ORGANIC LETTERS

2012
Vol. 14, No. 20
5210–5213

Three-Component Domino Reactions for Selective Formation of Indeno[1,2-*b*]indole Derivatives

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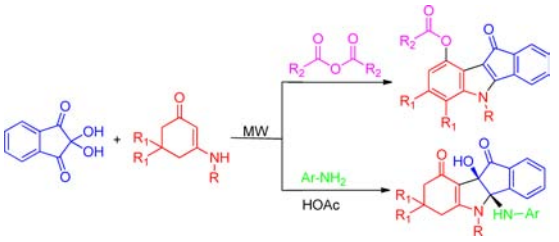
Received August 21, 2012

ABSTRACT



Efficient three-component domino strategies for the synthesis of multifunctionalized tetracyclic indeno[1,2-*b*]indole derivatives with different substituted patterns have been established successfully. The first pathway involves a novel sequential methyl migration, aromatization, and esterification, while a second reaction in HOAc leads to compounds 6 with high *syn* diastereoselectivity. Both reactions showed attractive features including mild conditions, convenient one-pot operation, short reaction times of 15−32 min, and excellent regio- and/or stereoselectivity.

Heterocycles of indole derivatives containing multiple rings widely exist in nature; they often serve as "privileged structures" in drug discovery and development based on their attractive capacity of binding to many cell receptors with high affinity[1] and subsequent potent biological and pharmaceutical profiles.[2] Among fused indole compounds, tetracyclic indeno[1,2-*b*]indole skeletons are particularly important because they have been widely used as building blocks in total synthesis of many natural products and display biological activities such as powerful lipid peroxidation inhibitors,[3] potassium channel openers,[4] DNS intercalators, and topoisomerase II inhibitors.[5] Therefore, these derivatives have attracted special attention in organic and medicinal fields. So far, many approaches to polycyclic indeno[1,2-*b*]indoles have been developed; most of these syntheses were achieved *via* cascade cyclization

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(1) For a review, see: (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.

(2) (a) Choi, T. A.; Czerwonka, R.; Frohner, W.; Krahl, M. P.; Reddy, K. R.; Franzbau, S. G.; Knolker, H.-J. *ChemMedChem* **2006**, *1*, 812. (b) Lescot, E.; Muzard, G.; Markovits, J.; Belleney, J.; Roques, B. P.; Le Pecq, J.-B. *J. Med. Chem.* **1986**, *29*, 1731. (c) Thevissen, K.; Marchand, A.; Chaltin, P.; Meert, E. M.K.; Cammue, B. P.A. *Curr. Med. Chem.* **2009**, *16*, 2205. (d) Conchon, E.; Anizon, F.; Aboab, B.; Prudhomme, M. *J. Med. Chem.* **2007**, *50*, 4669. (e) Alper, P. B.; Marsilje, T. H.; Mutnick, D.; Lu, W.; Chatterjee, A.; Roberts, M. J.; He, Y.; Karanewsky, D. S.; Chow, D.; Lao, J.; Gerken, A.; Tuntland, T.; Liu, B.; Chang, J.; Gordon, P.; Seidel, H. M.; Tian, S.-S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5255.

(3) Brown, D. W.; Graupner, P. R.; Sainsbury, M.; Shertzer, H. G. *Tetrahedron* **1991**, *47*, 4383.

(4) (a) Butera, J. A.; Antane, S. A.; Hirth, B.; Lennox, J. R.; Sheldon, J. H.; Norton, N. W.; Warga, D.; Argentieri, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2093. (b) Antane, S. A.; Butera, J. A.; Lennox, J. R. US 2001047026, 2001.

(5) (a) Bal, Ch.; Baldeyrou, B.; Moz, F.; Lansiaux, A.; Colson, P.; Kraus-Berthier, L.; Léonce, S.; Pierre, A.; Boussard, M.; Rousseau, A.; Wierzbicki, M.; Bailly, Ch. *Biochem. Pharmacol.* **2004**, *68*, 1911. (b) Wierzbicki, M.; Boussard, M.-F.; Rousseau, A.; Boutin, A.; Delagrange, P. EP 1245565, 2002

(6) (a) Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616–5620. (b) Chernyak, N.; Tilly, D.; Li, Z.; Gevorgyan, V. *ARKIVOC* **2011**, *v*, 76. (c) Zhao, Z.; Jaworski, A.; Piel, I.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2617.

