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

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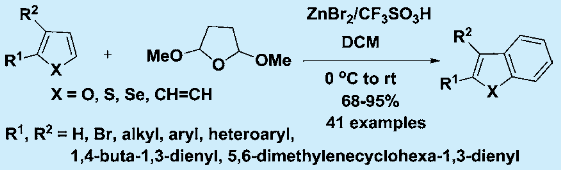
Supporting Information

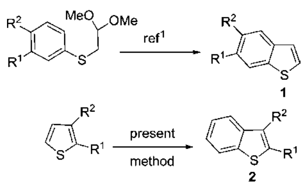
ABSTRACT: A facile preparation of benz-annulated heterocycles were achieved at rt involving a Lewis acid/Brönsted acid mediated annulation of heterocycles using 2,5-dimethoxytetrahydrofuran as a four-carbon synthon. The benz-/naphth-annulation was found to be successful with electron-rich arenes as well.



Benzo[*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-dicarboxaldehyde[3] 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-dimethoxynaphthalene[4] was realized in low yield via the interaction of 1,2-dimethoxybenzene 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]

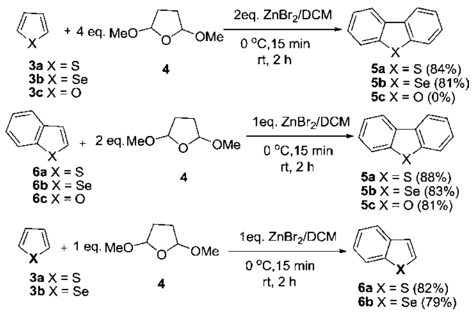
A similar type of benz-annulation of thiophene using DMTHF **4** as a four-carbon synthon is unexplored (Scheme 1). The promising optical applications of benz-annelated thienyl heterocycles[8] prompted us to carry out a systematic study on the benz-annulation of thiophene and its analogues. Further, 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.

Scheme 1. Synthesis of Benzo[*b*]thiophenes



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 °C for 15 min followed by 2 h at rt afforded dibenzothiophene **5a** in 84% yield (Scheme 2).

Scheme 2. LA-Mediated Benz-Annulation of Thiophene, Fuuran, and Selenophene Analogues



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 $ZnBr_2$ 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 $ZnBr_2$ 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 $BF_3{\cdot}OEt_2$	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_3CO_2H	DCE, ref, 24 h	10
9	1 equiv of CF_3SO_3H	DCM, rt, 2 h	92
10	1 equiv of CH_3SO_3H	DCM, rt, 3 h	83

[a] Reaction was performed using 1 equiv of **3a** and 4.4 equiv of **4**. [b] Isolated 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 $SnCl_4$ (entry 3). It should be noted that the bis-benz-annulation was smoothly performed at rt using Lewis acids such as $ZnBr_2$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ (entries 2–4). $CuBr_2$ required refluxing conditions and a longer reaction time (entry 5). The bis-benz-annulation was successfully performed using 20 mol % $InBr_3$ in 1,2-DCE at reflux for 24 h (entry 6). In the presence of 1 equiv of $FeCl_3$, the annulation was found to be complicated possibly due to the polymer formation. However, the annulation was achieved in moderate yield using 20 mol % $FeCl_3$ 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 $ZnBr_2$ 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 **5c′** in 35% yield. Under identical conditions, the naphth-annulation of **6c** using 4.4 equiv of DMTHF afforded **5c′** 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 $ZnBr_2$/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-/bis-benz-annulation could be achieved in a selective manner to afford respective heterocycles **5x** and **5n** in excellent yields (entry 14).

