A New and Efficient Ring Contraction of Dihydrobenzopyran to Dihydrobenzofuran Derivatives

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A simple and efficient synthesis of benzofuran from benzopyran is described. The ring contraction takes place in the presence of Lewis acid. BBr_3 in dichloromethane have proven to be the best conditions. A mechanism via an aziridinium intermediate is proposed.

Keywords: benzofuran, benzopyran, Lewis acid, ring contraction

In connection with our studies on heterocyclic derivatives with potential biological activity [1-7], we now report on an unusual ring contraction reaction of benzopyran to benzofuran derivatives [8-16]. This phenomenon is well recognized in benzothiopyranic serie [17]. Indeed, the formation of benzothiophenes by the ring contraction of benzothiopyrans is facilitated by the presence of suitable leaving groups at position 3. Benzopyrans, on the other hand, are not know to undergo a similar transformation possibly because of their inability to form the presumed bicyclo-oxiranium intermediate. However, Descotes and Missos first related the preparation of benzofurans from benzopyranic halohydrins [17]. Later, it was reported in moderate yield below 40%, and unusual ring contraction reaction of benzopyrans to benzofurans under basic conditions in the course of their work on the synthesis of structural analogues of cromakalim [18].

In this paper, we describe the one-pot synthesis of benzofurans by a Lewis acid mediated ring contraction. This study concerned essentially benzopyranic derivatives of type **A** which were substituted at position 3 with amino groups. Indeed, treatment of this compounds **A** with the appropriate Lewis acid led to the corresponding benzofuranic isomers of type **B** (scheme 1).

Experimental part

Scheme 1. Benzopyran to benzofuran ring contraction

General procedure for the ring contraction

Method A. A solution of boron tribromide (0.05 mL, 0.55 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of the appropriate benzopyran (0.5 mmol) in dry CH_2Cl_2 under argon. The reaction mixture was then refluxed for 24 h. After cooling, the reaction mixture was hydrolyzed. The aqueous phase was basified with a saturated solution of $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography, eluting with CH_2Cl_2/MeOH (100:0 to 90.10) to afford the corresponding benzofuran. Yields of the products are reported in Table 1.

Method B. Reactions were performed as mentioned above, excepted that 2.1 equiv. (1.05 mmol) of boron tribromide were used and that the reaction was refluxed 48 h.

2-(*N,N*-Dipropylaminomethyl)-2,3-dihydrobenzo[*b*] furan(2). Yellow oil; IR (film) 1230 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.86(t, *J* = 7.3 Hz, 6H, CH_2-C**H**$_3$), 1.39-1.55 (m, 4H, C**H**$_2$-CH_3), 2.47 (t, *J* = 7.3 Hz, 4H, *N*-C**H**$_2$-CH_2), 2.60 (dd, *J* = 5.9 Hz, *J* = 13.2 Hz, 1 H, CH(**H**)-NPr_2), 2.79 (dd, *J* = 6.6 Hz, *J* = 13.2 Hz, 1H, C**H**(H)-NPr_2), 2.97 (dd, *J* = 7.3 Hz, *J* = 15.4 Hz, 1H, **H**$_{3a}$), 3.24 (dd, *J* = 8.8 Hz, *J* = 15.4 Hz, 1H, **H**$_{3b}$), 4.84-4.89 (m, 1H, **H**$_2$), 6.76 (d, *J* = 7.4 Hz, 1H, **H**$_7$), 6.80 (t, *J* = 7.4 Hz, 1H, **H**$_5$), 7.08 (t, *J* = 7.4 Hz, 1H, **H**$_6$), 7.14 (d, *J* = 7.4 Hz, 1H, **H**$_4$); ^{13}C NMR ($CDCl_3$) δ: 11.8 (2 **C**H_3), 20.2 (2 **C**H_2-CH_3), 33.5 (**C**$_3$), 57.0 (2 N-**C**H_2-CH_2), 58.7 (**C**H_2-NPr_2), 81.5 (**C**$_2$), 109.4 (**C**$_7$), 120.1 (**C**$_5$), 124.9 (**C**$_4$), 126.6 (**C**$_{3a}$), 127.8 (**C**$_6$), 159.5 (**C**$_{7a}$); MS (CI/NH_3) *m/z* 234 (M+1). Anal. Calcd for $C_{15}H_{23}NO$: C,77.19; H, 9.95; N, 6.00. Found: C, 77.37; H, 10.06; N, 5.88.