(7) (a) Shapiro, R.; Chatterjie, N. J. *J. Org. Chem.* **1970**, *35*, 447. (b) Bullington, J. L.; Dodd, J. H. *J. Org. Chem.* **1993**, *58*, 4833. (c) Black, D. St. C.; Bowyer, M. C.; Condie, G. C.; Craig, D. C.; Kumar, N. *Tetrahedron* **1994**, *50*, 10983. (d) Hemmerling, H.-J.; Reiss, G. *Synthesis* **2009**, 985.

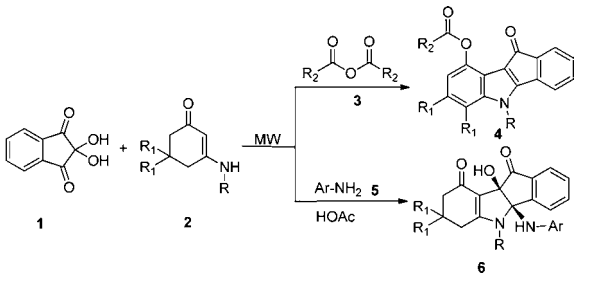
10.1021/ol3023038
Published on Web 10/01/2012

reactions in the presence of metal catalysts,[6] ninhydrin annulations,[7] intramolecular reductive *N*-heteroannulation,[8] and reductive cyclization of hydrazone[9] or 2-nitrobenzylide naphthalide.[10] The development of alternative step-economical methods for the assembly of these heterocyclic cores, producing less waste and byproducts, continues to be of considerable interest and important. However, to the best of our knowledge, a one-pot synthesis of tetracyclic indeno[1,2-*b*]indoles *via* a multicomponent domino strategy involving sequential methyl migration/aromatization/esterification has not been documented yet.

On the other hand, multicomponent domino reactions (MDRs) for total synthesis of natural products or natural-like structures are believed to be one of the key tools for assembling multiring-junction frameworks that can be predicted by controlling reaction processes.[11,12] These reactions have attracted special attention over the past few decades because of their high efficiency, synthetic economy, and ecology in the construction of complex heterocyclic frameworks.[13] In addition, multicomponent strategy often proceeds with impressive selectivity.[14] Designing multicomponent domino processes for constructing multiring-junction architectures provides a great challenge in modern organic synthesis.

In the past several years, we have been engaging in the development of unique MDRs that can provide easy access to new core structures of chemical and pharmaceutical interest.[15] During our study of this project, we now discovered novel multicomponent reactions of *N*-heteroannulations of enaminones, 2,2-dihydroxyindene-1,3-dione, and acid anhydride or aromatic amines; they can selectively provide multifunctionalized indeno[1,2-*b*]indoles with different substituted patterns **4** and **6** (Scheme 1). The great features of this multicomponent domino chemistry are shown by the fact that new fused pyrazoles (tetracyclic 6−5−5−6 skeleton) were readily formed in domino fashions that involved sequential nucleophilic substitution/cyclization/methyl migration/aromatization/esterification. The latter provided new *N*-arylamino substituted indeno[1,2-*b*]indole derivatives with excellent stereo- and regioselectivity; two quaternary centers including a quaternary amine functionality were controlled very well in a one-pot operation. The present work sets excellent examples for synthesizing such an important family of polysubstituted indeno-[1,2-*b*]indoles.

