A Facile and Efficient Synthesis of Thieno[3,2-*c*]- and Thieno[2,3-*c*]azepine Derivatives

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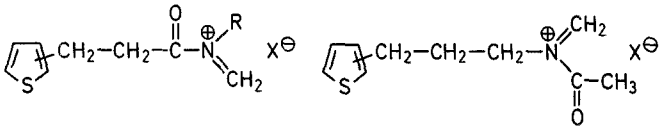
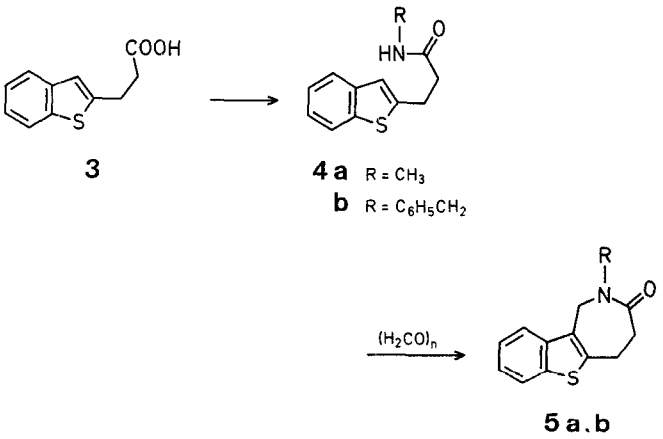
The 2-benzazepine skeleton is a key component of some Amaryllidaceae alkaloids[1] and 2-benzazepine derivatives are of interest to medicinal chemists because of their potential biological activities[2]. Much attention has been devoted to a synthesis of sulfur isosters of physiologically active compounds[3] for biological evaluation, since they often display similar or more effective activities than the parent compounds. Replacement of the benzene ring by thiophene has been used to get effective drugs[4]. Although 2-benzazepines, similar to isoquinolines, are easily obtained[2], it is difficult to prepare thienoazepines by these methods. In view of the current interests, synthetic efforts towards thieno[3,2-*c*]- and thieno[2,3-*c*]-azepines would be significant from both pharmacological and heterocyclic chemical points of view. We thus investigated a ring closure of two types of reactive *N*-acyliminium salts[5] **1** and **2** aimed at an efficient synthesis of thienoazepines.



1 **2**

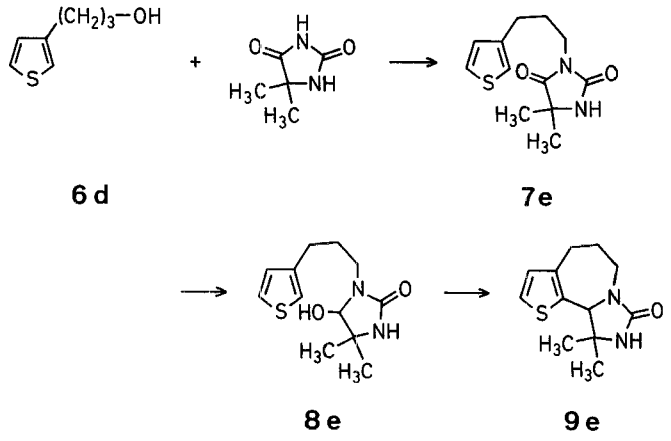
First, we explored cyclization of compounds of type **1**. The amides **4a** and **4b**, prepared from benzo[*b*]thieno-2-propanoic acid **(3)**[6] in the usual way, were heated with paraformaldehyde in formic acid at 60 °C for 14 h to yield the corresponding benzo[*b*]thieno[3,2-*c*]azepines **5a** and **5b**, respectively.

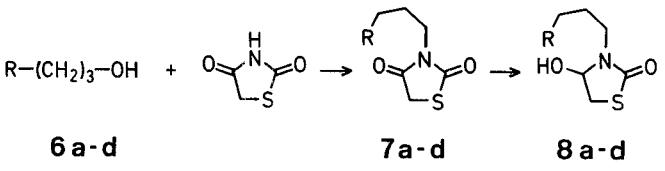


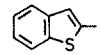
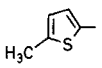
3 **4a** R = CH_3 **b** R = $C_6H_5CH_2$

