Notes

High-Yield Trifluoroacetic Acid-Mediated Intermolecular Condensation of 1-[2-Benzo[b]thienyl]cycloalkanols

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Introduction

As part of our studies toward the synthesis and biological activity of 1-(1-phenylcyclohexyl)piperidine (phencyclidine, 1, Chart 1) and its derivatives, we utilized the "azide method" (Scheme 1) as a route to many of these compounds. Trifluoroacetic acid (4 equiv) in the presence of sodium azide has proven to be an effective means of generating tertiary benzylic azides, which can then be reduced to the desired primary amines and further transformed.[1]

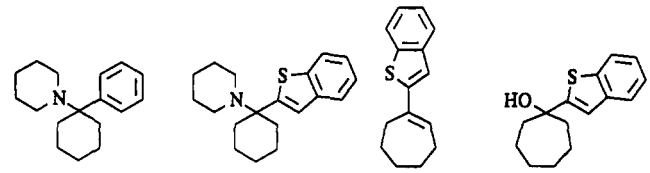
This method also proved to be very effective in the synthesis of the phencyclidine analog, 1-[1-(2-benzo[b]-thienyl)cyclohexyl]piperidine (BTCP, 2, Chart 1),[2] a high-affinity ligand for the cocaine receptor.[3]

We observed[4] the formation of a byproduct with a molecular weight corresponding to twice that of the expected elimination product 3 during the solvolysis of 1-[2-benzo[b]thienyl]cycloheptanol (4) with NaN_3/CF_3CO_2H.[5]

In the present study, we further investigate this phenomenon by treatment of 1-(2-benzo[b]thienyl)cycloalkanols, 1-phenylcycloheptanol, and 1-(2-benzo[b]thienyl)-cycloheptene with CF_3CO_2H and other acid catalysts under a variety of conditions (Table 1). The structures of the products were confirmed spectroscopically, by comparison with authentic samples, or by single crystal X-ray analysis.

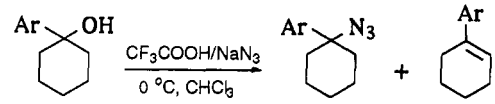
1-[2-Benzo[b]thienyl]cycloalkanols 4-6[2,5] (Table 1) were obtained in 57-100% yield by treatment of the corresponding cycloalkanones with 2-lithiobenzo[b]thiophene in ether at room temperature.[2] The products were obtained in pure form by recrystallization from hexanes.[2,5] 1-Phenylcycloheptanol (7)[6] was obtained in 92% yield by treatment of cycloheptanone with 2 mol equiv of PhMgBr in dry THF. *cis*-1-[2-(benzo[b]thienyl)]cyclohexane-1,4-diol (8) was synthesized as described previously.[2]

Chart 1



1 (PCP) 2 (BTCP) 3 4

Scheme 1



Results

Treatment of 1-[2-benzo[b]thienyl]cycloalkanols (4-6) with excess (4.0 mol equiv) trifluoroacetic acid (CF_3CO_2H) in $CHCl_3$ at 0 °C afforded quantitative yields of intermolecular condensation products 9-11 (Table 1). Evidence for the involvement of olefinic intermediates in this reaction was provided by the presence of 3 (20% of product mixture) when the reaction mixture of 4 was quenched after 5 min instead of 5 h (Table 1). The remainder (80%) of the product mixture corresponded to 9. Similarly, the presence of olefin was observed on quenching the reaction for 6 after 5 min. Treatment of 4 with excess (4.0 mol equiv) *p*-toluenesulfonic acid (instead of CF_3CO_2H) in $CHCl_3$ at 0 °C resulted in olefin 3 only (Table 1).

The involvement of carbenium ion intermediates in this condensation was evident from the lack of reactivity of olefin 3 to CF_3CO_2H in contrast to its high-yield transformation to 9 on replacing the CF_3CO_2H with CF_3SO_3H (4.0 mol equiv) (Table 1). The involvement of both olefinic and carbenium ion intermediates was further supported by the exclusive formation of 9 on treatment of a 1:1 mixture of olefin 3 and alcohol 4 with CF_3CO_2H (4 mol equiv) in $CHCl_3$ at 0 °C (Table 1).

