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Synthesis of heterospiranes by cyclization of dinucleophiles with 1,1-bis(tosyloxymethyl)cyclopropane and -cyclobutane

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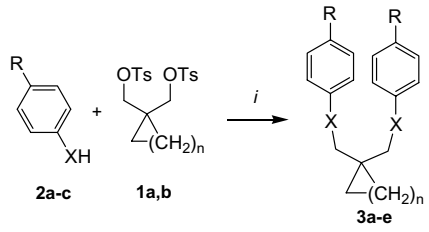
Abstract

A variety of heterocyclic spiranes were prepared by cyclization of dinucleophiles with 1,1-bis(tosyloxymethyl)cyclopropane and -cyclobutane.

Keywords: Cyclizations; Cyclopropanes; Cyclobutanes; Heterocycles; Spiranes

Spirocyclopropanes and -cyclobutanes are of considerable current interest, due to their pharmacological properties. For example, the illudins S and M represent cytotoxic constituents of the fungus *Omphalotus illudens*.[1] They possess a 1-hydroxyspiro[5.2]cyclooct-4-en-2-one structure. Synthetic analogues show a considerable anti-proliferative activity against human leukaemia HL 60 cells.[2] Spirocyclopropanes containing aromatic rings fused to the double bonds are present, for example, in the cytotoxic natural products CC-1065 and duocarmycin SA.[3] Spirocyclopropanes and spirocyclobutanes are also of considerable structural and theoretical interest.[4,5] However, these compounds are not readily available. In fact, known syntheses of heterocyclic spirocyclopropanes, which rely on cyclization reactions of 1,1-bis(bromomethyl)cyclopropane, suffer from very low yields and many side-reactions (vide infra). The synthesis of heterocyclic spirocyclobutanes has only scarcely been reported in the literature to date. Herein, we report a practical and high-yielding synthesis of various spirocyclopropanes and spirocyclobutanes based on cyclization reactions of 1,1-bis(tosyloxymethyl)cyclopropane and -cyclobutane. These reactions provide what is, to the best of our knowledge, the most efficient synthetic approach to heterocyclic spirocyclopropanes and -cyclobutanes at present.

Our strategy was benchmarked by the reaction of 1,1-bis(tosyloxymethyl)cyclopropane (**1a**), readily available in two steps from dimethyl cyclopropane-1,1-dicarboxylate,[5] with phenol (**2a**). The sodium hydroxide mediated reaction of **1a** with **2a** (DMF, 16 h, 160 °C) afforded 1,1-bis(phenyloxymethyl)cyclopropane (**3a**) in 60% yield (Scheme 1, Table 1). Noteworthy, the reaction of phenol with 1,1-bis(bromomethyl)cyclopropane was previously reported to give **3a** in only 8% yield.[6] The reaction of 4-bromophenol and 4-bromothiophenol with **1a** and its cyclobutane-analogue **1b** afforded the novel ethers and thioethers **3b–e** in good yields.



Scheme 1. Synthesis of **3a–e**. Reagents and conditions: (i) NaOH, DMF, 16 h, 160 °C.

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Table 1
Products and yields

3	n	X	R	%[a]
a	1	O	H	60[b]
b	1	O	Br	56
c	1	S	Br	72
d	2	O	Br	65
e	2	S	Br	72

[a] Isolated yields.
[b] Compound **3a** was previously prepared in 8% yield.[6]

The reaction of 1,2-dihydroxybenzene (**4a**) with 1,1-bis(bromomethyl)cyclopropane was previously reported to give spirocyclopropane **5a**, albeit, in only 7% yield.[7] The reaction of **4a** with bis(tosylate) **1a** afforded **5a** in 65% yield (Scheme 2, Table 2).[8] Spirocyclopropane **5b** was previously prepared from dithiol **4b** and 1,1-bis-(bromomethyl)cyclopropane in 28% yield.[6] The yield of **5b** could be again significantly improved (77%) by employment of **1a**. The cyclization of **4a** with 1,1-bis-(tosyloxymethyl)cyclobutane (**1b**) afforded the novel spirocyclobutane **5c** in a very good yield. The structure of **5c** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[9] The cyclization of **1b** with 1,2-dihydroxy-benzenes **4c** and **4d** afforded spirocyclobutanes **5d** and **5e**, respectively. The reaction of **1b** with 1,2-dihydroxy-3,5-di(*tert*-butyl)benzene (**4e**) was unsuccessful, due to the steric influence of the *tert*-butyl located next to the hydroxyl group. The cyclization of 2,3-dihydroxynaphthalene (**4f**) with **1a** and **1b** afforded spiranes **5g** and **5h** in very good yields, respectively. The cyclization of **4f** with 1,1-bis(bromomethyl)cyclopropane was previously reported to give **5g**, however, in only 6% yield.[7]