2-(Methylpyrrolidin)-2,3-dihydrobenzo[*b*] furan(6). Yellow oil; IR (film) 1220 (C-O-C)cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.76-1.86 (m, 4H, **H**$_{pyrrol}$), 2.58-2.70 (m, 5H, -C-CH(**H**)-N- and **H**$_{pyrrol}$), 2.90 (dd, *J* = 7.8 Hz, *J* = 12.8 Hz, 1H, -C**H**(H)-N-), 2.96 (dd, *J* = 7.9 Hz, *J* = 15.6 Hz, 1H, **H**$_{3a}$), 3.28 (dd, *J* = 9.1 Hz, *J* = 15.6 Hz, 1H, **H**$_{3b}$), 4.88-4.99 (m, 1H, **H**$_2$); 6.77-7.17 (m, 4H, **H**$_{arom}$); ^{13}C NMR ($CDCl_3$) δ: 23.5 (2N-CH_2-**C**H_2), 34.1 (**C**$_3$), 54.8 (2 N-**C**H_2-CH_2), 61.1 (C_2-**C**H_2), 81.6 (**C**$_2$), 109.6 (**C**$_7$), 120.3 (**C**$_5$), 124.9 (**C**$_4$), 126.5 (**C**$_{3a}$), 128.0 (**C**$_6$), 159.5 (**C**$_{7a}$); MS (CI/NH_3) *m/z* 204 (M+1). Anal. Calcd for $C_{13}H_{17}NO$: C,76.79; H, 8.45; N, 6.89. Found: C, 76.67; H, 8.54; N, 7.02.

2-*N*-Propylaminomethyl)-2,3-dihydrobenzo[*b*]furan (8). Yellow oil; IR (film) 1220 (C-O-C), 3320 (N-H)cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ: 0.94 (t, *J* = 7.4 Hz, 3H, -CH_2-C**H**$_3$), 1.50-1.64 (m, 2H, -C**H**$_2$-CH_3), 2.68 (t, *J* = 7.4 Hz, 2H, -NH-C**H**$_2$-CH_2-CH_3), 2.84-2.99 (m, 3H, -C**H**$_2$-NHPr, **H**$_{3a}$), 3.29 (dd, *J* = 9.2 Hz, *J* = 15.6 Hz, 1H, **H**$_{3b}$), 4.92-5.02 (m, 1H, **H**$_2$), 6.77 and 7.14 (2d, *J* = 7.4 Hz, 2H, **H**$_4$, **H**$_7$), 6.83 and 7.09 (2t, *J* = 7.4 Hz, 2H, **H**$_5$, **H**$_6$); ^{13}C NMR ($CDCl_3$) äδ: 11.3 (**C**H_3), 19.4 (**C**H_2-CH_3), 33.8 (**C**$_3$), 49.9, 50.8 (**C**H_2-N-**C**H_2), 77.6 (**C**$_2$), 110.3 (**C**$_7$), 121.3 (**C**$_5$), 124.9, 125.1 (**C**$_4$, **C**$_{3a}$), 128.5 (**C**$_6$), 158.2 (**C**$_{7a}$); MS (CI/NH_3) *m/z* 192 (M+1). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.34; H, 8.98; N, 7.32. Found: C, 75.44; H, 8.81; N, 7.39.

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2-(*N,N*-Dipropylaminomethyl)-2,3-dihydronaphto[1,2-*b*]furan (11). Yellow oil; IR (film) 1230 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.89 (t, *J* = 7.4 Hz, 6H, $-CH_2-CH_3$), 1.42-1.56 (m, 4H, $-CH_2-CH_3$), 2.53 (t, *J* = 7.4 Hz, 4H $N(CH_2-CH_2)$), 2.71 (dd, ^3J = 6.0 Hz, ^2J = 13.5 Hz, 1H, $-CH(H)-NPr_2$), 2.89 (dd, *J* = 6.7 Hz, *J* = 13.5 Hz, 1H, $-CH(H)-NPr_2$), 3.25 (dd, *J* = 7.1 Hz, *J* = 15.5 Hz, 1H, H_{3a}), 3.54 (dd, ^3J = 9.5 Hz, ^2J = 15.5 Hz, 1H, H_{3b}).503-5.15 (m, 1H, H_2), 7.07-7.82 (m, 6H, H_4, H_5, H_6, H_7, H_8, H_9); ^{13}C NMR ($CDCl_3$) δ: 11.9 (2 CH_3), 20.2 (2 CH_2-CH_3), 32.8 (C_3), 57.1 (2 $N-CH_2-CH_2$), 59.0 (CH_2-NPr_2), 82.3 (C_2), 112.2, 118.2, 122.7, 125.8, 126.5, 128.7, 128.8; 129.1, 130.9, 157.1 ; MS (CI/NH_3) *m/z* 284 (M+1). Anal. Calcd for $C_{19}H_{25}NO$: C, 80.50; H, 8.91; N, 4.94. Found: C, 80.59; H, 8.78; N, 4.90.

