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Lewis Acid/Brönsted Acid Mediated Benz-Annulation of Thiophenes and Electron-Rich Arenes

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Supporting Information

ABSTRACT: A facile preparation of benz-annulated heterocycles were achieved at rt involving a Lewis acid/Brönsted acid mediated annulation of heterocycles using 2,5-dimethoxytetrahydrofuran as a four-carbon synthon. The benz-/naphth-annulation was found to be successful with electron-rich arenes as well.

B enzo[*b*]thiophene and its analogues 1^1 are traditionally prepared involving an intramolecular cyclization of the respective arylthioalkyl derivatives. The optical and medicinal applications of annulated thienyl oligomers added further stimuli to the development of the plethora of synthetic protocols for benzo[*b*]thiophene and its derivatives.² The synthesis of benzo[*b*]thiophene-5,6-dicarboxaldehyde³ has been achieved in good yield by the reaction of thiophene-2,3-dicarboxaldehyde with 2,5-dimethoxytetrahydrofuran (DMTHF) in acetic acid under reflux conditions. A direct access to 2,3-dimethoxynaphthalene⁴ was realized in low yield via the interaction of 1,2dimethoxybenzene with DMTHF in the presence of sulfuric acid. Recently, DMTHF has been widely employed as a four-carbon synthon for the syntheses of heterocycles such as pyrrole,⁵ indole,⁶ and carbazole.⁷

A similar type of benz-annulation of thiophene using DMTHF 4 as a four-carbon synthon is unexplored (Scheme 1). The

Scheme 1. Synthesis of Benzo[b]thiophenes



promising optical applications of benz-annelated thienyl heterocycles⁸ prompted us to carry out a systematic study on the benzannulation of thiophene and its analogues. Further, in continuation of our interest in the synthesis of π -conjugated heterocycles,⁹ we report herein our preliminary results on the benz-annulation of thiophene and its analogues using a Lewis acid/Brönsted acid as a catalyst.

Based on our previous study on Lewis acid (LA)-mediated domino reactions,⁹ the benz-annulation of thiophene 3a was first initiated using $ZnBr_2$ as a catalyst. As expected, the reaction of thiophene 3a with 4 equiv of DMTHF 4 in the presence of $ZnBr_2$



at 0 $^{\circ}$ C for 15 min followed by 2 h at rt afforded dibenzothiophene **5a** in 84% yield (Scheme 2).





Under identical conditions, selenophene **3b** also underwent consecutive benz-annulations to afford dibenzoselenophene **5b**. However, the expected benz-annulation was found to be unsuccessful with furan **3c**, affording only a black polymeric material. The benz-annulation was then successfully performed with benzo fused heterocycles 6a-c to furnish the respective dibenzo heterocycles 5a-c in excellent yields. Controlled benz-annulation of the thiophene 3a/selenophene 3b using 1 equiv of the four-carbon synthon and ZnBr₂ led to the isolation of benzo[*b*]thiophene 5a/benzo[*b*]selenophene **5b** in 82% and 79% yields, respectively.

As a representative case, bis-benz-annulation of thiophene **3a** with 4.4 equiv of DMTHF **4** was then carried out using different Lewis acids/Brönsted acids, and the results obtained are presented in Table 1. In general, the reaction was found to be successful with Lewis and Brönsted acids (entries 1-10). The bis-benz-annulation of **3a** with DMTHF **4** using 1 equiv of ZnBr₂ in DCM at rt led to the isolation of dibenzothiophene **5a** in low