Scheme 1. Synthesis of Indeno[1,2-*b*]indoles **4** and **6**



Recently, we established a new three-component domino reaction of enaminones for the synthesis of multifunctionalized indole derivatives through allylic esterification.[15e,f] During the continuation of this project, we attempted to employ ninhydrin as a precursor to realize allylic esterification (Table 1). In the first attempt, the reaction of enaminones **2a** with 2,2-dihydroxyindene-1,3-dione **1** was heated in HOAc at 100 °C under microwave irradiation conditions (Table 1, entry 1). The reaction scarcely proceeded to give the desired product **7**, even at enhanced temperatures. When the solvent was changed to the cosolvent of HOAc/acetic anhydride (Table 1, entry 2), the reaction resulted in red solids. Surprisingly, we found that the product is not the expected allylic esterification product **7**. Instead, we found that an acetyl group was introduced in the final product in which H chemical shift of methylene on enaminone ring cannot be observed. Eventually, the structural elucidation was unequivocally determined by X-ray diffraction of a single crystal **4a** (Figure 1), and a novel polysubstituted indeno[1,2-*b*]indole derivative **4a** was produced in 35% yield (Table 1).

Encouraged by the above results, we set the reaction of **1** with **2a** as the model reaction in acetic anhydride for optimizing reaction conditions. Experiments were carried out in two cosolvents of TFA/Ac_2O and DMF/Ac_2O. The reaction failed to give the product **4a** in TFA/Ac_2O (Table 1, entry 3); an incomplete reaction was observed in DMF/Ac_2O (Table 1, entry 4). In another case, when Ac_2O was used as the solvent, the reaction proceeded more

(8) Janreddy, D.; Kavala, V.; Bosco, J. W. J.; Kuo, C.-W.; Yao, C.-F. *Eur. J. Org. Chem.* **2011**, 2360.

(9) (a) Graham, J.; Ninan, A.; Reza, K.; Sainsbury, M.; Shertzer, H. G. *Tetrahedron* **1992**, *48*, 167. (b) Brown, D. W.; Mahon, M. F.; Ninan, A.; Sainsbury, M.; Shertzer, H. G. *Tetrahedron* **1993**, *49*, 8919. (c) Wang, J.-B.; Ji, Q.-G.; Xu, J.; Wu, X.-H.; Xie, Y.-Y. *Synth. Commun.* **2005**, *35*, 581. (d) Butera, J. A.; Antane, S. A.; Hirth, B.; Lennox, J. R.; Sheldon, J. H.; Norton, N. W.; Warga, D.; Argentieri, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2093. (e) Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: Chichester, 1982.

(10) (a) Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron Lett.* **1993**, *34*, 6479. (b) Reboredo, F. J.; Treus, M.; Estévez, J. C.; Castedo, L.; Estévez, R. J. *Synlett* **2002**, 999.

(11) (a) Meijere, A. D.; Zezschwitz, P. V.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (b) Hussain, M. M.; Walsh, P. J. *Acc. Chem. Res.* **2008**, *41*, 883. (c) Sun, X. L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (d) Wasike, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (e) Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 11727. (f) Trost, B. M.; Gutierrez, A. C.; Livingston, R. C. *Org. Lett.* **2009**, *11*, 2539. (g) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (h) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

(12) (a) Santra, S.; Andreana, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418. (b) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (c) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (d) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784.

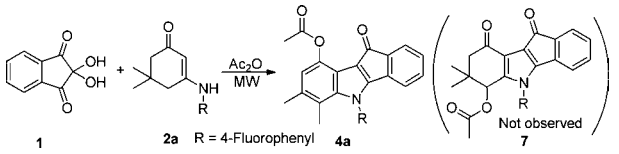
(13) (a) Zhu, J. P.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH, 2004. (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(14) (a) Willy, B.; Müller, T. J. J. *Curr. Org. Chem.* **2009**, *13*, 1777. (b) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem. Asian J.* **2010**, *5*, 2318. (c) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.

(15) (a) Jiang, B.; Li, C.; Shi, F.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. *J. Org. Chem.* **2010**, *75*, 296. (b) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660. (c) Li, G.; Wei, H. X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277. (d) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G. *Green Chem.* **2010**, *12*, 1357. (e) Jiang, B.; Yi, M.-S.; Shi, F.; Tu, S.-J.; Pindi, S.; McDowell, P.; Li, G. *Chem. Commun.* **2012**, 808. (f) Jiang, B.; Feng, B.-M.; Wang S.-L.; Tu, S.-J.; Li, G. *Chem.—Eur. J.* **2012**, *18*, 9823.

efficiently to give product **4a** in 76% isolated yield by flash chromatography (Table 1, entry 5). Subsequently, the reaction was performed in Ac_2O and repeated many times at different temperatures in a sealed vessel under microwave heating for 25 min. After a series of experiments, we found that in acetic anhydride, **1a** was converted into the product **4a** in 85% chemical yield at 120 °C. It turned out that in this reaction acetic anhydride behaved as the solvent at the same time as the esterification reagent.

