Thiazepine moiety-controlled regioselective rearrangements of 7-oxanorbornadiene derivatives†‡

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We have discovered thiazepine moiety-controlled regioselective skeletal rearrangements of 7-oxanorbornadiene derivatives (2, 7 and 12) with high regioselectivity and/or diastereoselectivity in the presence of Brønsted acid.

Due to the prevalence of thiazepine,[1] oxabicyclo[2.2.1],[2] and thiazole[3] cores in natural products as well as pharmaceuticals, ring transformations of these heterocycles are of particular interest both synthetically and theoretically.[4,5] While the acid-induced ring-opening of 7-oxanorbornadienes (**1**) is known,[2c,d] ring rearrangement reactions of their heterocyclic annulated derivatives have scarcely been investigated, in a way, because these substrates could not be easily constructed. Recently, we have disclosed a facile synthetic route to a new polycyclic architecture comprising a 1,4-thiazepine annulated to **1** (Fig. 1, **2**, **7** and **12**).[6] Intrigued by their unique skeletal structures, we have focused our efforts on the ring-opening reaction of these compounds. Herein, we wish to describe the regioselective Brønsted acid-induced rearrangements of thiazepine-fused 7-oxanorbornadienes (with an ester group at one of the bridgehead positions) rendering a set of heterocyclic compounds in good to excellent yields. Notably, these processes were controlled by thiazepine moiety and, as a result, a direct ring contraction of 1,4-thiazepine into thiazole ring was observed for the first time under acidic conditions.[7]

In a piloting experiment of keto-ester **2a** with CF_3CO_2H (TFA) in the presence of methanol, a regioselective ring-opening reaction of **2a** was observed to furnish *Z*-1-(thiazol-2-(3*H*)-ylidene)-2-one **3a** and dihydroisobenzofuran **4a** as the products (Scheme 1, Table 1, entry 1). The reaction was found not sensitive to moisture. Stronger acids such as conc. HCl, conc. H_2SO_4, *p*TsOH and TfOH conducted the *trans*-esterification reaction of **4a** simultaneously, thereby to give mixtures of **4a** and **5**, or **5** exclusively in addition to **3a** upon the reaction conditions.[8]

A series of keto-esters **2** involving various substituents afforded the corresponding (*Z*)-**3** and **4** in good to excellent yields by using a stoichiometric amount of TFA (Scheme 1, Table 1). It was shown that the substrates with electron-donating R^5 and R^6 groups were more reactive than those having electron-withdrawing groups. For example, **2e** was transformed into **3a** and **4e** in 97% yield within 0.5 h (Table 1, entry 5), while a huge excess of TFA (20 equiv.) was needed to convert **2b** after 21 h. In addition, the products **4h** (R^4 = Et) and **4i** (R^4 = Me) were constructed in the *Z*-configuration exclusively (Table 1, entries 8 and 9).[9]

Given the action of methanol, compound **2a** was studied as a model substrate to react with several other alcohols in the presence of TFA. As shown in Scheme 2, cyclohexanol, 2,2,2-trifluoroethanol, ethylene glycol, benzyl thiol and benzyl alcohol were well tolerated in the reaction, affording the corresponding products **6a–e** in addition to **3a** in 82–93% yields, respectively.

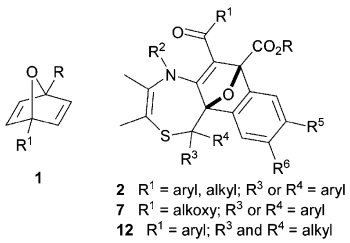
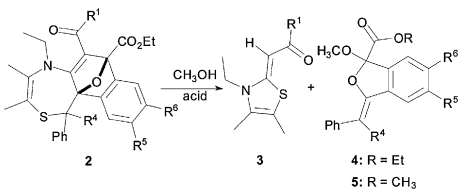


Fig. 1 Structures of substrates **2**, **7** and **12**.



Scheme 1 Brønsted acid-induced reactions of **2** in methanol.