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Table 1. Effect of Catalyst on Benz-Annulation of 3a

entry	LA/Brönsted acid	conditions ^a	yield $(\%)^b$
1	1 equiv of ZnBr ₂	DCM, rt, 2 h	20
2	2 equiv of ZnBr ₂	DCM, rt, 2 h	84
3	1 equiv of SnCl ₄	DCM, rt, 2.5 h	81
4	1 equiv of BF ₃ ·OEt ₂	DCM, rt, 2.5 h	78
5	1 equiv of CuBr ₂	DCE, ref, 36 h	53
6	20 mol % InBr ₃	DCE, ref, 24 h	62
7	20 mol % FeCl ₃	DCE, ref, 24 h	56
8	1 equiv of CH ₃ CO ₂ H	DCE, ref, 24 h	10
9	1 equiv of CF ₃ SO ₃ H	DCM, rt, 2 h	92
10	1 equiv of CH ₃ SO ₃ H	DCM, rt, 3 h	83
a	<i>с</i> 1		

^aReaction was performed using 1 equiv of 3a and 4.4 equiv of 4. ^bIsolated yield of dibenzothiophene 5a.

yield (entry 1). However, the successive benz-annulation of 3a could be performed in excellent yield using 2 equiv of $ZnBr_2$ (entry 2).

A comparable yield of the product 5a was obtained using 1 equiv of SnCl₄ (entry 3). It should be noted that the bis-benzannulation was smoothly performed at rt using Lewis acids such as ZnBr₂, SnCl₄, and BF₃·OEt₂ (entries 2–4). CuBr₂ required refluxing conditions and a longer reaction time (entry 5). The bis-benz-annulation was successfully performed using 20 mol % InBr₃ in 1,2-DCE at reflux for 24 h (entry 6). In the presence of 1 equiv of FeCl₃, the annulation was found to be complicated possibly due to the polymer formation. However, the annulation was achieved in moderate yield using 20 mol % FeCl₃ in 1,2-DCE at reflux for 24 h (entry 7). The bis-benz-annulation of 3a was found to be slow with acetic acid, even under refluxing conditions affording only a poor yield (10%) of 5a (entry 8). Among the Brönsted acids employed for the bis-benz-annulation of 3a, triflic acid gave the maximum yield (entry 9). The reaction was also found to be successful with methanesulfonic acid affording the 5a in an excellent yield (entry 10).

A comprehensive study on the benz-annulation of thiophene 3a confirmed 2 equiv of ZnBr₂ or 1 equiv of triflic acid at rt as the most suitable conditions. To further understand the substrate scope and limitations, the benz-annulation reaction was explored with substituted thiophenes, benzo[b]heterocycles, and electron-rich arenes (Table 2). The reaction was found to be successful for 2-bromo-3-methylthiophene 3d affording the expected benzo [b] thiophene 6d in 89% yield. The 3-methylthiophene 3e failed to give the expected product 3-methylbenzo[b]thiophene **6e** possibly due to a competing reaction at the 2-position of thiophene. In the case of 3-hexylthiophene 3f, the preferential reaction at the 5-position gave the annulation product 6f. Surprisingly, the reaction was found to be complex with bithiophene 3h and failed to give any characterizable product. The benz-annulation of 2-thienyl lactone 3i was unsuccessful probably due to the reduced nucleophilicity of the thiophene unit. The reaction was found to be successful with a wide variety of benzo[b]heterocycles **6a**–**f** with the exception of *N*-hexylindole 6d' (entries 3–5). It should be noted that even though the benz-annulation of N-hexylindole 6d' failed to produce the N-hexylcarbazole (entry 3), under identical conditions, N-phenylsulfonylindole underwent benz-annulation to furnish N-phenylsulfonyl carbazole in excellent yield.^{7b} This clearly confirms that the LA/triflic acid reacts at the 3-position of *N*-hexylindole **6d**['] to deter the benz-annulation. To our surprise, the benz-annulation of 6c with 2.2 equiv of DMTHF in the presence of triflic led to the formation of naphth-annulated

benzo[*c*]furan **5***c*′ in 35% yield. Under identical conditions, the naphth-annulation of **6***c* using 4.4 equiv of DMTHF afforded **5***c*′ in 76% yield (entry 3). The naphtho[2,1-*b*]thiophene **6g**¹⁰/ naphtho[1,2-*b*]thiophene **6h**¹⁰ underwent smooth benz-annulation to afford **5g**/**5h** in excellent yield. The benz-annualtion of 4,7-dimethoxybenzo[*b*]thiophene **6i** with DMTHF **4** using ZnBr₂/triflic acid in DCM at rt followed by column chromatographic purification led to the isolation of respective quinone **5i**′ as a yellow solid (entry 5).