5a,b

The effective synthesis of thienoazepines fused with other heterocycles was realized by cyclization of compounds of type **2**. 3-(2-Benzo[*b*]thienyl)-propyl alcohol **(6a)**[7], 3-(2-thienyl)-propyl alcohol **(6b)**[8], 3-(5-methyl-2-thienyl)-propyl alcohol **(6c)**[9] and 3-(3-thienyl)-propyl alcohol **(6d)**[8] were coupled with 2,4-thiazolidinedione[10], by a reported method[11] with the exception that diisopropyl azodicarboxylate was used instead of diethyl azodicarboxylate, to give the corresponding *N*-substituted 2,4-thiazolidinediones **7a–d**, respectively. *N*-Substituted 5,5-dimethylhydantoin **(7e)** was also obtained from **6d** and 5,5-dimethylhydantoin by the same procedure. The products **7a–e** were reduced with diisobutylaluminium hydride in toluene at −78 °C for 1 h to afford the corresponding hydroxy derivatives **8a–e**, which were subjected to the cyclization reaction without purification. Treatment of **8b** with formic acid at room temperature for 14 h gave the dehydration product **10** and formation of the cyclization product **9b** was not observed. However, **8a–e** were heated under reflux with trifluoroacetic acid for 3 h to give the corresponding cyclization products **(9a–e)**, respectively.





6,7,8	a	b	c	d
R				

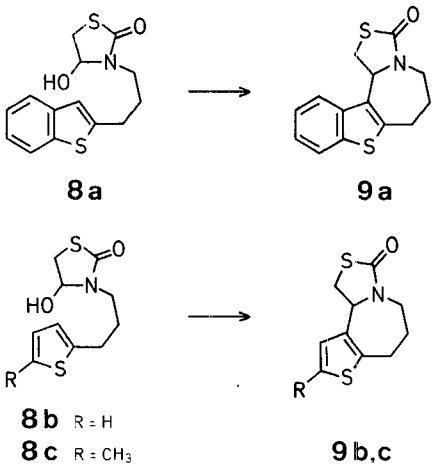
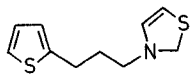


Table. Compounds **5**, **7**, and **9** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. *m/e* [M^+]
5a	45	164–165°	$C_{13}H_{13}NOS$ (231.3)	2.9–3.3 (m, 4H); 3.10 (s, 3H); 4.62 (s, 2H); 7.2–7.5 (m, 3H); 7.6–7.8 (m, 1H)	231
5b	47	122–123°	$C_{19}H_{17}NOS$ (307.4)	2.9–3.2 (m, 4H); 4.35 (s, 2H); 4.62 (s, 2H); 7.1–7.3 (m, 8H); 7.6–7.8 (m, 1H)	307
7a	55	74–76°	$C_{14}H_{13}NO_2S_2$ (291.4)	1.8–2.1 (m, 2H); 2.84 (t, 2H, J=7 Hz); 3.64 (s, 2H); 3.60 (t, 2H, J=7 Hz); 6.99 (s, 1H); 7.2–7.3 (m, 3H); 7.6–7.8 (m, 1H)	291
7b	62	oil	—	1.8–2.2 (m, 2H); 2.88 (t, 2H, J=7 Hz); 3.71 (t, 2H, J=7 Hz); 3.88 (s, 2H); 6.8–7.0 (m, 2H); 7.1–7.2 (m, 1H)	241
7c	58	oil	—	1.8–2.1 (m, 2H); 2.42 (s, 3H); 2.78 (t, 2H, J=7 Hz); 3.69 (t, 2H, J=7 Hz); 3.86 (s, 2H); 6.60 (s, 2H)	255
7d	60	oil	—	1.8–2.1 (m, 2H); 2.34 (t, 2H, J=7 Hz); 3.68 (t, 2H, J=7 Hz); 3.81 (s, 2H); 6.9–7.1 (m, 1H); 7.2–7.4 (m, 2H)	241
7e	57	oil	—	1.40 (s, 6H); 1.8–2.1 (m, 2H); 2.68 (t, 2H, J=7 Hz); 3.56 (t, 2H, J=7 Hz); 7.0–7.1 (m, 1H); 7.2–7.6 (m, 2H)	252
9a	65	oil	—	1.6–2.1 (m, 1H); 2.2–2.5 (m, 1H); 2.6–3.8 (m, 5H); 4.1–4.4 (m, 1H); 5.40 (dd, 1H, J=7 Hz, 18 Hz); 6.8–7.6 (m, 3H); 7.7–7.9 (m, 1H)	275
9b	67	117–118°	$C_{10}H_{11}NOS_2$ (225.3)	1.7–2.2 (m, 2H); 2.7–3.7 (m, 5H); 4.2–4.4 (m, 1H); 5.02 (t, 1H, J=7 Hz); 6.96 (d, 1H, J=5 Hz); 7.13 (d, 1H, J=5 Hz)	225
9c	65	110–112°	$C_{11}H_{13}NOS_2$ (239.3)	1.7–2.2 (m, 2H); 2.7–3.7 (m, 5H); 4.2–4.4 (m, 1H); 5.02 (t, 1H, J=7 Hz); 6.96 (d, 1H, J=5 Hz); 7.13 (d, 1H, J=5 Hz)	239
9d	67	82–83°	$C_{10}H_{11}NOS_2$ (225.3)	1.6–2.0 (m, 2H); 2.6–3.8 (m, 5H); 4.2–4.5 (m, 1H); 5.16 (dd, 1H, J=4 Hz, 6 Hz); 6.86 (d, 1H, J=5 Hz); 7.17 (d, 1H, J=5 Hz)	225
9e	65	157–158°	$C_{12}H_{16}N_2OS$ (236.3)	1.01 (s, 3H); 1.48 (s, 3H); 1.6–2.0 (m, 1H); 2.1–2.3 (m, 1H); 2.5–3.2 (m, 3H); 3.9–4.2 (m, 1H); 4.66 (s, 1H); 6.84 (d, 1H, J=5 Hz); 7.19 (d, 1H, J=5 Hz)	236