Brief treatment (2 min) of 4 with a catalytic quantity (0.05 mol equiv) of *p*-toluenesulfonic acid (PTSA) in boiling toluene afforded elimination product 3 only. Similarly, 3 was formed in quantitative yield from 4 at room temperature in the presence of a trace (0.05 mol equiv) of CF_3CO_2H (Table 1). In order to determine if this condensation reaction could be repeated for simple aromatic systems, 1-phenylcycloheptanol (7)[6] was treated as for 4-6. However, dehydration to 12 was observed within 5 min at 0 °C with no further change evident after 1 h at 20 °C. Similar treatment of *cis* cyclohexane-1,4-diol 8[2] yielded the olefin 13[2] as the only product.

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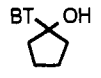
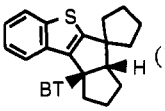
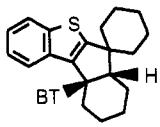
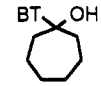
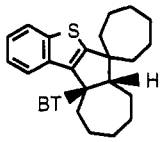
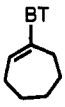
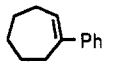
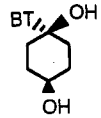
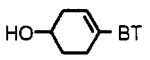
(1) Geneste, P.; Herrmann, P.; Kamenka, J.-M.; Pons, A. *Bull. Soc. Chim. Fr.* **1975**, 1619 (in French).
(2) de Costa, B. R.; George, C.; Dominguez, C. *J. Chem. Soc. Perkins Trans 1* **1992**, 1671.
(3) (a) Vignon, J.; Pinet, V.; Cerruti, C.; Kamenka, J.-M.; Chicheportiche, R. *Eur. J. Pharmacol.* **1988**, *148*, 427. (b) Kamenka, J.-M.; Privat, A.; Chicheportiche, R. R.; Costentin, J. Eur. Patent 0,406,111,A1, filed June 27, 1990.
(4) He, X.-S., unpublished observation.
(5) He, X.-S.; Raymon, L. P.; Mattson, M. V.; Eldefrawi, M. E.; de Costa, B. R. *J. Med. Chem.* **1993**, *36*, 1188.
(6) Khan, A. M.; McQuillin, F. J.; Jardine, I. *J. Chem. Soc. C* **1967**, *2*, 136.

Table 1[a,b]

alcohol	acid cat. (mol equiv)	solvent	temp (°C)	time	product(s) (yield(s))
 5	CF_3CO_2H (4.0)	$CHCl_3$	0	5 min	 (100%) 10
 6	CF_3CO_2H (4.0)	$CHCl_3$	0	3 h	 (100%) 11
 4	CF_3CO_2H (4.0)	$CHCl_3$	0	5 h	 (100%) 9
4	CF_3CO_2H (4.0)	$CHCl_3$	0	5 min	9 +  (4 : 1) (100%) 3
4	PTSA (4.0)	$CHCl_3$	0	5 h	3 (77%)
4	PTSA (0.05)	toluene	110 (reflux)	2 min	3 (100%)
3	CF_3CO_2H (4.0)	$CHCl_3$	20	28 h	unchanged starting material (100%)
3 + 4	CF_3CO_2H (4.0)	$CHCl_3$	0	5 h	9 (92%)
3	CF_3SO_3H (4.0)	$CHCl_3$	0	3 h	9 (95%)
 7	CF_3CO_2H (4.0)	$CHCl_3$	0	5 min	 12 (100%)
 8	CF_3CO_2H (4.0)	$CHCl_3$	0	5 min	 13 (97%)
4	CF_3CO_2H (0.05)	$CHCl_3$	0	1 h	starting material (92%) + 3 (8%)
4	CF_3CO_2H (0.05)	$CHCl_3$	20	24 h	3 (100%)

[a] BT = 2-benzo[b]thienyl. [b] Reactions were performed as described in the Experimental Section.