The benz-annulation could be successfully performed with naphtho[*b*]thiophenes $6j-m^{11}$ to afford the respective heterocycles 5j-m in good yields (entries 6, 7). The benz-annulation of 2-aryl substituted thiophenes $6n-t^{12}$ and naphtho[*b*]thiophenes 6v and 6w proceeded in good yields (entries 8–14). As in the case of *N*-hexylindole 6d', the preferential protonation at the 6-position of *N*-hexylcarbazole 6u may disfavor the benz-annulation (entry 11). In the case of naphtho[*b*]thiophene $6x^{13}$ depending upon the equivalents of DMTHF, mono-/bisbenz-annulation could be achieved in a selective manner to afford respective heterocycles 5x and 5n in excellent yields (entry 14).

The controlled mono-benz-annulation of benzodithiophene $6y^{14}$ using 1 equiv of DMTHF 4 furnished heterocycle 5y in 86% yield. The bis-benz-annulation of thienyl heterocycle $7a^{15}$ and dithienylanthracene $7b^{16}$ using 4.4 equiv of DMTHF 4 led to the isolation of respective annulated products 8a and 8b in excellent yields (entries 16 and 17). All attempts to perform the mono-//bis-benz-annualtion of 1,3-dithienylbenzo[c]thiophene $7c^{17}$ were unsuccessful and led to the formation of an intractable black material. Finally, the benz-annulation reaction was then achieved with electron-rich arenes 9a-f to afford corresponding benz-annulated compounds 10a-f (entries 19 and 20). As a representative case, the structure of naphthodibenzothiophene 5t was confirmed by a single crystal X-ray diffraction analysis.¹⁸

A facile benz-annulation of a wide variety of arenes and heteroarenes, at rt, prompted us to explore a naphth-annulation reaction using 1,3-dimethoxy-1,3-dihydroisobenzofuran 11.¹⁹ The expected naphth-annulation of 9a/9b with isobenzofuran 11 in the presence of triflic acid at rt for 2 h followed by workup and column chromatographic purification led to the isolation of anthracenes 12a,b and anthraquinones 13a,b. The formation of 13a,b can be visualized through the aerial oxidation of respective 9-hydroxyanthracene.

To our delight, when the naphth-annulation of 9a/9b was performed in the presence of ethanol as a reducing agent, the anthracene 12a/12b was obtained as a sole product in excellent yield. Using similar conditions, naphth-annulation of 2,3-disubstituted naphthalene 10a/10c also afforded annulated compound 14a/14c, avoiding the formation of respective quinones (Scheme 3).

A plausible mechanism for annulation of 1,2-dimethoxybenzene 9a with furan 4/11 is presented in Scheme 4. The benzannulation of 9a in the presence of $ZnBr_2$ may proceed through the formation of the intermediate 15 and/or 16. Successive eliminations of water/MeOH from these intermediates may give product 10a. In the case of a five-member heterocycle such as thiophene 3a, the benz-annulation is expected to occur via bicyclic intermediate 17. Obviously, the corresponding intermediate 18 formed during naphth-annulation of 9a underwent ethanol-mediated reductive cleavage followed by dehydration to furnish 2,3-dimethoxyanthracene 12a as a sole product. In the absence of ethanol, the methanol produced during the reaction led to a reductive cleavage as well as ring-opening of the furan unit to give respective intermediates 19 and 20. The intermediate



Table 2. Scope and Limitation of Triflic Acid/LA-Mediated Benz-Annulation of Thiophenes/Electron-Rich Arenes (NR: No Reaction)

