ORGANIC LETTERS

2013
Vol. 15, No. 8
1794–1797

$Sc(OTf)_3$-Catalyzed Dehydrogenative Cyclization for Synthesis of *N*-Methylacridones

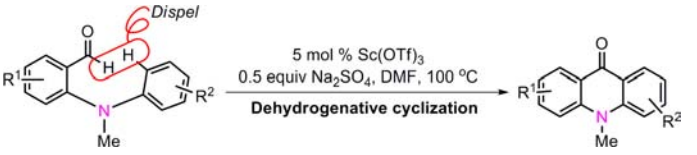
Xi-An Li,[†] Hong-Li Wang,[†] and Shang-Dong Yang*[,†,‡]

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China, and State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Lanzhou 730000, P. R. China

yangshd@lzu.edu.cn

Received December 17, 2012

ABSTRACT



A novel method has been developed for the synthesis of substituted *N*-methylacridones from 2-(*N*-methyl-*N*-phenylamino)benzaldehydes via dehydrogenative cyclization. This transformation involves two primary processes: the aldehyde first coordinates with $Sc(OTf)_3$ and induces the aromatic electrophilic substitution (S_EAr) reaction to form the active intermediate *N*-methyl-acridin-9-ol, which is then quickly oxidized in situ to afford the acridones. Furthermore, the procedure involved is both environmental friendly and atom efficient; H_2O is the only byproduct in this reaction.

Acridone and its derivatives are versatile heteroaromatic compounds that exhibit a variety of biological activities and pharmacological properties. Uses include anti-HIV and antiviral activity, against bovine viral diarrhea virus (BVDV), as well as antihelminthic, antimalarial, anticancer, antitumor, and antifungal activities.[1] Common methods for the synthesis of acridones are the acid-induced ring closure of *N*-phenyl anthranilic acids, which can be obtained from Ullmann condensation of anilines with *ortho*-halogen-substituted benzoic acids.[2] Recently, the Larock group has reported a new approach based on an annulation reaction utilizing salicylates and silylaryl triflates plus CsF.[3] A similar method was reported in 2009 by Greaney's group, who accessed acridones from readily available *o*-halobenzamides through initial aryne α-insertion, followed by in situ S_NAr reactions.[4] Moreover, Snieckus disclosed a new method for the synthesis of acridones through an application of a combined Buchwald–Hartwig

[†] Lanzhou University.
[‡] Lanzhou Institute of Chemical Physics.

(1) (a) Taraporewala, I. B.; Cessac, J. W.; Chanh, T. C.; Delgado, A. V.; Schinazig, R. F. *J. Med. Chem.* **1992**, *35*, 2744. (b) Kirk, S. R.; Luedtke, N. W.; Toy, Y. *J. Am. Chem. Soc.* **2000**, *122*, 980. (c) Tabarrini, O.; Manfroni, G.; Fravolini, A.; Cecchetti, V.; Sabatini, S.; Clercq, E. D.; Rozenski, J.; Canard, B.; Dutartre, H.; Paeshuyse, J.; Neyts, J. *J. Med. Chem.* **2006**, *49*, 2621. (d) Inman, W. D.; ONeill-Johnson, M.; Crews, P. *J. Am. Chem. Soc.* **1990**, *112*, 1. (e) Albert, A. *The Acridine*; Edward Arnold: London, 1966. (f) Martins, E. T.; Baruah, H.; Kramarczyk, J.; Saaluta, G.; Day, C. S.; Kucera, G. L.; Bierbach, U. *J. Med. Chem.* **2001**, *44*, 4492. (g) Gimenez-Arnau, E.; Missailids, S.; Stevens, M. F. G. *Anti-Cancer Drug Res.* **1998**, *13*, 431. (h) McCarthy, P. T.; Pitts, T. P.; Gunawardana, G. P.; Kelly-Borges, M.; Pomponi, S. A. *J. Nat. Prod.* **1992**, *55*, 1664. (i) Elomri, A.; Mitaku, S.; Michel, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pierre, A.; Guilbaud, N.; Léonce, S.; Berthier, L. K.; Rolland, Y.; Atassi, G. *J. Med. Chem.* **1996**, *39*, 4762. (j) Harrison, R. J.; Reszka, A. P.; Haider, S. M.; Romagnoli, B.; Morrell, J.; Read, M. A.; Gowan, S. M.; Incles, C. M.; Kellandc, L. R.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5845.