Table 1. Optimization for the Synthesis of **4a** under MW



1 2a R = 4-Fluorophenyl 4a 7

entry	solvent	temp/°C	time (min)	yield[b] (%)
1	HOAc	100	25	no
2	AcOH/Ac_2O[a]	100	25	35
3	TFA/Ac_2O[a]	100	25	trace
4	DMF/Ac_2O[a]	100	25	27
5	Ac_2O	100	25	76
6	Ac_2O	120	25	85

[a] Cosolvent: v/v = 1:1. [b] Isolated yields.

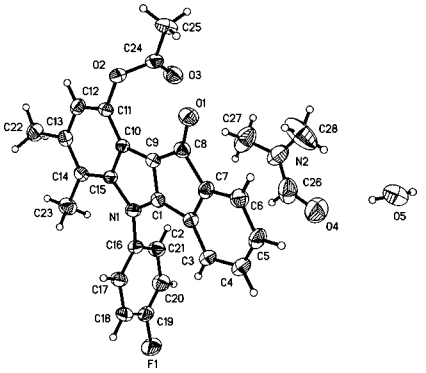
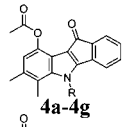
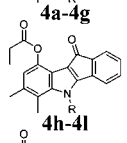
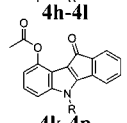
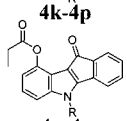


Figure 1. X-ray structure of **4a**.

With the optimized system in hand, we next explored its scope using various readily available starting materials. The results are presented in Table 2. As usual, the reactions can be finished in 20−32 min. A range of valuable indeno-[1,2-*b*]indoles can be synthesized in high yields. The reaction is easy to perform simply by heating a mixture of cyclic enaminones and 2,2-dihydroxyindene-1,3-dione **1** in acetic anhydride with microwave. We found that reactants can be not only *N*-arylenaminones **2a**, **2h**, and **2j**, which possess electron-withdrawing substituents such as fluoro, bromo, and chloro groups at the para position of the benzene ring, but also **2c**−**e** and **2l** having electron-donating substituents such as methyl and methoxy groups to give the corresponding *N*-arylindeno[1,2-*b*]indole derivatives **4c**−**e** and **4o** in good to high yields. The bulky *o*-substituted *N*-arylenaminone **2f** was converted into the corresponding indeno[1,2-*b*]indole **4f** in 76% yield (entry 6).

In addition to *N*-aryl substitutents, *N*-methyl and *N*-cyclopropyl were also found to be suitable for the present three-component domino reaction to afford the expected *N*-methyl- and *N*-cyclopropylindeno[1,2-*b*]indole derivatives **4g** and **4p** in 74% and 69% yields, respectively (entries 7 and 16). The propionic andydride was also suitable for the reaction and smoothly gave desired products **4h**−**j** and **4q**−**r** in good yields of 63−81%. The results showed the good scope and generality of the novel methyl migration under domino condition with respect to a range of enaminone substrates.