^{*a*}Reaction conditions: Substrate (0.5 mmol), DMTHF 4 (1.1 mmol), and CF₃SO₃H (0.5 mmol) in DCM. ^{*b*}Substrate (0.5 mmol), DMTHF 4 (2.2 mmol), and CF₃SO₃H (1 mmol) in DCM. ^{*c*}Substrate (0.5 mmol), DMTHF 4 (1.1 mmol), and ZnBr₂ (0.5 mmol) in DCM. ^{*d*}Substrate (0.5 mmol), DMTHF 4 (0.5 mmol), and CF₃SO₃H (0.5 mmol) in DCM.

20 upon elimination of methanol followed by aerial oxidation afforded anthraquinone **13a**.

In summary, for the first time, a facile benz-annulation of substituted thiophenes and electron-rich arenes was achieved under mild conditions. For some selected heterocycles, depending upon the equivalents of DMTHF and LA/triflic acid, monoand bis-benz-annulation were performed in acceptable yields. The reaction could be successfully extended for the naphthannulation of electron-rich arenes. However, the benzannulation was found to be unsuccessful with electron-rich heterocycles such as furan, indole, and carbazole. Reasonable mechanisms for benz-/naphth-annulation were proposed.

Scheme 3. Triflic Acid Mediated Naphth-Annulation of Arenes



Scheme 4. Mechanism of Annulation for Arene 9a and Thiophene 3a



Further studies on similar types of annulations with analogues of DMTHF are in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, copies of NMR spectra (for new compounds), and X-ray crystallographic data of **5t** (CIF). This material is available for free of charge via the Internet at http:// pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Tedjamulia, M. L.; Tominaga, Y.; Castle, R. N.; Lee, M. L. J. *Heterocycl. Chem.* **1983**, *20*, 1143. (b) Mukherjee, C.; Kamila, S.; De, A. *Tetrahedron* **2003**, *59*, 4767. (c) Jeong, H. J.; Yoon, U. Y.; Jang, S. H.; Yoo, U. A.; Kim, S. N.; Troung, B. T.; Shin, S. C.; Yoon, Y. J.; Singh, O. M.; Lee, S. G. Synlett **2007**, *9*, 1407. (d) Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ikeda, M.; Kuwabara, H. Org.

Lett. 2009, 11, 2473. (e) Katritzky, A. R.; Serdyuk, L.; Xie, L.; Ghiviriga, I. J. Org. Chem. 1997, 62, 6215. (f) Yamamoto, T.; Katsuta, H.; Toyota, K.; Iwamoto, T.; Morita, N. Bull. Chem. Soc. Jpn. 2012, 85, 613.

(2) (a) Payne, M. M.; Odom, S. A.; Parkin, S. R.; Anthony, J. E. Org. Lett. 2004, 6, 3325. (b) Sun, L. L.; Deng, C. L.; Tang, R. Y.; Zhang, X. G. J. Org. Chem. 2011, 76, 7546. (c) Anxionnat, B.; Pardo, D. G.; Ricci, G.; Rossen, K.; Cossy, J. Org. Lett. 2013, 15, 3876. (d) Yu, H.; Zhang, M.; Li, Y. J. Org. Chem. 2013, 78, 8898. (e) Tang, D. T. D.; Collins, K. D.; Glorius, F. J. Am. Chem. Soc. 2013, 135, 7450. (f) Yoshida, S.; Yorimitsu, H.; Oshima, K. Org. Lett. 2007, 9, 5573.

(3) Antonio, A.; Giacomo, F.; Gaetano, G.; Salvatore, L. C. Chemistry & Industry (London) 1977, 3, 128.

(4) El-Borai, M.; Abdel-Megeed, M. F.; Hassien, M.; Fahmy, M. Sulfur Lett. 1987, 6, 99.