(2) (a) Nishio, R.; Wessely, S.; Sugiura, M.; Kobayashi, S. *J. Comb. Chem.* **2006**, *8*, 459. (b) Goodell, J. R.; Madhok, A. A.; Hiasa, H.; Ferguson, D. M. *Bioorg. Med. Chem.* **2006**, *14*, 5467. (c) Pal, C.; Kundu, M. K.; Bandyopadhyay, U.; Adhikari, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3563. (d) Allen, C. F. H.; Mckee, G. H. W. *Org. Syn.* **1943**, *2*, 15.

(3) (a) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583. (b) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (c) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2011**, *13*, 4136.

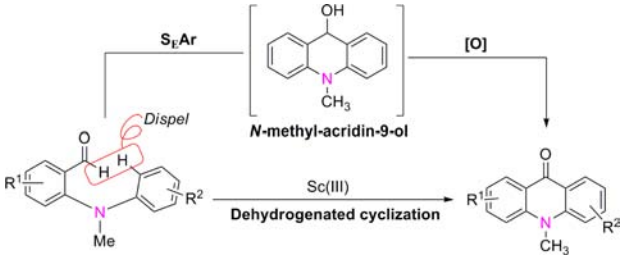
(4) (a) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (b) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199. (c) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589. (d) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426.

(5) (a) Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531. (b) MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem.* **2008**, *73*, 9710. (c) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; pp 1051. (d) Hartwig, J. F. In *Modern Amination Methods*; Wiley-VCH: Toronto, 2000; pp 195. (e) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

10.1021/ol400371h
Published on Web 03/29/2013

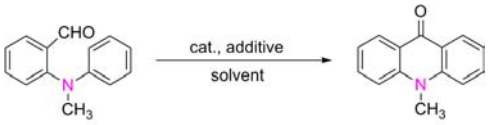
aryl amination−Drem protocol.[5] However, all the aforementioned methods generally require stringent reaction conditions and tedious workup procedures or demand the use of excess amounts of a base, acid, or oxidant. Thus, the development of new and more efficient methods is still a formidable challenge. Recently, transition-metal-catalyzed cross-dehydrogenative coupling between aromatic C−H bonds and arylated aldehyde C−H bonds represents a valuable and atom-efficient protocol for the construction of diaryl ketones.[6] Herein, we report a Sc(III)-catalyzed single-step synthesis of *N*-methylacridones by intramolecular dehydrogenative cyclizations (Scheme 1). To the best of our knowledge, this transformation is very different from the other transition metal-catalyzed aromatic C−H activation of aldehydes.[6,7] It involves two primary processes: first, the aldehyde coordinates with $Sc(OTf)_3$ and the aromatic electrophilic substitution (S_EAr) reaction occurs to form the active intermediate *N*-methyl-acridin-9-ol, which is then quickly oxidated in situ to afford the acridones (Scheme 1). Compared to previous reports involved in the Friedel−Crafts reaction of aldehydes, our method does not need preliminary activation through the addition of extra nucleophilic reagents.[8] Moreover, our method displays other very attractive features: (1) it represents the first example of an aldehyde directly participating in the intramolecular Friedel−Crafts alkylation reaction; (2) the reaction exhibits a novel catalytic system; this reaction perfectly combines Friedel−Crafts alkylation with oxidation; (3) the reaction avoids the use of excess amounts of a base, acid, or oxidant; and (4) in a process that is both environmental friendly and atom efficient, H_2O is the only byproduct in this reaction.