[a] Satisfactory microanalyses obtained: C ±0.26, H ±0.22, N ±0.18.

8d 9d



10

N-Methyl-2-benzo[*b*]thienylpropanamide (4a):
A mixture of **3** (2.06 g, 10 mmol), thionyl chloride (1.43 g, 12 mmol), and dry benzene (40 ml) is heated under reflux for 2 h. After cooling, to this stirred solution methylamine hydrochloride (1.35 g, 20 mmol) and sodium carbonate (2.12 g, 20 mmol) are added under ice-cooling. After 5 min, water (5 ml) is added at the same temperature under stirring. After stirring at room temperature for 14 h, the mixture is washed with water (20 ml), dried with sodium sulfate, and evaporated to give **4a**; yield: 1.7 g (78%); m.p. 131–132 °C.

$C_{12}H_{13}NOS$	calc.	C 65.72	H 5.98	N 6.39
(219.3)	found	65.46	6.06	6.20

N-Benzyl-2-benzo[*b*]thienylpropanamide (4b):
A mixture of **3** (2.06 g, 10 mmol), thionyl chloride (1.43 g, 12 mmol), and benzene (40 ml) is heated under reflux for 2 h. After cooling, to this stirred solution triethylamine (10 ml) and benzylamine (1.07 g, 10 mmol) are added under ice-cooling. After stirring for 5 h, the mixture is washed with 10% sodium hydroxide solution (30 ml), 10% hydrochloric acid (30 ml), and water (30 ml). Removal of the solvent gives **4b**; yield: 2.51 g (85%); m.p. 147–148 °C.

$C_{18}H_{17}NOS$	calc.	C 73.19	H 5.80	N 4.75
(295.4)	found	72.91	5.68	4.67

2-Substituted 2,3,4,5-Tetrahydro-1*H*-benzo[*b*]thieno[3,2-*c*]azepin-3-ones (5a) and (5b):
A mixture of the amide **4** (10 mmol), paraformaldehyde (1.6 g, 50 mmol), and formic acid (25 ml) is heated at 60 °C under stirring for 14 h. After evaporation of the formic acid, the mixture is extracted with chloroform (100 ml). The extract is washed with water (50 ml), dried with sodium sulfate, and evaporated. The resulting residue is chromatographed over silica gel (15 g) using benzene as an eluent. Removal of the solvent affords **5** (Table).

Compound 7a–e; General Procedure:
To a stirred mixture of **6** (20 mmol), triphenylphosphine (5.2 g, 20 mmol), 2,4-thiazolidinedione (2.34 g, 20 mmol), and dry tetrahydrofuran (30 ml) a solution of diisopropyl azodicarboxylate (4.04 g, 20 mmol) in tetrahydrofuran (15 ml) is added under ice-cooling. For the preparation of **7e**, 5,5-dimethylhydantoin (3.16 g, 20 mmol) is used. After stirring for 14 h at room temperature, the solvent is evaporated. The resulting residue is chromatographed over silica gel (30 g) using benzene/hexane (1 : 1) as eluent. The products are collected by monitoring with T.L.C. to give **7** as oils, except for **7a**, which are used without further purification.