Table 1 The fragmentations of **2a–k** in the presence of TFA[a]

Entry	2	R^1	R^4	R^5, R^6	t^b/h	Products[c] (%)
1	**2a**	4-BrC_4H_6	Ph	H, H	3	**3a** + **4a**, 92
2[d]	**2b**	4-BrC_4H_6	Ph	F, F	21	**3a** + **4b**, 82
3	**2c**	4-BrC_4H_6	Ph	CH_3, CH_3	3	**3a** + **4c**, 93
4	**2d**	4-BrC_4H_6	Ph	$-(CH_2)_3-$	3	**3a** + **4d**, 95
5	**2e**	4-BrC_4H_6	Ph	$-O(CH_2)_2O-$	0.5	**3a** + **4e**, 97
6	**2f**	4-BrC_4H_6	Ph	Ph, H	2.5	**3a** + **4f**, 95
7	**2g**	4-BrC_4H_6	Ph	Ph, H	2.5	**3a** + **4g**, 95
8	**2h**	4-BrC_4H_6	Et	H, H	3	**3a** + **4h**, 91
9	**2i**	4-BrC_4H_6	Me	H, H	3	**3a** + **4i**, 92
10	**2j**	Ph	Ph	H, H	3	**3b** + **4a**, 94
11	**2k**	*t*-Bu	Ph	H, H	3	**3c** + **4a**, 84

[a] Unless otherwise specified, the reaction was performed at 0.065 M with 100 mol% of Brønsted acid in MeOH–CH_2Cl_2 (1 : 5) at RT. [b] Time for consuming the starting material. [c] Yield of isolated products **4**. [d] 20 equiv. TFA was used.

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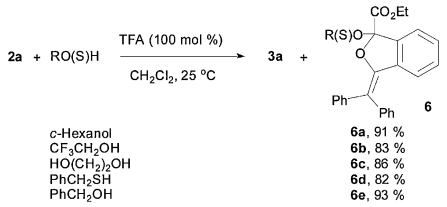
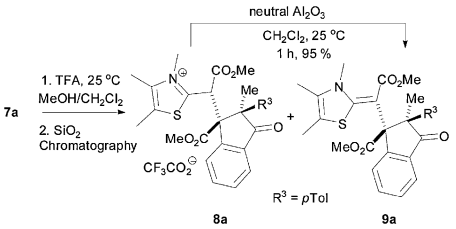
† Electronic supplementary information (ESI) available: Experimental details, ^1H and ^{13}C NMR data for all new products. CCDC 653549 (**3a**), 653550 (**5**), 653551 (**8a**), 653552 (**9b**) and 682292 (**13b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b813371a



Scheme 2 Reactions of **2a** with various alcohols.



Scheme 3 The rearrangement of **7a** to **8a** and **9a**.

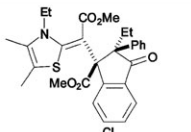
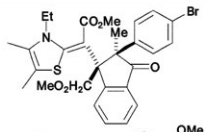
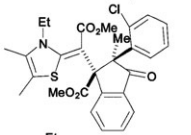
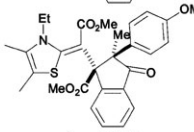
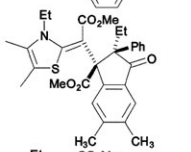
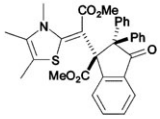
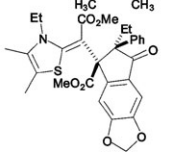
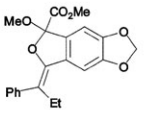
Surprisingly, in contrast to their keto ester analogous of **2**, diester **7a** gave a mixture of ionic-type product **8a** and indan-1-one **9a** (*ca.* 10 : 1 by TLC) under the same conditions (Fig. 1, Scheme 3). Nevertheless, **8a** was found unstable in solvent and slowly lost one molecule of TFA to yield **9a**. Further experiments revealed that treatment of **8a** with neutral Al_2O_3 in CH_2Cl_2 accelerated the exclusion of TFA to cleanly afford **9a** as a single product in excellent yield.

Purified by neutral Al_2O_3 chromatography instead silica gel, a variety of indan-1-ones **9b–g** were derived from the corresponding diesters **7b–g**, respectively (Scheme 3, Table 2). The more crowded substrates led to the desired products, such as **9d** and **9g**, in diminished yields presumably due to the steric hindrance in the cyclization steps (Table 2, entries 3 and 6). Exceptionally, ester **7h** bearing powerful electron-donating groups (–OCH_2O–) gave indan-1-one **9h** along with dihydroisobenzofuran **10** in 16% yield (Table 2, entry 7). Of primary importance, all reactions performed in this study resulted in the selective formation of a single diastereomer.[10]