Scheme 1. $Sc(OTf)_3$-Catalyzed Dehydrogenated Cyclization of Aldehyde



In our previous research, we found that some triflate salts act as the Lewis acid and coordinate with carbonyls to prompt successful homologous cyclization.[9] Acridone and its derivatives are incredibly important structures to pharmaceuticals. We therefore wished to employ our aforementioned strategy to the synthesis of acridones with the goal of developing a simpler, more effective method of synthesis. In an initial study, we chose the 2-(*N*-methyl-*N*-phenylamino)benzaldehyde **1a** as the model substrate and examined a series of triflate salts. As we expected, the formyl group of **1a** could be activited by some triflate salts and afforded the desired product of *N*-methylacridone **2a** with different yields (Table 1, entries 1−6). Encouraged by this result, we selected the best $Sc(OTf)_3$ as a catalyst and further optimized the reaction conditions. Screening of different solvents showed that DMF is the best choice. Indeed, **2a** was obtained in 70% yield (Table 1, entries 7−13). A little of **1a** did not entirely convert, however; neither increasing the reaction temperature nor prolonging the reaction times could

Table 1. Reaction Condition Screening[a]



entry	cat. (mol %)	additive (equiv)	solvent	yield[b] (%)
1	$Cu(OTf)_2$ (5.0)		toluene	2
2	$Fe(OTf)_2$ (5.0)		toluene	33
3	$Zn(OTf)_2$ (5.0)		toluene	19
4	$AI(OTf)_3$ (5.0)		toluene	8
5	$Yb(OTf)_3$ (5.0)		toluene	41
6	$Sc(OTf)_3$ (5.0)		toluene	53
7	$Sc(OTf)_3$ (5.0)		DCE	44
8	$Sc(OTf)_3$ (5.0)		DMF	67
9	$Sc(OTf)_3$ (5.0)		DMSO	32
10	$Sc(OTf)_3$ (5.0)		NMP	55
11	$Sc(OTf)_3$ (5.0)		xylene	54
12	$Sc(OTf)_3$ (5.0)		PhCl	39
13	$Sc(OTf)_3$ (10.0)		DMF	70
14	$Sc(OTf)_3$ (5.0)	Na_2SO_4(1.0)	DMF	82
15	$Sc(OTf)_3$ (5.0)	Na_2SO_4 (0.5)	DMF	82
16	$Sc(OTf)_3$ (5.0)	Na_2SO_4 (0.2)	DMF	71
17	$Sc(OTf)_3$ (5.0)	$MgSO_4$ (0.5)	DMF	79
18	$Sc(OTf)_3$ (5.0)	Cs_2CO_3 (0.5)	DMF	60
19	$Sc(OTf)_3$ (5.0)	Na_2CO_3(0.5)	DMF	57
20	$Sc(OTf)_3$ (5.0)	$NaHCO_3$ (0.5)	DMF	66
21	$Sc(OTf)_3$ (5.0)	LiO^tBu (0.5)	DMF	62
22	$Sc(OTf)_3$ (5.0)	NaO^tBu (0.5)	DMF	48
23	$Sc(OTf)_3$, (5.0)	4A MS (0.5)	DMF	59

[a] Reaction conditions: **1a** (0.3 mmol), catalyst (5 mol %), solvent (2 mL), additive (50 mol %), at 100 °C (oil-bath temperature), under argon atmosphere for 20 h. [b] Isolated yield; DCE = 1,1-dichloroethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, NMP = *N*-methyl-2-pyrrolidinone.

(6) (a) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Liu, Y.; Zhou, M.-B.; Wei, W.-T.; Deng, G.-B.; Yin, D.-L.; Li, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8900. (b) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (c) Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W. -Y. *Org. Lett.* **2010**, *12*, 3926. (d) Basle, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1145. (e) Wang, P.; Rao, H.; Hua, R.; Li, C.-J. *Org. Lett.* **2012**, *14*, 902.

