o-arylated *N*-tosylbenzaldimines

Xufen Yu, Xiyan Lu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ARTICLE INFO

ABSTRACT

green method.

Article history: Available online 28 October 2010

Dedicated to Professor Harry Wasserman on the occasion of his 90th birthday

Keywords: Cu(OTf)₂ 9-Tosylaminofluorene Aza-Friedel–Crafts reaction o-Arylated N-tosylbenzaldimines

The aza-Friedel–Crafts reactions (AFCR) have attracted much attention as a synthetically outstanding carbon–carbon bond-forming process that leads to functionalized amines in a green transformation and completely atom–economic way.¹ However, in spite of its significance, a great deal of potential problems related to arene nucleophile, electrophilic substrate, or functional group tolerance still remain for this transformation. For an example, the aza-Friedel–Crafts reaction seems to be restricted to highly electrophilic substrates, such as trifluoromethyl imines,² or α -imino esters³, and highly nucleophilic substrates, such as indoles,^{3f,g,4} electron-rich arenes^{3c,5} due to the low reactivity of imines.^{1d,2a,3f,g,6}

In recent years, the fluorene structural moiety serves as a rigidly planar biphenyl unit within the molecular backbone. Those unique properties, such as highly efficient photoluminescence, the electroluminescence, thermal, and oxidative stability, good solubility, and emission of the polarized blue light make the polyfluorene and its derivatives as promising candidates of blue-light-emitting materials.^{7–10} During past decades, remarkable advances have been made in the production of high-molecular-weight and structurally welldefined polyfluorene derivatives.⁸ Moreover, substitution of an amino group on the polyfluorene backbone may introduce special characteristics to this polymer, such as good solubility in water. In another point of view, N-substituted 9-aminofluorenes, by virtue of their inimitable importance in biological materials and medicines, their synthesis offer a great challenge to organic chemists. One of the most general strategies for their formation is the addition of organometallic reagents toward N-substituted 9-fluorenei-

mines.¹¹ Recently, direct N-functionization of sp³ C-H bond has emerged to provide an appealing approach for the synthesis of valuable nitrogen-containing compounds.^{12,13} However, these methods only gave poor yield in terms of 9-aminofluorenes because of steric hindrance. In view of some limitations associated with their synthesis, it is highly desirable to put considerable efforts to develop alternative methods to circumvent this difficulty. In order to obtain 9-aminoflourenes, we focused on the addition reactions of arenes to N-tosylimines, using metal triflates as the Lewis acid (aza-Friedel-Crafts reaction). However, the reactions of nitrogen-containing compounds are also limited due to the deactivation by the strong coordination of the nitrogen atom to the Lewis acids. In many cases, stoichiometric amounts of the Lewis acids are required.¹⁴ Recently, the copper Lewis acids have been developed for addition reactions to imines, including process such as the ene reaction,¹⁵ Mannich-type reaction,¹⁶ allylation¹⁷ and aza-Diels-Alder reactions.¹⁸ Reports on the catalytic addition of imines to unactivated arenes are very few, to the best of our knowledge, only examples of the addition of an activated imine to indole, pyrrole and electron-rich arenes have been reported.^{3g,4b,19} In this Letter, we wish to report the convenient and expeditious Cu(OTf)₂-catalyzed aza-Friedel-Crafts reaction of o-arylated *N*-tosylbenzaldimines leading to 9-aminofluorene derivatives

The 9-tosylaminofluorene derivatives were synthesized conveniently by Cu(OTf)₂-catalyzed aza-Friedel–

Crafts reaction of o-arylated N-tosylbenzaldimines in high yields. This is an efficient, atom-economic, and

The substrate o-arylated *N*-tosylbenzaldimines (1) was synthesized in high yield from o-arylated arylaldehydes and tosylamine as shown in Scheme 1.

Table 1 presents selected optimization experiments using **1a** as the substrate. Firstly, a variety of Lewis acids were employed to perform the intramolecular aza-Friedel–Crafts reaction. Using $Pd(OAc)_2$, $Pd(O_2CCF_3)_2$ and cationic palladium complexes,





© 2010 Elsevier Ltd. All rights reserved.