Table 2. Domino Synthesis of Indeno[1,2-*b*]indoles **4**

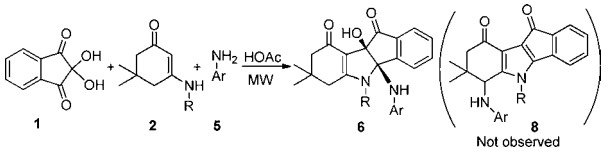
entry	product 4[a]	R	time[b]	yield[c]/ %
1	 **4a-4g**	**4a** 4-Fluorophenyl (**2a**)	25	85
2		**4b** Phenyl (**2b**)	24	80
3		**4c** 4-Methylphenyl (**2c**)	20	83
4		**4d** 3-Methylphenyl(**2d**)	26	84
5		**4e** 4-Methoxyphenyl(**2e**)	20	79
6	 **4h-4l**	**4f** 2-Methoxyphenyl (**2f**)	28	76
7		**4g** Methyl (**2g**)	30	74
8		**4h** 4-Methylphenyl (**2c**)	20	77
9		**4i** 4-Methoxyphenyl (**2e**)	22	81
10	 **4k-4p**	**4j** 2-Methoxyphenyl (**2f**)	30	63
11		**4k** 4-Bromophenyl (**2h**)	26	72
12		**4l** 4-Fluorophenyl(**2i**)	28	87
13		**4m** 4-Chlorophenyl(**2j**)	26	86
14	 **4q-4r**	**4n** Phenyl (**2k**)	25	80
15		**4o** 4-Methylphenyl (**2l**)	22	82
16		**4p** Cyclopropyl (**2m**)	28	69
17		**4q** 4-Fluorophenyl(**2i**)	32	72
18		**4r** Cyclopropyl (**2m**)	25	74

[a] Reagents and conditions: Ac_2O, (1.5 mL), 120 °C, microwave heating. [b] Time (min). [c] Isolated yields.

After the above reaction was achieved, we then turned our attention to investigate the three-component reaction of enaminones **2**, 2,2-dihydroxyindene-1,3-dione **1**, and aromatic amines **5**. Due to nucleophilicity of aromatic amines which is stronger than that of carboxylic acid, allylic amination was expected to be realized using aromatic amines as a nucleophile (Table 3). On the basis of this analysis, 2,2-dihydroxyindene-1,3-dione **1** was subjected to the reaction of **2a** with 4-chloroaniline **3a** in different acids, such as formic acid (HCOOH), HOAc, and TFA, at 120 °C for 24 min under microwave heating. The expected product **8** was not observed in all acidic solvents that we examined. Instead, a polysubstituted indeno[1,2-*b*]indole derivative **6a** was generated regioselectively to give 32% yield in HCOOH solvent, but this product cannot be formed in another acidic solvent, TFA. The best yield (82%) of product **6a** was obtained in HOAc which was thus chosen for the substrate scope investigation. Next, the reactions of *N*-substituted 5,5-dimethyl-3-aminocyclohex-2-enones

(**2b**, **2c**, **2e**, **2h** and 4-chlorophenyl **2n**) with various aromatic amines **5** and **1** in acetic acid were performed for short periods (15−28 min), leading to formation of a series of new polysubstituted indeno[1,2-*b*]indoles with excellent regio- and stereoselectivity as listed in Table 3. Both electron-deficient and electron-rich aromatic groups on the *N*-substituted 5,5-dimethyl-3-aminocyclohex-2-enones showed very good chemical yields of **6a**−**m** (entries 1−13). *N*-Phenyl-3-aminocyclohex-2-enone **2o** was converted into the corresponding arylamino-substituted indeno[1,2-*b*]indoles **6n** and **6o** in 65% and 80% yields, respectively. The tolerance of functionalities, such as chloro, bromo in this protocol provides the opportunity of their various further chemical manipulations in products. The structural elucidation and attribution of relative regio- and stereoselectivity were determined by NMR analysis and X-ray diffraction of single crystal **6d** (see the Supporting Information).

Table 3. Domino Synthesis of Indeno[1,2-*b*]indoles **6**[a]