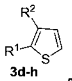
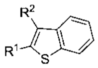
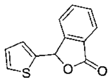
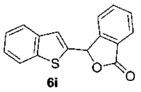
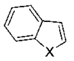
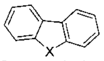
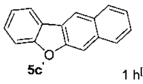
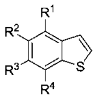
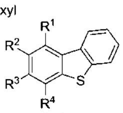
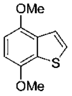
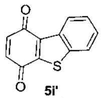
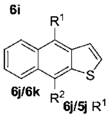
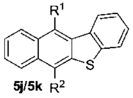
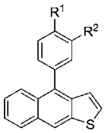
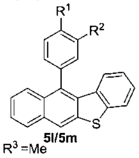
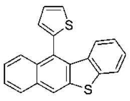
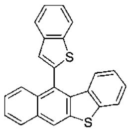
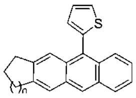
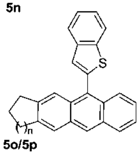
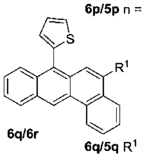
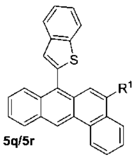
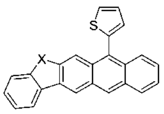
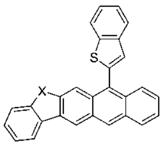
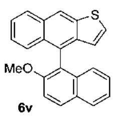
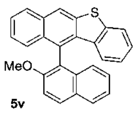
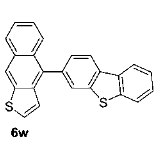
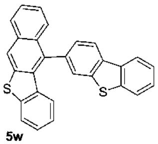
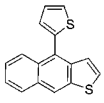
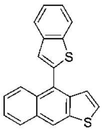
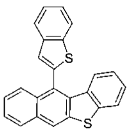
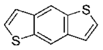
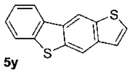
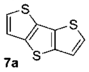
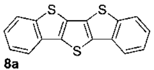
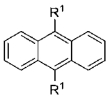
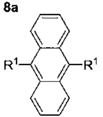
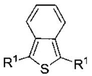
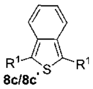
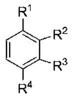
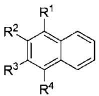
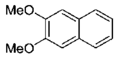
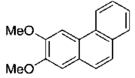
The controlled mono-benz-annulation of benzodithiophene **6y**[14] using 1 equiv of DMTHF **4** furnished heterocycle **5y** in 86% yield. The bis-benz-annulation of thienyl heterocycle **7a**[15] and dithienylanthracene **7b**[16] using 4.4 equiv of DMTHF **4** led to the isolation of respective annulated 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 benz-annulation 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)