^{*} Corresponding author. Tel.: +86 21 54925158; fax: +86 21 64166128. *E-mail address*: xylu@mail.sioc.ac.cn (X. Lu).

^{0040-4039/\$ -} see front matter @ 2010 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2010.10.110



Scheme 1. Synthesis of the substrates.

Table 1

Optimization of the conditions of the aza-Friedel-Crafts reaction^a



Entry	Lewis acid (10 mol %)	<i>T</i> (°C)	<i>t</i> (h)	Yield ^b (%)
1	$Pd(OAc)_2$	120	10	NR
2	$[dpppPd(H_2O)_2](BF_4)_2$	120	10	NR
3	$Pd(O_2CCF_3)_2$	120	10	NR
4	$Pd(CH_3CN)_4(OTs)_2$	120	10	NR
5	In(OTf) ₃	80	12	_c
6	Yb(OTf) ₃	80	12	63
7	FeCl ₃ ·6H ₂ O	80	12	_c
8	FeCl ₃	80	12	c
9	Cu(OTf) ₂	80	15	100
10	CuOTf	80	12	Trace
11	Sc(OTf) ₃	80	25	100
12	La(OTf) ₂	80	12	NR
13	Cu(OTf) ₂	rt	24	NR
14 ^d	Cu(OTf) ₂	80	24	NR
15 ^e	Cu(OTf) ₂	80	24	NR
16 ^f	Cu(OTf) ₂	80	24	NR

 $^a\,$ Reaction conditions: catalyst (10 mol %) and 1a (0.2 mmol) were stirred in 2 mL of toluene.

^b Yield refers to pure product after column chromatography.

^c The reaction was disordered.

^d Dioxane was used as the solvent.

^e Dichloroethane was used as the solvent.

^f THF was used as the solvent.

 $[dpppPd(H_2O)_2](BF_4)_2$ or $Pd(CH_3CN)_4(OTs)_2$ as the catalysts, all the reactions failed even raising the temperature to reflux (Table 1, entries 1-4). At the same time, neither FeCl₃·6H₂O nor FeCl₃ could produce the corresponding 9-aminofluorene (Table 1, entries 7 and 8). Then we turn our attention to the metal triflates due to their high activity toward imines.²⁰ No product was obtained using In (OTf)₃ and La(OTf)₂ (Table 1, entries 5 and 12). While Yb(OTf)₃ was used, the product was generated in 63% yield (Table 1, entry 6). Finally, Cu(OTf)₂ and Sc(OTf)₃ showed high activities to afford the expected product 2a in quantitative yield (Table 1, entries 9 and 11). The reaction could not proceed at room temperature (Table 1, entry 13). Interestingly, only trace of the product was observed when using CuOTf as the catalyst (Table 1, entry 10). We also examined the effect of the solvent on the reaction and found that toluene was the best (Table 1, entry 9). Therefore, 10 mol % of Cu(OTf)₂ as the catalyst in toluene at 80 °C was chosen as the standard reaction conditions.

The scope and the generality of this reaction were investigated under the optimized reaction conditions as shown in Table 2. o-Arylated-*N*-tosylbenzaldimines substituted with electron-donating or withdrawing groups could react smoothly to give the corre-



Substrate scope for Cu(OTf)2-catalyzed aza-Friedel-Crafts reaction^a



 $^a\,$ Reaction conditions: Cu(OTf)_2 (10 mol %) and 1 (0.2 mmol) were stirred in toluene (2 mL) at 80 °C.

^b Yield refers to pure product after column chromatography.

sponding 9-aminofluorene derivatives in moderate to high yield. Treating the tosylimine **1** with a methyl group at the *para* or *meta* position of the arene moiety also gave the corresponding product in excellent yield (Table 2, entries 2 and 3). Substrate with a methyl group at *ortho* position of the arene gave **2d** in a slightly lower 72% yield probably due to the steric hindrance (Table 2, entry 4). On the other hand, when the benzene ring was substituted by a methoxy, a phenyl, a trifluoromethoxy, or a chlorine atom in the *para* position, the reactions go smoothly in all cases (Table 2, entries 5–8). However, when an electron-withdrawing substituent, such as trifluoromethyl group or a fluorine atom was placed in the *para* position, the reaction also occurred smoothly to give rise to the product in 88% and 94% yield, respectively (Table 2, entries 9 and 10). These results illustrated the catalytic reactions showed high substrates tolerance, affording a series of diverse in general excellent yields.