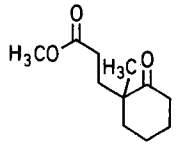
Compounds 9a–e; General Procedure:
To a stirred solution of **7** (10 mmol) in dry toluene (40 ml) diisobutylaluminum hydride (2.84 g, 13.1 ml of 25% toluene solution, 20 mmol) is added at −78 °C under a nitrogen atmosphere. After stirring for 1 h, the mixture is decomposed with 5% sulfuric acid (50 ml) and extracted with chloroform (100 ml). The extract is washed with water (50 ml), dried with sodium sulfate, and evaporated. The residue is heated with trifluoroacetic acid (20 ml) under reflux for 3 h. The mixture is made basic with 28% ammonia (25 ml) and extracted with chloroform (25 ml). The extract is washed with water (50 ml), dried with sodium sulfate, and evaporated. The residue is chromatographed over silica gel (15 g) using benzene as eluent. Evaporation of the solvent affords **9** (Table).

Received: January 24, 1983

[1] T. Kametani, *The Chemistry of The Isoquinoline Alkaloids*. Vol. 1, Hirokawa Publishing Company, Inc., Tokyo, 1968.
[2] S. Kapark, *Adv. Heterocycl. Chem.* **17**, 45 (1974).
[3] For instance, (a) K. C. Nicolau, W. E. Barnette, G. P. Gacic, R. L. Magolda, *J. Am. Chem. Soc.* **99**, 7736 (1977).
(b) M. Shibasaki, S. Ikegami, *Tetrahedron Lett.* **1978**, 559.
[4] For instance, (a) M. Nakanishi, T. Tahara, K. Araki, M. Shiraki, T. Tsumagari, Y. Takigawa, *J. Med. Chem.* **16**, 214 (1973).
(b) F. Tinney, J. P. Sanches, J. A. Nogas, *J. Med. Chem.* **17**, 624 (1974).
[5] J. A. M. Hamersma, W. N. Speckamp, *Tetrahedron Lett.* **23**, 3811 (1982), and references cited therein.
[6] W. Ried, H. Bender, *Chem. Ber.* **88**, 34 (1955).
[7] A. H. A. Tinnemans, D. C. Neckers, *J. Org. Chem.* **43**, 2493 (1978).
[8] P. Cagninant, G. Merle, D. Cagninant, *Bull. Soc. Chim. Fr.* **1970**, 308.
P. Cagninant, G. Marle, *C. R. Acad. Sci. Paris, Ser. C* **267**, 156 (1968).
[9] V. G. Kharchenk, N. A. Markushina, T. I. Gubina, *Dokl. Akad. Nauk SSSR* **255**, 1144 (1980); *C. A.* **94**, 192031 (1981).
[10] Commercially available from Aldrich Chemical Co.
[11] O. Mitsunobu, W. Wada, T. Sano, *J. Am. Chem. Soc.* **94**, 679 (1972).

J. K. Whitesell, M. A. Whitesell, *Synthesis* **1983** (7), 517–536:

Compound **14** (p. 521) should be named 3-methoxycarbonylmethyl-8a-methyl-5-methylene-2-oxo-6-(2,2-dimethylpropanoyloxy)-*trans*-decalin. The structure of compound **25** (p. 522) should be:



25

T. Kolasa, *Synthesis* **1983** (7), 539:

The heading for the 6th column in the Table should be (*Z*/*E*)-Ratio.

S. Kano, Y. Yuasa, T. Yokomatsu, S. Shibuya, *Synthesis* **1983** (7), 585–587:

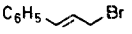
Compounds **5** should be named 3-oxo-2,3,4,5-tetrahydro-1*H*-azepino[4,3-*b*][1]benzothiophenes.

M. Sawada, Y. Furukawa, Y. Takai, T. Hanafusa, *Synthesis* **1983** (7), 593–595:

Compounds **4** and **5** should be named 2,4-dialkyl-1,3,6-trioxo-2,3,4,4a,5,6-hexahydro-1*H*-[1,3,5]triazino[1,2-*a*]quinolines and 1,3-dimethyl-2,4,8-trioxo-1,2,3,4,7,8-hexahydro-8a*H*-pyrido[1,2-*a*][1,3,5]triazine, respectively.

R. B. Cheikh, R. Chaabouni, A. Laurent, P. Mison, A. Nafti, *Synthesis* **1983** (9), 685–700:

The first substrate in Table 3 (p. 689) should be:



Y. Imai, A. Mochizuki, K. Kakimoto, *Synthesis* **1983** (10), 851:

The title compounds **4** should be named 4*H*-1,2,4-benzothiadiazine 1,1-dioxides.