(7) (a) Shi, Z. Z.; Schroder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8092. (b) Garralda, M. *Dalton Trans.* **2009**, 3635. (c) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (e) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 15356. (f) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608. (g) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4564.

(8) (a) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-i. *J. Org. Chem.* **1997**, *62*, 6997. (b) Gary, B. W.; Angeles, J. G.; Fanelli, V. E.; Heyer, C. A. *J. Org. Chem.* **2007**, *72*, 7046. (c) Li, H.; Yang, J.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 6797.

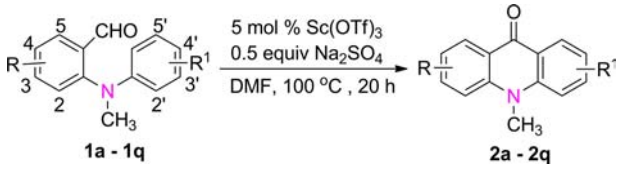
(9) Wang, H.-L.; Li, Z.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.* **2011**, *47*, 11336.

solve this. We therefore concentrated our optimization efforts on different additives and were pleased to discover that additives and bases have a pivotal effect on the reaction (Table 1, entries 14–22). We were gratified to find that Na_2SO_4 is superior to others, and **2a** was obtained in 82% yield (Table 1, entry 14). We further investigated the 4 Å molecular sieves in the reaction. The product **2a** was obtained in only 59% yield (Table 1, entry 23). Thus, we determined that in the presence of 5 mol % $Sc(OTf)_3$, 0.5 equiv Na_2SO_4 and DMF with solvent were the optimal reaction conditions (Table 1, entry 15).

With the optimal reaction conditions in hand, we explored different substituted 2-(*N*-methyl-*N*-phenylamino) benzaldehydes. The results are listed in Table 2. Various substituted acridones afforded moderate to excellent yields bearing both electron-donating and electron-withdrawing substituents. We were delighted to note that the substituents, which include Me, MeO, F, Cl, and Br, were consistent with the optimal reaction conditions. Electron-donating substituents were superior to electron-withdrawing ones and gave relatively higher yields. Substrates with a *para*-substituted Me, F, Cl, and Br smoothly underwent the reaction to afford corresponding products in good to excellent yields. For example, *p*-methyl-substituted (Table 2, entry **2d**) was a suitable substrate, leading to the target product in excellent yield. However, *o*-methyl substituent substrate (Table 2, entry **2b**) reduced the yield, possibly as a result of the steric effect. A dimethyl-substituted substrate (Table 2, entry 2n) was also tolerated in this reaction to produce a 48% yield. Interestingly, the aryl-substituted substrate (Table 2, entry **2n**) was compatible with the optimal reaction condition to provide (**2q**) in 60% yield. In addition, although we tried to extend our method to construct seven-membered ring molecules, we regret to report that the attempt failed.

The tricyclic carbinol derivatives are effective antiallergics and inflammation inhibitors.[10] Thus, the development of simple and efficient ways to construct these compounds are highly desirable. Herein, we choose product of acridone **2a** to react with the Grignard reagents derived from 4-chloro-1-methylpiperidine through nucleophilic carbonyl addition to yield the antiallergics and inflammation inhibitor of **2aa** in 76% yield, showing utility of our chemistry (Scheme 2).