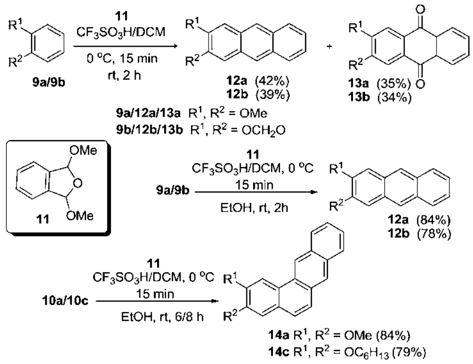
entry	substrate	product	condition	yield (%)
1	 **3d-h**	 **6d-h** **3d/6d** R^1 = Br, R^2 = Me **3e/6e** R^1 = H, R^2 = Me **3f/6f** R^1 = H,R^2 = C_6H_{13} **3g/6g** R^1 = Me, R^2 = H **3h/6h** R^1 = thienyl,R^2 = H	2 h[a] 2 h[a,c] 2 h[a] 2 h[a] 12 h[a,c]	89 NR 90 84 NR
2	 **3i**	 **6i**	12 h[a, c]	NR
3	 **6a-d′**	 **5a/5b/5d**  **5c′** **6a/5a** X = S **6b/5b** X = Se **6c** X = O **6d′/5d** X = N-hexyl	1 h[a] 12 h[a] 12 h[a,b] 12 h[a,c]	87 81 35, 76 NR
4	 **6e-h**	 **5e-h** **6e/5e** R^1, R^4 = H R^2, R^3 = OMe **6f/5f** R^1, R^4 = H R^2, R^3 = -OCH_2O- **6g/5g** R^1, R^2 = -C_4H_4, R^3, R^4 = H **6h/5h** R^1, R^2 = H R^3, R^4 = -C_4H_4	2 h[a,c] 2 h[a] 1 h[a] 1 h[a]	85, 81 83 88 90
5	 **6i**	 **5i′**	1 h[a,c]	81, 76
6	 **6j/6k** **6j/5j** R^1, R^2 = H **6k/5k** R^1, R^2 = OC_6H_{13}	 **5j/5k**	2 h[a] 2 h[a, c]	87 72, 80
7	 **6l/6m**	 **5l/5m** **6l/5l** R^1 = H, R^2, R^3 =Me **6m/5m** R^1, R^2, R^3 = H	2 h[a] 6 h[a]	85 82
8	 **6n**	 **5n**	3 h[a]	81
9	 **6o/6p** **6o/5o** n = 1 **6p/5p** n = 2	 **5o/5p**	6 h[a] 12 h[a, c]	85 83,78
10	 **6q/6r** **6q/5q** R^1 = H **6r/5r** R^1 = Me	 **5q/5r**	2 h[a, c] 2 h[a, c]	83, 75 92, 81
11	 **6s-u** **6s/5s**X = O **6t/5t** X = S **6u/5u** X= N-hexyl	 **5s-u**	4 h[a] 5 h[a] 24 h[a]	88 93 NR
12	 **6v**	 **5v**	8 h[a]	82
13	 **6w**	 **5w**	12 h[a]	85
14	 **6x**	 **5x**  **5n**	**5x** 3 h[d, c] **5n** 12 h[b]	78, 71 82
15	 **6y**	 **5y**	2 h[d]	86
16	 **7a**	 **8a**	12 h[b]	81
17	 **7b** R^1 = 2-thienyl	 **8b** R^1 = benzo[*b*]-2-thienyl	7 h[b]	83
18	 **7c** R^1 = 2-thienyl	 **8c/8c′** **8c** R^1 = 2-thienyl, benzo[*b*]-2-thienyl **8c′** R^1 = benzo[*b*]-2-thienyl	12 h[a,c] 12 h[b]	NR NR
19	 **9a-e**	 **10a-e** **9a/10a** R^1, R^4 = H, R^2, R^3 = OMe, **9b/10b** R^1, R^4 = H, R^2, R^3 = OCH_2O **9c/10c**R^1, R^4 = H, R^2, R^3 = OC_6H_{13} **9d/10d** R^1, R^4 = OMe, R^2, R^3 = H **9e/10e** R^1, R^2, R^3 = OMe, R^4 = H	2 h[a, c] 2 h[a] 2 h[a, c] 12 h[a] 2 h[a]	95, 88 83 93, 85 68 84
20	 **9f**	 **10f**	12 h[a]	83

[a] Reaction conditions: Substrate (0.5 mmol), DMTHF **4** (1.1 mmol), and CF_3SO_3H (0.5 mmol) in DCM. [b] Substrate (0.5 mmol), DMTHF **4** (2.2 mmol), and CF_3SO_3H (1 mmol) in DCM. [c] Substrate (0.5 mmol), DMTHF **4** (1.1 mmol), and $ZnBr_2$ (0.5 mmol) in DCM. [d] Substrate (0.5 mmol), DMTHF **4** (0.5 mmol), and CF_3SO_3H (0.5 mmol) in DCM.

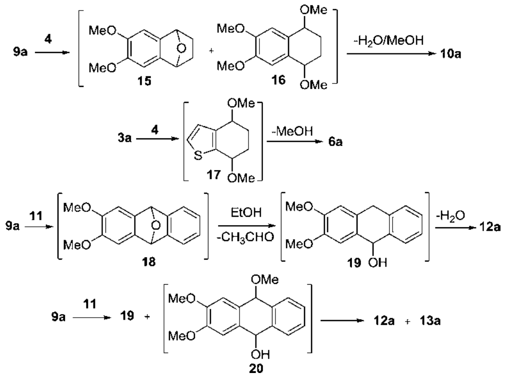
20 upon elimination of methanol followed by aerial oxidation afforded anthraquinone **13a**.

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, mono- and bis-benz-annulation were performed in acceptable yields. The reaction could be successfully extended for the naphth-annulation of electron-rich arenes. However, the benz-annulation 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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