Single crystals of 9 and 11 were grown by slow cooling of saturated solutions of these compounds in 2,2,4-trimethylpentane. The results (see X-ray analysis section later and Figures 1 and 2) confirmed their structures (Table 1). Products 9–11 all displayed a characteristic signal in the ^{1}H-NMR spectra (2.91–3.24 ppm) corresponding to the methine proton oriented *cis* to the benzo[*b*]thienyl ring. The presence of two doublets (d, dd, dm) located at ca 7.8 and 7.7 ppm in the ^{1}H-NMR spectra of 9–11 is characteristic of the 1,2-fused benzothienyl ring. The ^{13}C-NMR spectra of 9–11 displayed seven signals between 130–160 ppm corresponding to seven quaternary aromatic carbons, nine signals between 119–125 ppm corresponding to the aromatic "CH" carbons, and signals between 20–75 ppm corresponding to the appropriate number of aliphatic carbons. Analysis of 9 by DEPT confirmed the ^{13}C assignments.

Discussion

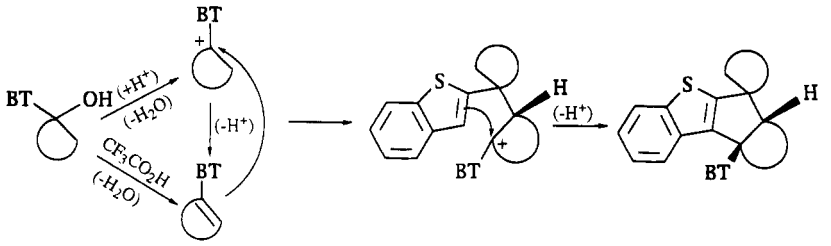
A plausible mechanism for this reaction is depicted in Scheme 2. The reaction appears to be sensitive to the nature of the acid since treatment of 4 with PTSA (4 mol equiv) resulted only in elimination. The *cis* relation between the benzo[*b*]thienyl ring and methine H can readily be seen in the ORTEP plots for 9 and 11 (Figures 1 and 2).

Repetition of the reaction of 4 with the same molar concentration of CF_3CO_2H but using a 100-fold lower concentration of 4 still furnished 9 as the major product with no significant change in the rate of the reaction suggesting the presence of H- or π-bonded dimers of 4 in $CHCl_3$ at 0 °C.

The inability of 1-phenylcycloheptanol (7) and *cis*-1-(2-benzo[*b*]thienyl)cyclohexane-1,4-diol (8) to show condensation reactions in the presence of excess CF_3CO_2H is due to the absence of a suitably activated aromatic ring in the former case and a cyclohexane ring conformation favoring elimination in the latter case (Scheme 3). ^{1}H-NMR analysis of 8[2] indicated an equatorial 4-hydroxy group as depicted in Scheme 3.

In conclusion, this novel CF_3CO_2H-mediated condensation is of interest since it may account for lowered yields that sometimes occur during acid-induced dehydrations of 1-arylcycloalkanols.

Scheme 2



[a] BT = 2-benzo[*b*]thienyl.

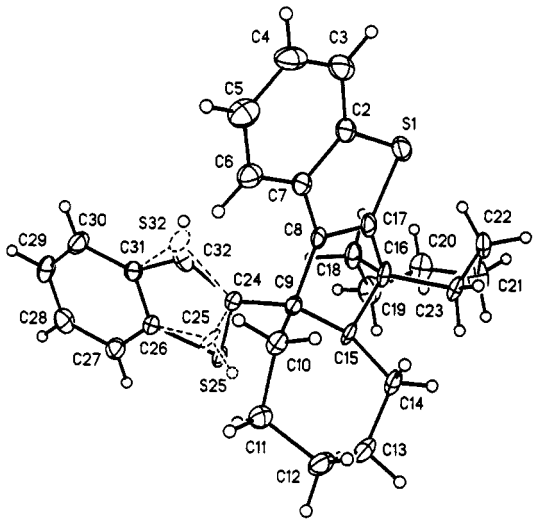


Figure 1. The molecular structure and numbering scheme for 9. The dotted atoms and bonds represent alternate positions for those atoms. Disordered atoms in spiro ring omitted for clarity.