(5) (a) Panteleev, J.; Geyer, K.; Aguilar, A. A.; Wang, L.; Lautens, M. Org. Lett. 2010, 12, 5092. (b) Mukherjee, C.; Kamila, S.; De, A. Tetrahedron 2012, 68, 4767. (c) Kumar, I.; Mir, N. A.; Ramarajua, P.; Wakhloo, B. P. RSC Adv. 2012, 2, 8922. (d) Azizi, N.; Davoudpou, A.; Eskandari, F.; Batebi, E. Monatshefte fuer Chemie 2013, 144, 405. (e) Chatzopoulou, M.; Kotsampasakou, E.; Demopoulos, V. J. Synth. Commun. 2013, 43, 2949. (f) Baig, R. B. N.; Varma, R. S. Green Chem. 2013, 15, 398.

(6) Abid, M.; De Paolis, O.; Tŏrŏk, B. Synlett 2008, 13, 4010.

(7) (a) Lee, D. H.; Lee, S. G.; Jung, D. I.; Hahn, J. T. Asian J. Chem. 2013, 25, 501. (b) Abid, M.; Teixeira, L.; Török, B. Tetrahedron Lett. 2007, 48, 4047.

(8) (a) Lu, G.; Usta, H.; Risko, C.; Wang, L.; Facchetti, A.; Ratner, M. A.; Marks, T. J. *J. Am. Chem. Soc.* 2008, *130*, 7670. (b) Palayangoda, S. S.; Mondal, R.; Shah, B. K.; Neckers, D. C. *J. Org. Chem.* 2007, *72*, 6584.
(c) Shinamura, S.; Miyazaki, E.; Takiyama, K. *J. Org. Chem.* 2010, *75*, 1228. (d) Delcamp, J. H.; Yella, A.; Holcombe, T. W.; Nazeeruddin, M. K.; Grätzel, M. Angew. Chem. 2013, *52*, 376.

(9) (a) Sureshbabu, R.; Saravanan, V.; Dhayalan, V.; Mohanakrishnan, A. K. *Eur. J. Org. Chem.* **2011**, 922. (b) Arul Clement, J.; Sivasakthikumaran, R.; Mohanakrishnan, A. K.; Sundaramoorthy, S.; Velmurugan, D. *Eur. J. Org. Chem.* **2011**, 569. (c) Dhayalan, V.; Arul Clement, J.; Jagan, R.; Mohanakrishnan, A. K. *Eur. J. Org. Chem.* **2009**, 531.

(10) Rungtaweevoranit, B.; Butsuri, A.; Wongmaa, K.; Sadorna, K.; Neranona, K.; Nerungsi, C.; Thongpanchang, T. *Tetrahedron Lett.* **2012**, *53*, 1816.

(11) For preparation of **6j** and **6k**: (a) Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. J. Org. Chem. **2011**, 76, 7005. (b) Kanimozhi, C.; Balraju, P.; Sharma, G. D.; Patil, S. J. Phys. Chem. B **2010**, 114, 3095.

(12) Starting compounds **61**–**w** were prepared adopting the published procedure. See Supporting Information (SI) for further details.

(13) Li, G.; Zhou, S.; Su, Y.; Liu, Y.; Wang, P. G. J. Org. Chem. **200**7, 72, 9830.

(14) He, M.; Zhang, F. J. Org. Chem. 2007, 72, 442.

(15) Takimiya, K.; Konda, Y.; Ebata, H.; Niihara, N.; Otsubo, T. J. Org. Chem. 2004, 69, 5568.

- (16) Ghosh, A. K.; Kotha, S. Synlett 2002, 3, 451.
- (17) Mohanakrishnan, A. K.; Lakshmikantham, M. V.; Mc Dougal, C.;

Cava, M. P.; Baldwin, J. W.; Metzger, R. M. J. Org. Chem. **1998**, 63, 3105. (18) Structure was confirmed by single-crystal X-ray data. CCDC

number for compound **5t**: 994367 (see SI).

(19) Mirsadeghi, S.; Rickborn, B. J. Org. Chem. 1987, 52, 787.