To broaden the applicability and scope of the present reaction, o-heterocycle substituted *N*-tosylbenzaldimines were tested. The results were shown in Scheme 2. When thiophene was used as the heteroaromatic nucleophile, the reaction provided the addition product **2n** in 88% yield after 12 h. While using the furan as the corresponding heteroaromatic moiety, the substrate decomposed at 80 °C or room temperature probably due to the strong coordination of the Cu(OTf)₂ with oxygen atom.

In addition, under the appropriate reaction conditions, the scope of the methodology was investigated with other substituted *N*-tosylimines in order to give access to a series of novel derivatives. The experiments were illustrated in Scheme 3. Disappointingly, no addition product was formed under the optimized reaction conditions with the substrate **1p**. However, when using **1q** as the reactant, the product **3q** was obtained in 40% yield without any 9-amino derivative. A change of counterions of the copper(II) Lewis acid from TfO⁻ to ClO₄⁻ gave the same product. Combined with the results of substrate **1o** in Scheme 2, it was supposed that the more Lewis basic oxygen atom in the substrates might coordinate with the copper catalyst giving the product in lower yield.

In summary, we have developed a novel and efficient Cu(OTf)₂catalyzed intramolecular aza-Friedel–Crafts reaction of o-arylated *N*-tosylbenzaldimines to provide a series of the 9-aminofluorene derivatives,²¹ which show potential applicability in various fields of the chemistry. In addition, this highly reactive protocol displays a wide substituents tolerance with respect to o-arylated *N*-tosylbenzaldimines. Further work aimed at the asymmetric version of this reaction is underway in our laboratory.



Scheme 2. Cu(OTf)₂ catalyzed reaction of o-heterocycle substituted *N*-tosylbenzaldimines.



Scheme 3. The reaction of other N-tosylbenzaldimines.

Acknowledgments

We thank the National Basic Research Program of China (2009CB825300), National Natural Science Foundation of China (20732005), and Chinese Academy of Sciences for financial support.

Supplementary data

Supplementary data (experimental procedures and data for products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.110.