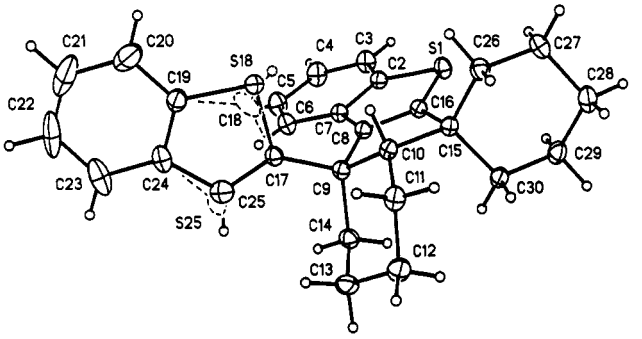


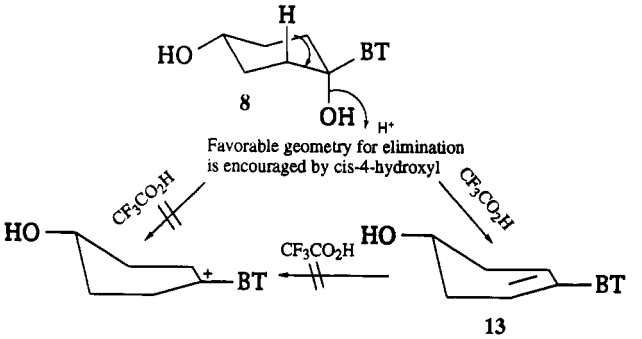
Figure 2. Thermal ellipsoid plot for 11. The dotted atoms and bonds represent alternate positions for those atoms.

Experimental Methods

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed at Atlantic Microlabs, Atlanta, GA. Chemical ionization mass spectra (CIMS) were obtained using a Finnigan 1015 mass spectrometer. Electron ionization mass spectra (EIMS) and high-resolution mass measurements (HRMS) were obtained using a VG-Micro Mass 7070F mass spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded from $CDCl_3$ solutions using a Varian XL-300 spectrometer. Results are recorded as ppm downfield relative to TMS and $CHCl_3$ internal standards, respectively.

1-Phenylcycloheptanol (7). In a modification of the previously reported[6] method, cycloheptanone (50 g, 0.5 mol) was added dropwise to a stirred solution of PhMgBr (0.932 mol) in THF (800 mL) and the product was isolated using standard conditions to give 7 (88%) as a colorless liquid (bp 115 °C/1 mmHg, lit.[6] 100 °C/0.5 mm): ^{1}H-NMR δ 7.50 (dist d, J = 7.4 Hz, 2H, ArH), 7.32 (dist t, J = 7.5 Hz, 2H, ArH), 7.22 (m, 1H, ArH), 2.00–2.12 (m, 2H), 1.84–1.94 (m, 2H), 1.51–1.84 (complex m, 8H).

Scheme 3



[a] BT = 2-benzo[*b*]thienyl.

Intermolecular Condensation Products (9–11, Table 1). To a stirred solution of 1-(2-benzo[*b*]thienyl)cycloalkanol (1 mmol) in chloroform (1 mL) at 0 °C was added in one portion trifluoroacetic acid (0.31 mL, 4 mol equiv). A deep red color formed in the solution during the addition and persisted during the reaction. The reaction was allowed to proceed until complete (^{1}H-NMR analysis), diluted with $CHCl_3$ (4 mL), and then poured into saturated $NaHCO_3$ (5 mL) and extracted by thorough shaking. The $CHCl_3$ layer was separated and back-washed with water. Evaporation of the solvent furnished the products 9–11 in quantitative yield.