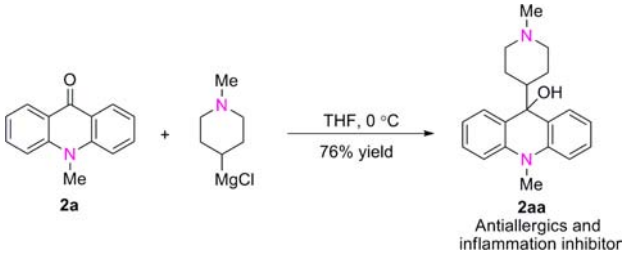
Table 2. Dehydrogenative Cyclization of Different Aldehydes[a,b]



entry	R	R^1	yield (%)
2a	H	H	82
2b	2-CH_3	H	69
2c	3-CH_3	H	43
2d	4-CH_3	H	91
2e	2-OCH_3	H	75
2f	4-OCH_3	H	72
2g	3-CI	H	20
2h	3-Br	H	65
2i	4-CI	H	80
2j	4-Br	H	23
2k	2-F	H	53
21	3-F	H	29
2m	4-F	H	61
2n	3,4-dimethyl	H	42
2o	H	4′-CH_3	50
2p	H	4′-Br	28
2q	naphthalenyl	H	60

[a] Reaction conditions: **1** (0.3 mmol), $Sc(OTf)_3$ (5 mol %), DMF (2 mL), Na_2SO_4 (50 mol %), at 100 °C (oil bath temperature), under argon atmosphere for 20 h. [b] Isolated yield.

Scheme 2. Synthesis of the Antiallergics and Inflammation Inhibitor of **2aa**



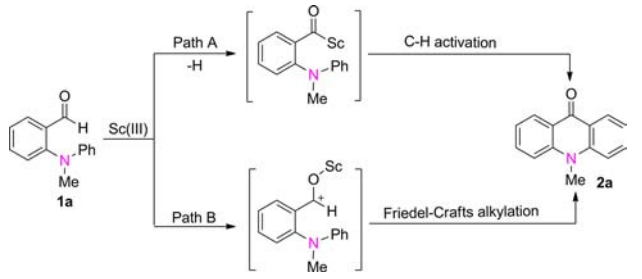
Although a detailed mechanism for this novel transformation is unknown, we propose that the $Sc(OTf)_3$-catalyzed cyclization of aldehyde has two possible pathways (Scheme 3). One possible mechanism is similar to Rh-catalyzed C–H activation of aldehyde:[7] namely, $Sc(OTf)_3$ reacts with aldehyde by electronic substitution and forms the carbonyl Sc(III) intermediate, which attacks the aromatic ring through a second C–H activation. Finally, reductive-elimination produces the acridone. The other possible mechanistic pathway involves Friedel–Crafts alkylation, we propose that the $Sc(OTf)_3$ coordinates with the oxygen of a carbonyl as Lewis Acid to form the carbocation intermediate. The following Friedel–Crafts alkylation proceeds to obtain the active intermediate *N*-methyl-acridin-9-ol, which then is quickly dehydrogenated through oxidation to afford the acridones. However, how does the $Sc(OTf)_3$ combine with the substrate and which pathway is more reasonable? To elucidate this reaction mechanism, we performed relative control experiments and kinetic isotope effects (KIE).

The intramolecular KIE experiment was carried out with the deuterium-labeled substrates **1a-*d*$_1$** (Scheme 4, a). No kinetic isotope effect was observed (the intramolecular $k_H/k_D = 1.0$ in the different reaction times), which indicates that the C–H bond activation does not occur in this

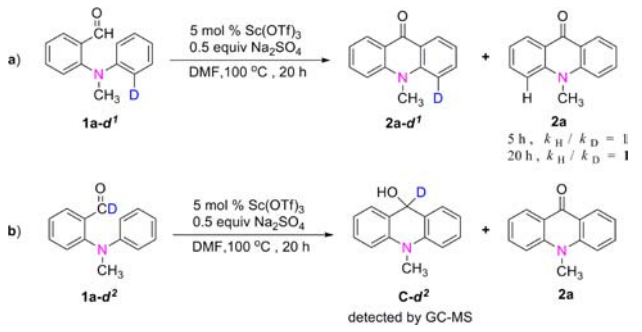
(10) (a) Wong, J. K.; Piwinski, J. J. US 5561117 A 19961001, 1996; (b) Chopra, A.; Dorton, D. C.; Ogle, C. A. *Main Group Metal Chem.* **1997**, *20*, 783. (c) Loughhead, D. G. *Tetrahedron Lett.* **1988**, *29*, 5701. (d) Kaiser, C.; Fowler, P. J.; Tedeschi, D. H.; Lester, B. M.; Garvey, E.; Zirkle, C. L.; Nodiff, E. A.; Saggiomo, A. J. *J. Med. Chem.* **1974**, *17*, 57.