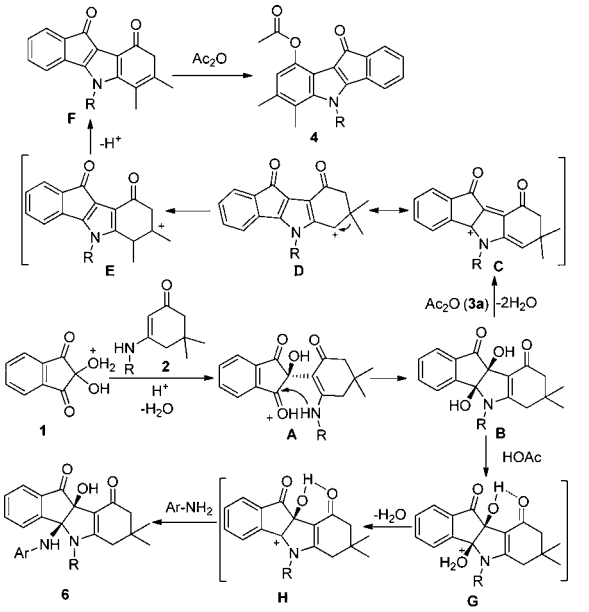
entry	product		2	Ar	time[b]	yield[c]/ %
1		**6a**	**2b**	4-ClPh (**5a**)	24	82
2		**6b**	**2b**	Ph (**5b**)	20	86
3		**6c**	**2b**	4-MePh (**5c**)	15	80
4		**6d**	**2c**	4-ClPh (**5a**)	25	84
5		**6e**	**2c**	Ph (**5b**)	16	78
6	**6a-6m**	**6f**	**2c**	4-BrPh (**5d**)	22	83
7		**6g**	**2e**	4-ClPh (**5a**)	20	80
8		**6h**	**2h**	4-ClPh (**5a**)	26	85
9		**6i**	**2h**	Ph (**5b**)	18	78
10		**6j**	**2h**	4-MePh (**5c**)	20	82
11		**6k**	**2h**	4-BrPh (**5d**)	25	74
12	**6n-6o**	**6l**	**2n**	Ph (**5b**)	25	67
13		**6m**	**2n**	4-BrPh (**5d**)	28	72
14		**6n**	**2o**	4-ClPh (**5a**)	20	80
15		**6o**	**2o**	4-BrPh (**5d**)	26	65

[a] Reagents and conditions: HOAc (1.5 mL), 120 °C, microwave heating. [b] Time (min). [c] Isolated yield.

In general, the reaction can be finished efficiently with all cases within 15−32 min. Water is nearly a sole byproduct, which makes the workup convenient. In most cases, the products precipitated out after cold water was poured into the reaction mixture. During these two domino reaction processes, the construction of fused indole skeleton, methyl (H) migration, and esterification were readily achieved via regioselective three-component domino reaction in a one-pot operation, and two stereogenetic centers have been completely controlled including a quaternary amine center attached on the indene ring in the latter.

The mechanism hypothesis for these reactions was proposed and is shown in Scheme 2. The former involves the ring closure cascade reactions that consist of initial nucleophilic substitution (**1** to **A**), intramolecular cyclization (**A** to **B**), dehydration (**B** to **C**), isomerization of the carbocation (**C** to **D**), methyl (H) migration (**D** to **E**), deprotonation (**E** to **F**), and final aromatization/esterification (**F** to **4**). The reason of methyl (H) migration is attributed to the stability of the resulting positive cations. The stability of tertiary carbocation is higher than that of secondary one. Similar to the former, the latter involves nucleophilic substitution and intramolecular cyclization (**1** to **B**), which underwent S_N1 type reaction with aromatic amines to regioselectively yield thermodynamically stable *N*-arylamino-substituted indeno[1,2-*b*]indoles due to its intramolecular hydrogen bonding (**G** and **H**).

Scheme 2. Possible Mechanism for Products **4** and **6**



In conclusion, we have successfully established new three-component domino reactions for the synthesis of polyfunctionalized indeno[1,2-*b*]indoles with different substituted patterns. The reaction mechanism involves novel methyl (H) migration and esterification. The reactions were shown to have attractive features of mild conditions, convenient one-pot operation, short reaction reaction times of 15−32 min, and excellent regio- and stereoselectivity.

Acknowledgment. We are grateful for financial support from the NSFC (Nos. 20928001, 21232004, 21072163, 21002083, and 21102124) and PAPD of Jiangsu Higher Education Institutions and the Robert A. Welch Foundation (D-1361) and NIH (R21DA031860-01).

Supporting Information Available. Experimental procedures and 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.