9: mp 178–179 °C (hexanes); ^{1}H-NMR δ 7.82 (d, J = 4.2 Hz, 1H, ArH), 7.79 (dd, J = 3.7, 1.3 Hz, 1H, ArH), 7.70 (d, J = 7.6 Hz, 1H, ArH), 7.56 (dd, J = 7.1, 1.5 Hz, 1H, ArH), 7.16–7.36 (complex m, 4H, ArH), 6.93 (s, 1H, ArH), 3.24 (dd, J = 8.1, 4.1 Hz, 1H), 2.73 (m, 1H), 2.37 (m, 1H), 1.98–2.15 (complex m, 2H), 1.32–1.96 (complex m, 18H); ^{13}C-NMR δ 157.9, 155.1, 144.2, 140.0, 139.8, 139.2, 135.2, 124.5, 124.2, 123.9, 123.6, 123.3, 122.6, 122.2, 119.7, 68.8, 57.4, 52.8, 43.0, 39.4, 36.3, 31.4, 30.9, 29.4, 28.0, 25.9, 24.4, 23.8; EIMS (M^+ calcd for $C_{30}H_{32}S_2$) 456, found 456. Anal. Calcd for $C_{30}H_{32}S_2$: C, 78.90; H, 7.06%. Found: C, 78.71; H, 7.09%.

10 (oil): ^{1}H-NMR δ 7.82 (dm, J = 7.1 Hz, 1H, ArH), 7.72 (d, J = 7.3 Hz, 1H, ArH), 7.54 (m, 1H, ArH), 7.52 (m, 1H, ArH), 7.17–7.31 (complex m, 4H, ArH), 6.81 (s, 1H, ArH), 3.07 (t, J = 7.3 Hz, 1H), 2.54 (m, 1H), 2.42 (m, 1H), 1.50–2.20 (complex m, 12H); ^{13}C-NMR δ 155.6, 152.4, 144.8, 140.7, 140.1, 139.6, 134.3, 124.5, 124.3, 124.0, 123.7, 123.5, 123.2, 122.3, 122.1, 119.6, 70.6, 58.7, 56.7, 43.0, 40.6, 35.1, 31.4, 27.9, 24.3, 24.0; CIMS (MH^+ calcd for $C_{26}H_{24}S_2$) 401, found 401; HRMS (M^+ calcd for $C_{26}H_{24}S_2$) 400.1319, found 400.1333. Anal. Calcd for $C_{26}H_{24}S_2$: C, 77.96; H, 6.04%. Found: C, 77.87; H, 6.45%.

11: mp 160–161 °C (hexanes); ^{1}H-NMR δ 7.77 (d, J = 8.1 Hz, 1H, ArH), 7.70 (d, J = 8.1 Hz, 2H, ArH), 7.31 (s, 1H, ArH), 7.28–7.36 (m, 2H, ArH), 7.05–7.25 (complex m, 3H, ArH), 2.91 (dd, J = 6.4, 2.3 Hz, 1H), 2.84 (m, 1H), 1.66–1.98 (complex m, 15H), 1.63 (m, 1H), 1.32 (m, 1H); ^{13}C-NMR δ 154.9, 149.3, 144.5, 144.4, 140.2, 139.7, 134.1, 124.3, 124.2, 123.9, 123.4, 123.31, 123.27, 122.4, 121.6, 121.2, 64.0, 51.2, 50.1, 38.5, 35.3, 34.8, 25.6, 24.7, 23.5, 23.0, 22.5, 22.4; CIMS (MH^+ calcd for $C_{28}H_{28}S_2$) 429, found 429. Anal. Calcd for $C_{28}H_{28}S_2$: C, 78.46; H, 6.58%. Found: C, 78.49; H, 6.76%.

Trifluoroacetic, Trifluoromethanesulfonic, or *p*-Toluenesulfonic Acid Treatment of 3, 4, 7, and 8 under Different Conditions (Table 1). To solutions of olefin 3[5] (0.25 g, 1.1 mmol); alcohol 4[5] (1.00 g, 4.06 mmol); mixture of alcohol 4[5] (0.25 g, 1

mmol) and olefin **3** (0.23 g, 1 mmol); alcohol **7**[6] (1 g, 5.3 mmol); diol **8**[2] (0.25 g, 1 mmol) in $CHCl_3$ (1 mL/mmol substrate except **8** which required 2 mL/mmol to obtain a homogeneous solution) at the appropriate temperature (Table 1) was added the appropriate acid (Table 1) (0.05–4.0 mol equiv) in one portion.