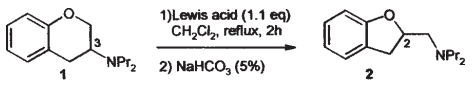
2-Aminomethyl-2,3-dihydrobenzo[*b*]furan (14). oil; IR (KBr) 1230 (C-O-C), 3300 (N-H) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.57 (br s, 2H, NH_2), 2.79 (m, 1H, H_{3a}, $CH(H)-NH_2$), 3.28 (dd, 1H, $CH(H)-NH_2$, *J* = 8.8 Hz, *J* = 15.4 Hz, 1H, H_{3b}), 4.84-4.89 (m, 1H, H_2), 6.77 (d, ^3J = 7.4 Hz, 1H, H_7), 6.83 (t, *J* = 7.4 Hz, 1H, H_5), 7.11 (t, *J* = 7.4 Hz, 1H, H_6), 7.15 (d, *J* = 7.4 Hz, 1H, H_4); ^{13}C NMR ($CDCl_3$) δ: 32.5 (C_3), 43.1 (CH_2-NH_2), 79.9 (C_2), 109.5 (C_7), 120.9 (C_5), 125.4 (C_4), 126.6 (C_{3a}), 128.1 (C_6), 158.6 (C_{7a}); MS (CI/NH_3) *m/z* 150 (M+1). Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.51; H. ,7.36; N,9.48.

Results and discussions

As far as we know, the formation of benzofurans from benzopyrans mediated ring contraction reaction *via* Lewis acid has only been described in the literature by our group [19]. In the present paper, results of the performed reaction are presented and a possible mechanism is proposed.

Our initial studies of this process were focused on the 3-aminochromanic derivative **1** [1] which was chosen as model (scheme 2).

Attempts to obtain compound **2** from **1** by ring contraction reaction were carried out in the presence of different Lewis acids and one Brönsted acid in similar conditions using 1.1 equivalent of acid in refluxing dichloromethane for 2 h (*Method A*). The complexed Lewis acids such as boron trifluoride/diethyl etherate and boron tribromide/methyl sulfide as well as Brönsted acids such as the camphorsulfonic acid did not give the expected reaction. In contrast, Lewis acids such as titanium tetrachloride, aluminium trichloride and boron tribromide allowed us to isolate the benzofuran **2** respectively in 63%, 83% and 88% yield. The structure of this compound has



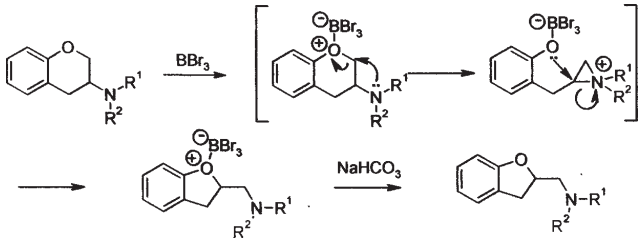
Lewis Acid	Yields of 1 (%)	Yield of 2 (%)
$AlCl_3$	-	83
BBr_3	-	88
BBr_3•Me_2S	100	-
BF_3•Et_2O	100	-
$TiCl_4$	23	63
Camphorsulfonic acid	100	-

Scheme 2. Evaluation of few Lewis acids

been elucidated and confirmed by ^1H and ^{13}C NMR spectroscopic data and two-dimensional NMR experiments.

In the light of these results, boron tribromide was retained to evaluate the scope and limitations of the reaction.

As shown in scheme 3, formation of the benzofuran **2** can be explained in terms of complexation between the oxygen of the methoxy moiety and the boron (III) bromide. At this stage, the increased polarization of the carbon-oxygen bond allows an intramolecular nucleophilic attack by the amine function. The resulting azinidinium ion is then subsequently opened to provide, after neutralization, the benzofuran **2**. In this tetrahedral system, in term of Baldwin rules, the cyclisation occurs in a favored 5-*exo-tet* process whereas the other possible six-*endo-tet* is disfavoured [20]. This phenomenon was also observed in recent works in piperidine series [21,22].