References and notes

- For reviews on Friedel-Crafts reaction, see: (a) Organic Synthesis; Smith, M. D., Ed.; McGraw-Hill: New York, 1994; p 1313; (b) Heaney, H. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 733; (c) Uraguchi, D.; Sorimachi, K.; Terada, M. J. Am. Chem. Soc. 2004, 126, 11804-11805; (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. Angew. Chem., Int. Ed. 2004, 43, 550-556; (e) Jøgensen, K. A. Synthesis 2003, 1117-1125; (f) Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. Org. Lett. 2007, 9, 4065-4068; (g) Shirakawa, S.; Kobayashi, S. Org. Lett. 2006, 8, 4932-4936; (h) Terada, M.; Sorimachi, K. J. Am. Chem. Soc. 2007, 129, 292-293.
- (a) Gong, Y.; Kato, K.; Kimoto, H. Synlett 2000, 1058–1060; (b) Gong, Y. Tetrahedron: Asymmetry 2001, 12, 2121–2123.
- (a) Hao, J.; Taktak, S.; Áilawa, K.; Yusa, Y.; Hatano, M.; Mikami, K. Synlett 2001, 1443–1445; (b) Jiang, B.; Huang, Z.-G. Synthesis 2005, 2198–2204; (c) Luo, Y.; Li, C.-J. Chem. Commun. 2004, 1930–1931; (d) Chen, Y.-J.; Lei, F.; Liu, L.; Wang, D. Tetrahedron 2003, 59, 7609–7614; (e) Lei, F.; Chen, Y.-J.; Siu, Y.; Liu, L.; Wang, D. Synlett 2003, 1160–1164; (f) Saaby, S.; Bayón, P.; Aburel, P. S.; Jøgensen, K. A. J. Org. Chem. 2002, 67, 4352–4361; (g) Saaby, S.; Fang, X.; Gathergood, N.; Jøgensen, K. A. Angew. Chem., Int. Ed. 2000, 39, 4114–4116; (h) Chen, Y.-J.; Ge, C.-S.; Wang, D. Synlett 2000, 1429–1432.
- A few examples of selective AFC reaction of indoles to imines were reported; see: (a) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. Org. Lett. 2006, 8, 1621–1624; (b) Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. Angew. Chem., Int. Ed. 2006, 45, 629–633; (c) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. J. Am. Chem. Soc. 2006, 128, 8156–8157; (d) Kang, Q.; Zhao, Z.-A.; You, S.-L. J. Am. Chem. Soc. 2007, 129, 1484–1485; (e) Shirakawa, S.; Kobayashi, S. Org. Lett. 2006, 8, 4939–4942; (f) Alonso, I.; Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. J. Org. Chem. 2008, 73, 6401–6404; (g) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. Tetrahedron Lett. 2004, 45, 4567–4670; (i) Xie, W.; Bloomfield, K. M.; Jin, Y.; Dolney, N. Y.; Wang, P.-G. Synlett 1999, 498–500.
- 5. Huang, T.; Li, C.-J. Tetrahedron Lett. 2000, 41, 6715–6719.
- (a) Bigi, F.; Casnati, G.; Sartori, G.; Dalprato, C.; Bortolini, R. Tetrahedron: Asymmetry **1990**, *1*, 861–864; (b) Bigi, F.; Bocelli, G.; Maggi, R.; Sartori, G. J. Org. Chem. **1999**, *64*, 5004–5009. and references cited therein; (c) Gong, Y.; Kato, K.; Kimoto, H. Bull. Chem. Soc. Jpn. **2002**, *75*, 2637–2645; (d) Thalji, R. K.; Ahrendt, A.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. **2001**, *123*, 9692– 9693.
- (a) Pei, Q.; Yang, Y. J. Am. Chem. Soc. **1996**, *118*, 7416–7417;
 (b) Grell, M.; Bradley, D. D. C.; Inbasekaran, M.; Woo, E. P. Adv. Mater. **1997**, 9, 798–802;
 (c) Kreyenschmidt, M.; Klaerner, G.; Fuhrer, T. Macromolecules **1998**, *31*, 1099–1103;
 (d) Grice, A. W.; Bradley, D. D. C.; Bernius, M. T. Appl. Phys. Lett. **1998**, *73*, 629–631;
 (e) Miteva, T.; Meisel, A.; Knoll, W. Adv. Mater. **2001**, *13*, 565–570;
 (f) Grell, M.; Knoll, W.; Lupo, D. Adv. Mater. **1999**, *11*, 671–675;
 (g) Cho, N. S.; Hwang, D. H.; Lee, J. I. Macromolecules **2002**, *35*, 1224–1228;
 (h) Lu, H. H.; Liu, C. H. Y.; Chang, C. H. H.; Chen, S. A. Adv. Mater. **2007**, *19*, 2574–2579;
 (i) Huang, F.; Niu, Y. H.; Zhang, Y. Adv. Mater. **2007**, *19*, 2010–2014.
- 8. Lim, E.; Jung, B.-J.; Shim, H.-K. Macromolecules 2003, 36, 4239-4288.
- (a) Marsitzky, D.; Vestberg, R.; Blainey, P. J. Am. Chem. Soc. 2001, 123, 6965–6972; (b) Janietz, S.; Bradley, D. D. C.; Grell, M. Appl. Phys. Lett. 1998, 73, 2453–2459; (c) Yu, W. L.; Pei, Y.; Cao, Y. Chem. Commun. 1999, 1837–1838; (d) Pschirer, N. G.; Bunz, U. H. F. Macromolecules 2000, 33, 3961–3963; (e) Scherf, U.; List, E. J. Adv. Mater. 2002, 14, 477–487; (f) Monteserín, M.; Burrows, H. D.; Valente, A. J. M. J. Phys. Chem. B 2007, 111, 13560–13569; (g) Xue, C. H.; Venkat, R. R. D.; Liu, H. Y. Macromolecules 2006, 39, 5747–5752.
- (a) Kim, S.; Jackie, J.; Robinson, E. Macromolecules **1998**, *31*, 964–974; (b) Baur, J. W.; Kim, S.; Balanda, P. B. Adv. Mater. **1998**, *10*, 1452–1455; (c) Yin, Y.; Fang, J.; Watari, T. Mater. Chem. **2004**, *14*, 1062; (d) Zotti, G.; Zecchin, S.; Schiavon, G.; Groenedaal, L. B. Macromol. Chem. Phys. **2002**, *203*, 1958–1964; (e) Gu, Z.; Shen, Q. D.; Zhang, J. J. Appl. Polym. Sci. **2006**, *100*, 2930–2936; (f) Wang, H. Q.; Lu, P.; Wang, B. L. Macromol. Rapid Commun. **2007**, *28*, 1645–1650.
- 11. Fan, C.; Xu, J.; Chen, W.; Dong, B. J. Phys. Chem. C 2008, 112, 12012– 12017.
- 12. Bradamante, S.; Colombo, S.; Pagani, G. A.; Rpelens, S. Helv. Chim. Acta 1981, 64, 2524–2527.
- 13. Fan, R.; Li, W.; Pu, D.; Zhang, L. Org. Lett. 2009, 11, 1425-1428.
- (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. J. Org. Chem. 2001, 66, 809–823; (b) Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. Tetrahedron Lett. 1996, 37, 2809–2812.