The reactions were stirred at the stated temperature and times (Table 1), diluted with fresh $CHCl_3$ (4 mL/mL reaction solvent), and quenched by pouring into saturated aqueous $NaHCO_3$ (5 mL/mL of reaction solvent). The reaction mixtures were shaken thoroughly, and the organic layer was separated and back-washed with water (equivolume). The solvent was evaporated in vacuo to give the products **3**, **9**, **12**, and **13** in yields shown in Table 1. The dehydration of **4** with *p*-toluenesulfonic acid in toluene at reflux utilized previously described conditions.[5]

3: mp 69–70 °C (hexanes) (lit.[5] mp 69–70 °C); ^{1}H-NMR δ 6.45 (t, J = 6.8 Hz, 1H, olefinic CH), 2.68 (m, 2H, allylic CH_2).

12 (liquid): bp 110–115 °C/8 mmHg, lit.[7] bp 113–115 °C/8 mmHg; ^{1}H-NMR δ 7.15-7.38 (complex m, 5H, ArH), 6.09 (t, J = 6.7 Hz, 1H, olefinic CH).

13: mp 163–164 °C (2-propanol), lit.[2] mp 163–163.5 °C; ^{1}H-NMR δ 7.12 (s, 1H, ArH), 6.17 (m, 1H, olefinic CH), 4.08 (m, 1H, CHOH).

Single Crystal X-ray Analysis of 9 and 11. Crystals of **9** and **11** were grown by slow cooling of hot saturated solutions of these compounds in 2,2,4-trimethylpentane.

9 ($C_{30}H_{32}S_2$): FW = 456.7, monoclinic space group $P2_1/c$, a = 7.495(2), b = 17.618(2), c = 18.382(1) Å, β = 97.27(1)°, V = 2407.8(7) Å^3, Z = 4, ρ_{calcd} = 1.257 mg mm^{-3}, λ(Cu Kα) = 1.54184 Å, μ = 2.10 mm^{-1}, F(000) = 972, T = 295 K.

11 ($C_{28}H_{28}S_2$): FW = 428.6, monoclinic space group $P2_1/n$, a = 10.988(2), b = 11.176(2), c = 18.198(3) Å, β = 92.32(1)°, V = 2232.9(7) Å^3, Z = 4, ρ_{calcd} = 1.275 mg mm^{-3}, λ(Cu Kα) = 1.54184 Å, μ = 2.240 mm^{-1}, F(000) = 912, T = 295 K. The following parameters are common to **9** and **11** and where different they are indicated by enclosure in brackets for **11**.

A clear colorless 0.10 × 0.24 × 0.36 [0.20 × 0.34 × 0.44] mm crystal was used for data collection on an automated Siemens R3m/V diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 25 centered reflections within $48 \le 2\theta \le 60°$ [$66 \le 2\theta \le 85°$]. The data collection range of hkl was: $0 \le h \le 8, 0 \le k \le 19, -20 \le l \le 19$, [$-12 \le h \le 12, 0 \le k \le 12, 0 \le l \le 19$], with $\{(\sin\theta)/\lambda\}_{max} = 0.55$. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.5 [1.9] % during the data collection. A set of 3712 [3560] reflections was collected in the $\theta/2\theta$ scan mode, with scan width [$2\theta(K_{\alpha1}) - 1.0$] to [$2\theta(K_{\alpha2}) + 1.0$]° and ω scan rate (a function of count rate) from 7.5 [10.0]°/min to 30.0°/min. There were 3307 [3062] unique reflections, and 1988 [2723] were observed with $F_o > 4\sigma(F_o)$. The structure was solved with SHELXTL[8] and refined with the aid of the SHELX93 system of programs. The full-matrix least-squares refinement varied 337 [292] parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C–H distances set to 0.96–0.93 Å, H angles idealized, U_{iso}(H) were set to 1.1 U_{eq}(C)]. Final residuals were R = 0.062 [0.040] with final difference Fourier excursions of 0.39 and −0.19 [0.22 and −0.22] eÅ^{-3}.

In both **9** and **11** (see ORTEP plots in Figures 1 and 2) the benzo[*b*]thienyl group is disordered such that the sulfur may be located on either side of the five-membered ring with nearly equal occupancy. The spiro-bonded seven-membered ring in **9** is also disordered. Tables of coordinates, bond distances and bond angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EW, England.

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