(11) (a) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440. (b) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley & Sons: New York, 1990; pp 25.

Scheme 3. Possible Mechanisms of Cyclization



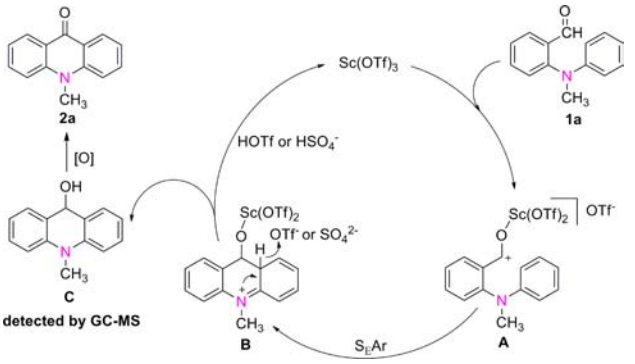
Scheme 4. Kinetic Isotope Effect Experiments



reaction.[11] Thus, we were able to exclude the forenamed pathway involved in C−H bond activation process as potential pathway. Regarding the mechanistic pathway of Friedel−Crafts alkylation, we proposed that the Sc(III) coordinates with carbonyl to form the carbocation. However, when this occurs, the aromatic electrophilic substitution (S_EAr) reaction forms the active intermediate *N*-methylacridin-9-ol. We tried to separate and obtain this important intermediate, but failed. Fortunately, we did detect the intermediate (**C**) alcohol by GC−MS. To further affirm this analysis, the reaction of deuterated aldehyde was also carried out (Scheme 4, b). The deuterated alcohol of **C-*d*^{2}** was observed. Based on these results, we conclude that this transformation should be a result of the Friedel−Crafts alkylation procedure.

(12) (a) Jeffrey, B. A. *Tetrahedron* **2001**, *57*, 9765. (b) Adam, W.; Saha-Moller, C. R.; Zhao, C. G. *J. Org. Chem.* **1999**, *64*, 7492. (c) Anne, A.; Moiroux, J. *J. Org. Chem.* **2007**, *55*, 4608.

Scheme 5. Proposed Mechanism for Scandium-Catalyzed Cyclization of Aldehyde



On the basis of the observed experimental results, we outline a proposed mechanism for scandium-catalyzed cyclization of aldehyde by dehydrogenation and oxidation in Scheme 5. In the initial step, the $Sc(OTf)_3$ coordinates with carbonyl of **1a** and forms the carbocation intermediate **A**, following a typical S_EAr reaction to give the complex **B**. Then, the OTf^- or SO_4^{2-}-assisted to remove proton and scandium disssocation occurs to afford the active intermediate *N*-methyl-acridin-9-ol **C**, which then is quickly dehydrogenated through oxidation to afford the acridones **2a**.[12] Though we detected the alcohol of **C** by the GC−MS, the details of oxidization are still not clear.

In summary, we have developed a novel method of $Sc(OTf)_3$-catalyzed aldehydes through intramolecular cyclization to synthesize substituted *N*-methylacridones via Friedel−Crafts alkylation and oxidation. The method displays environmentally procedures and atom efficiency. Further applications will be reported in the future.

Acknowledgment. We are grateful for financial support from the NSFC (Nos. 21072079 and 21272100) and Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1138).

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.