Scheme 3. Possible mechanism for the ring contraction

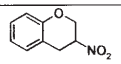
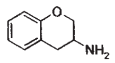
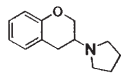
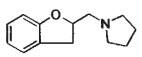
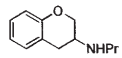
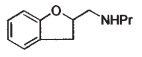
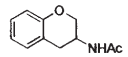
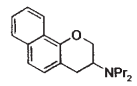
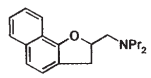
In order to generalize this methodology, the experimental parameters, previously established (Method A : 1.1 equiv of BBr_3, CH_2Cl_2, reflux, 2h) were applied to benzopyranic and naphtopyranic derivatives, which present from the pattern compounds a variation of the substitution on the nitrogen atom or on the homocycle. To optimize the reaction, the number of equivalents of boron tribromide and the time of the reaction were increased simultaneously (Method B : 2.1 equiv of BBr_3, CH_2Cl_2, reflux, 24h) (table 1).

As depicted in table 1, benzopyranic and naphtopyranic derivatives **5** (obtained by alkylation of aminochromane **4** with 1,4-dibromobutane in the presence of triethylamine in DMF) and **10** (obtained by reduction of 3-nitro-2*H*-benzo[*h*] chromene [23] and *N*-alkylation with 1-iodopropane in the presence of K_2CO_3 in DMF), respectively led in high yields to the corresponding furans **6** and **11** (run 3 and 6). On the other hand, compounds **4** [24] and **7** [25] did not allow the formation of the expected products. Nevertheless, using method B with benzopyran **7**, benzofuran product **8** was isolated in a poor yield and the starting material was predominantly recovered. It should be noted that no ring contraction reaction occurred with compounds **3** [1-3] and **9** [22] bearing a nitro or acetamido group. This result is in agreement with the suggested mechanism.

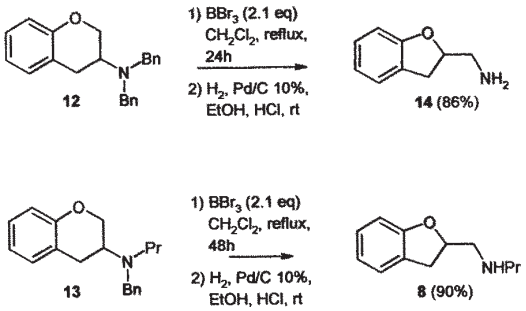
In order to find an efficient route that would allow the preparation of benzofurans **8** and **14**, we investigated the ring contraction reaction from 3-aminochromans **12** and **13** (scheme 4) which were respectively alkylated on the nitrogen atom by reacting aminochromans **4** and **7** with benzyl bromide in DMF at 60°C in the presence of K_2CO_3 and a catalytic amount of potassium iodide in 72% and 93% yields.

Thus, ring contraction process followed by hydrogenolysis could lead to the expected benzofurans. Indeed, treatment of compound **12** with 2.1 equiv. of boron tribromide in refluxing dichloromethane during 24 hours followed by hydrogenolysis led to the 2-amino-

Table 1
SCOPE AND LIMITATIONS OF THE RING CONTRACTION

Run	Starting Benzopyrans	Methods[a]	Products	Yield (%)
1	 **3**	A	no product	-[b]
		B		-[b]
2	 **4**	A	no product	-[c]
		B		-[c]
3	 **5**	A	 **6**	54
		B		80
4	 **7**	A	 **8**	-[b]
		B		26
5	 **9**	A	no product	-[b]
		B		-[b]
6	 **10**	A	 **11**	68
		B		85

[a] ***Method A***: 1.1 equiv. BBr_3, CH_2Cl_2, reflux, 2h. ***Method B***: 2.1 equiv. BBr_3, CH_2Cl_2, reflux, 24h. [b] Starting material was recovered. [c] Degradation products were observed.



Scheme 4. Improved synthesis to benzofurans 8 and 14

methylbenzofuran **14** in 86 % yield. Under similar conditions but during 48 hours, benzopyran **13** led to benzofuran **8** in 90% yield.

Conclusions

In conclusion, the few examples described here suggest that the Lewis acid mediated ring contraction reaction represents a new and potentially useful methodology for the formation of benzofuranic derivatives from the corresponding benzopyranic isomers.

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