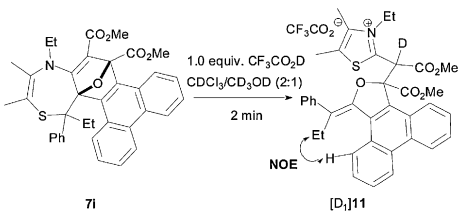
We therefore deduced that the rearrangement reactions of **2** and **7** proceeded *via* a similar intermediate. Further *in situ* NMR experiments of **7a** and **7i** demonstrated that a ring contraction of the thiazepine moiety to a thiazole ring proceeded, at least formally, prior to the cleavage of the oxa-bridge in current cascade procedures (Scheme 4).[11]

A sharply different ring-opening of keto esters **12a–c** (both R^3 and R^4 are alkyl groups) was observed resulting in unique spirocyclic products **13a–c** in good yields (Scheme 5). In this case, the heterolytic cleavage of the oxa-bridge of **12a–c** did not occur as the classical sequence induced by Brønsted acid. As for substrate **12a**, the reaction gave only trace amount of the product in the absence of methanol; however, the yield of **13a** could not be improved when the reaction was run in large excess of H_2O, although it was shown that one molecule of H_2O was added to construct the final product. Moreover, trifluoroacetic anhydride could also give the rearranged product **13a** upon treatment with water or silica gel. These results demonstrated that the tandem process was completed *via* a terminal hydrolyzation step. It is noteworthy that the complicated thiazepinone derivative of **13b** with two spirocyclic units could be easily constructed *via* this strategy.

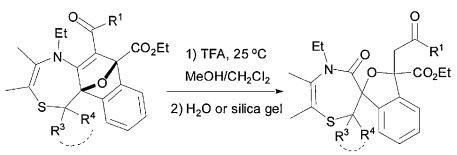
Table 2 The products **9b–9h** and **10** from substrates **7b–h**[a]

Entry	Product[b]		Entry	Product[b]	
1		**9b** 96%	2		**9c** 93%
3		**9d** 72%	4		**9e** 90%
5		**9f** 93%	6		**9g** 66%
7		**9h** 79%	and		**10** 16%

[a] The reaction was performed at 0.065 M with 1.0 equiv. TFA at RT in MeOH–CH_2Cl_2 (1 : 5). [b] Yield of isolated products.



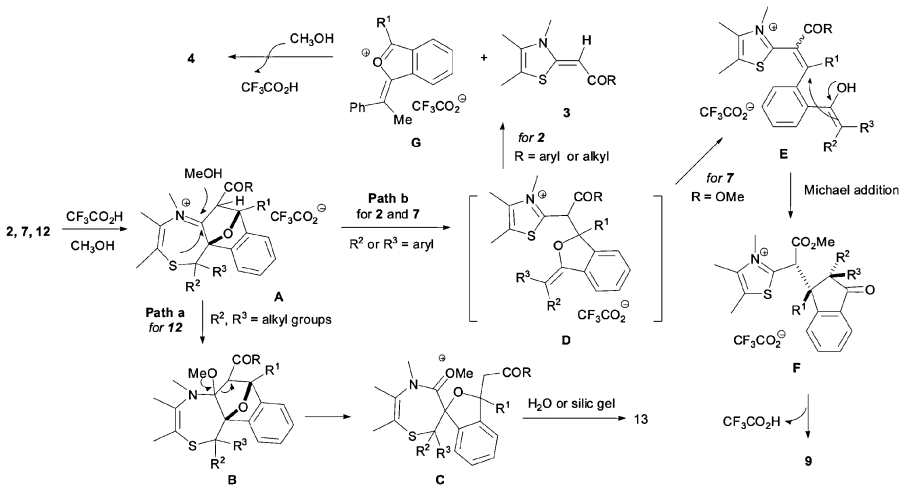
Scheme 4 The *in situ* NMR experiment of **7i**.



12a-c	R^1	R^3	R^4	Yield	13a-c
13a	4-BrC_6H_4	Me	Me	92%	
13b	4-BrC_6H_4	-$(C_2H_6)_5$-		90%	
13c	4-MeC_6H_4	Me	Et	87%	

Scheme 5 Rearrangements of compounds **12a–c**.