R. Rastogi, S. Sharma, *Synthesis* **1983** (11); 861–882:

Compound **109** (p. 870) should be named: 7,12-dioxo-6,7-dihydro-12*H*-benzimidazo[1,2-*b*][2,4]benzodiazepine.

P. Kutschy, J. Imrich, J. Bernát, *Synthesis* **1983** (11), 929–931:

The title compounds **4** should be named 2-amino-4-oxo-4*H*-[1]benzothieno[2,3-*e*]-1,3-thiazines.

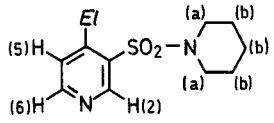
P. Breant, M. Marsais, G. Quéguiner, *Synthesis* **1983** (10), 822–824:

The following data should be added to the ^{1}H-N.M.R. spectra of compounds **3a–c** (p. 824):

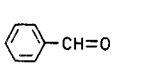
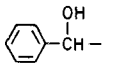
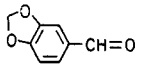
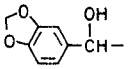
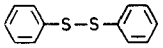
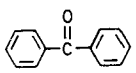
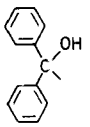
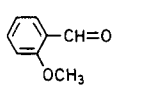
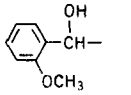
For compounds **3a–c**, $J_{H\text{-}4,H\text{-}5}$ = 8 Hz; $J_{H\text{-}5,H\text{-}6}$ = 5 Hz; $J_{H\text{-}4,H\text{-}6}$ = 2 Hz; $J_{H\text{-}4,H\text{-}2}$ = 2 Hz.

Tables 1 and 2 (p. 823) should be read as follows:

Table 1. 4-Substituted 3-Piperidinosulfonylpyridines prepared



5a, 7a-10a

Electrophile	*El*	Product	Yield [%]	m.p. [°C]	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][b]
		**5a**	80	127°	$C_{17}H_{18}N_2O_3S$ (330.4)	1.5 [m, 6 H(b)]; 3.1 [m, 4 H(a)]; 4.0 (m, OH); 5.3 (m, 1 H); 6.7 (m, 5 H); 7.53 (d, H-5); 8.63 (d, H-6); 8.93 (s, H-2)
		**7a**	60	80° (dec)	$C_{18}H_{18}N_2O_5S$ (374.4)	1.6 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 5.96 (s, 2 H); 6.63 (s, 1 H); 6.9 (m, 3 H); 7.50 (d, H-5); 8.86 (d, H-6); 8.93 (s, H-2)
$(H_3C)_3Si-Cl$	$(H_3C)_3Si-$	**8a**	42	<50°	$C_{13}H_{20}N_2O_2SSi$ (296.5)	0.50 (s, 9 H); 1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 7.70 (d, H-5); 8.70 (d, H-6); 8.95 (s, H-2)
		**9a**	80	82°	$C_{16}H_{16}N_2O_2S_2$ (332.4)	1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 6.70 (d, H-5); 7.56 (s, 5 H); 8.30 (d, H-6); 8.93 (s, H-2)
		**6a**	95	195°	$C_{23}H_{22}N_2O_3S$ (406.5)	1.5 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 6.70 (s, OH); 6.75 (d, H-5); 7.30 (s, 10 H); 8.51 (d, H-6); 9.06 (s, H-2)
		**10a**	53	164°	$C_{18}H_{20}N_2O_4S$ (360.4)	1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 3.70 (s, 3 H); 4.2 (m, OH); 6.70 (s, 1 H); 7.15 (d, H-5); 7.5 (m, 4 H); 8.80 (d, H-6); 9.06 (s, H-2)
–	–	**12**	–	–	–[c]	1.7 [m, 6 H(b)]; 3.3 [m, 4 H(a)]; 4.6 (m, OH); 5.96 (d, 1 H, J = 3 Hz); 7.85 (d, H-5); 8.86 (d, H-6); 9.00 (s, H-2)
–	–	**13**	–	–	–[c]	1.7 [m, 6 H(b)]; 3.3 [m, 4 H(a)]; 5.83 (d, 1 H, J = 3 Hz); 7.60 (d, H-5); 8.83 (d, H-6); 9.13 (s, H-2)

[a] Satisfactory microanalyses obtained: C ±0.38, H ±0.32, N ±0.14; exception: **7**: C −0.70%.

[b] $J_{H\text{-}5,H\text{-}6}$ = 5 Hz for all products.

[c] See text.