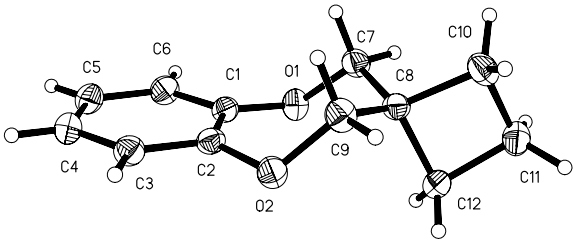
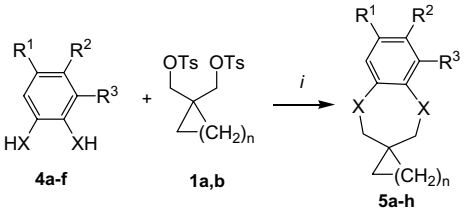


Fig. 1. ORTEP plot of **5c**.

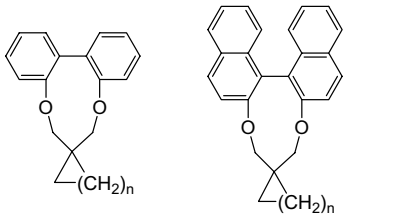


Scheme 2. Synthesis of spiranes **5a**–**h**. Reagents and conditions: (i) NaOH, DMF, 16 h, 160 °C.

Table 2
Products and yields

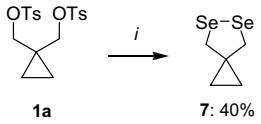
4	5	n	X	R^1	R^2	R^3	% (**5**)[a]
a	**a**	1	O	H	H	H	65 (7)
b	**b**	1	S	H	H	H	77 (28)
a	**c**	2	O	H	H	H	80
c	**d**	2	O	Me	H	H	60
d	**e**	2	O	*t*Bu	H	H	63
e	**f**	2	O	*t*Bu	H	*t*Bu	0
f	**g**	1	O	$-C_4H_4-$		H	77 (6)
f	**h**	2	O	$-C_4H_4-$		H	81

[a] Isolated yields; previously reported[7] yields of compounds **5** are given in parentheses.



6a (n = 1): 30% (10%)[7] **6c** (n = 1): 32% (9%)[7]
6b (n = 2): 49% **6d** (n = 2): 50%

Scheme 3. Synthesis of spiranes **6a**,**b**. Reagents and conditions: (i) NaOH, DMF, 16 h, 160 °C.



Scheme 4. Synthesis of diselenaspirane **7**. Reagents and conditions: (i) $NaBH_4$, Se, EtOH, 72 h, reflux.

The cyclization of **1a** and **1b** with (racemic) 2,2′-dihydroxybiphenyl afforded spiranes **6a** and **6b**, respectively (Scheme 3). Spiranes **6c** and **6d** were prepared by cyclization of **1a**,**b** with (racemic) 2,2′-dihydroxybinaphthyl. The synthesis of spirocyclopropanes **6a** and **6c** was previously reported, albeit, in only 10% and 9% yield, respectively.[7]

The cyclization of **1a** with disodium diselenide,[10a] generated in situ by the reaction of sodium boronhydride with selenium in ethanol,[10b] afforded the novel 2,3-diselenaspiro[2.4]cycloheptane (**7**) (Scheme 4). The synthesis of the sulfur analogue of **7** was previously reported.[11]

In conclusion, an efficient method for the synthesis of heterocyclic spiranes based on cyclization reactions of dinucleophiles with 1,1-bis(tosyloxymethyl)cyclopropane and -cyclobutane was reported. These reactions provide a convenient access to spirocyclopropanes and -butanes, which are not readily available by other methods.

Acknowledgement

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8. *Typical procedure*: A solution of 1,1-bis(tosyloxy)cyclopropane **1a** (205 mg, 0.50 mmol), NaOH (46 mg, 1.15 mmol), catechol (**4a**) (58 mg, 0.53 mmol) and DMF (10 mL) was heated in a sealed tube for 16 h at 160 °C. After cooling to room temperature, water (50 mL) was added and the solution was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate = 5:1) to give spirane **5a** (57 mg, 65%) as a colourless solid; mp 68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (s, 4H, CH_2), 3.90 (s, 4H, OCH_2), 6.94–6.97 (m, 2H, Ar), 6.99 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.2 (2 CH_2), 23.0 (C), 78.3 (2 OCH_2), 122.1 (2 CH_{Ar}), 123.8 (2 CH_{Ar}), 151.4 (2C_{Ar}). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3377 (br, m), 2924 (s), 2855 (s), 1596 (m), 1492 (s), 1456 (s), 1260 (br, m), 752 (br, m). MS (EI, 70 eV): *m/z* (%) = 176 ($[M]^+$, 49), 148 (100), 121 (22), 110 (37), 80 (13), 67 (25), 52 (20). HRMS (EI): ($[M]^+$) calcd for $C_{11}H_{12}O_2$, 176.08318; found, 176.08285.
9. CCDC 665157 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.
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