- (a) Drury, W. J., Ill; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. J. Am. Chem. Soc. 1998, 120, 11006–11007; (b) Yao, S.; Fang, X.; Jøgensen, K. A. Chem. Commun. 1998, 2547–2548.
- (a) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. Angew. Chem., Int. Ed. 1999, 38, 3504–3506; (b) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., Ill; Lectka, T. J. Org. Chem. 1999, 64, 2168–2169; (c) Fujii, A.; Hagiwara, E.; Sodeoka, M. J. Am. Chem. Soc. 1999, 121, 5450–5458.
- (a) Nakamura, K.; Nakamura, H.; Yamamoto, Y. J. Org. Chem. **1999**, 64, 2614–2615;
 (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jøgensen, K. A. J. Org. Chem. **1999**, 64, 4844–4849.
- (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. Angew. Chem., Int. Ed. **1998**, 37, 979–981; (b) Yao, S.; Johannsen, M.; Hazell, R. G.; Jøgensen, K. A. Angew. Chem., Int. Ed. **1998**, 37, 3121–3124; (c) Yao, S.; Saaby, S.; Hazell, R. G.; Jøgensen, K. A. Chem. Eur. J. **2000**, 6, 2435–2448.
- 19. Johannsen, M. Chem. Commun. 1999, 2233-2234.
- (a) Kobayashi, S. Synlett 1994, 689–701; (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. L. Chem. Rev. 2002, 102, 2227–2302.
- 21. Typical procedure for Cu(OTf)₂ catalyzed synthesis of 9-aminofluorene derivatives: a dried schenk tube was charged with **1a** (33.5 mg, 0.1 mmol), and toluene 2 mL. Cu(OTf)₂ (10 mol %) was then added to the mixture and the solution was stirred at 80 °C overnight. The progress of the reaction was monitored by TLC (EtOAc/petroleum ether = 1:7). Upon completion, the solution was concentrated under reduced pressure and the mixture was purified by flash column chromatography (pure petroleum ether, then ethyl acetate/petroleum ether = 1:7) to obtain the product **2a**. Yield: 99% (see Table 2).

Compound **2a**: white solid; mp 199–201 °C (lit.²² 199 °C); ¹H NMR (300 MHz, CDCl₃): δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.41–7.29 (m, 4H), 7.22–7.18 (m, 4H), 5.37 (d, *J* = 9.6 Hz, 1H), 4.80 (d, *J* = 9.3 Hz, 1H), 2.49 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 143.7, 143.3, 139.9, 138.3, 129.9, 128.8, 127.3, 125.2, 119.9, 58.3, 21.6; IR (KBr) v 3268, 1448, 1405, 1328, 1165, 670, 567 cm⁻¹; MS (70 eV, EI) *m/z* (%): 336 (M⁺), 335, 180 (100), 179, 165, 152, 91.

22. Haruka, B.; Hideo, T. Tetrahedron Lett. 2010, 51, 2063-2066.