Proposed mechanisms for these Brønsted acid-triggered regioselective rearrangements of **2**, **7** and **12** are disclosed in Scheme 6. Thus, triggered by TFA, the iminium salt **A** was initially generated instead of a heterolytic cleavage of the ether bridge in the oxabicyclic core. In path a, as for keto esters **12** (R^2, R^3 = alkyl), a nucleophilic addition of MeOH onto **A** resulted in intermediate **B**, followed by an acyl cleavage to yield oxonium **C**. Subsequent hydrolyzation of **C** afforded the product **13** *via* silica gel chromatography, while for substrates **2** and **7** (R^2 or R^3 = aryl, in path b), the ring rearrangement of **A** into **D** was performed.[12] In the next steps, as for diester **7** (R = OMe), the isomerization of **D** to enol **E** was followed by an intramolecular Michael addition to give **F**, which was converted into indan-1-one **9** by spontaneous or neutral Al_2O_3-assisted exclusion of TFA. On the other hand, for keto



Scheme 6 Proposed mechanism for the rearrangements of **2**, **7** and **12**.

esters **2** (R = aryl, alkyl), probably due to the stronger electron-withdrawing effects of ketone group, salt **D** was directly split into **3** and intermediate **G**, which was intercepted by MeOH to furnish dihydroisobenzofuran **4**.

In conclusion, we have discovered three unprecedented 1,4-thiazepine moiety-controlled skeletal rearrangements of easily available 7-oxanorbornadiene derivatives induced by Brønsted acid. The mechanistic course of these novel rearrangements including the factors responsible for promoting the pathways over the conventional sequence was explored. Further studies into the mechanism details, scope, and synthetic applications of the current methodology are ongoing.

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Notes and references

‡ *Crystal data*: for **3a**: $C_{15}H_{16}BrNOS$; M = 338.26; T = 295(2) K; triclinic; space group: $P\bar{1}$; a = 6.952(4), b = 7.636(6), c = 15.489(11) Å, α = 78.16(3), β = 87.74(3), γ = 66.38(3)°, V = 736.4(9) Å^3; Z = 2; reflections collected: 7311, unique: 3345; R_{int} = 0.0244; R_1 = 0. 0392, wR_2 = 0.0798 (observed data). For **5**: $C_{24}H_{20}O_4$; M = 372.40; T = 295(2) K; monoclinic; space group: $P2_1/c$; a = 11.979(4), b = 8.876(4), c = 18.629(7) Å, β = 98.484(14)°, V = 1959.1(13) Å^3; Z = 4; reflections collected: 18 781, unique: 4476; R_{int} = 0.0285; R_1 = 0.0408, wR_2 = 0.0962 (observed data). For **8a**: $C_{60}H_{70}F_6N_2O_{19}S_2$; M = 1301.30; T = 293(2) K; triclinic; space group: $P\bar{1}$; a = 14.258(3), b = 15.677(3), c = 17.381(4) Å, α = 97.49(3), β = 106.18(3), γ = 115.38(3)°, V = 3228.4(19) Å^3; Z = 2; reflections collected: 26 071, unique: 11 577; R_{int} = 0.0680; R_1 = 0.1158, wR_2 = 0.3182 (observed data). Attempts to control the geometry in the disordered solvent groups C(60), F(4)–F(9) and C(59)–O(11) failed. It was not possible to find the hydrogen atoms on O(3W). The final *R*-factors and residual electron density are high due to the poor modelling of the disordered solvent molecules. For **9b**: $C_{29}H_{31}NO_5S$; M = 505.61; T = 295(2) K; triclinic; space group: $P\bar{1}$; a = 9.0846(18), b = 11.400(2), c = 13.728(3) Å, α = 89.60(3), β = 77.09(3), γ = 72.33(3)°, V = 1317.7(5) Å^3; Z = 2; reflections collected: 9633, unique: 4525; R_{int} = 0.0414; R_1 = 0.0452, wR_2 = 0.1184 (observed data). For **13b**: $C_{32.50}H_{38.50}BrNO_{5.75}S$; M = 647.11; T = 296(1) K; monoclinic; space group: $P2_1/c$; a = 26.911(1), b = 10.0719(3), c = 27.669(1) Å, β = 116.880(1)°, V = 6689.3(4) Å^3; Z = 8; reflections collected: 46 569, unique: 11340; R_{int} = 0.0561; R_1 = 0.0754, wR_2 = 0.2164 (observed data). The bond lengths C(58)–C(59) and C(63)–C(64) are too short due to the impossibility of modelling disorder or restraining the geometry in these groups. The solvent molecules O(1)–C(81)–C(82), O(1W) and O(2W) have been refined with isotropic displacement parameters due to unmodelled disorder.

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8 Compound **4a** can be converted into **5** by catalytic TfOH in almost quantitative yield after 1 h.

9 *E*-configuration products were not evident by ^{1}H NMR analysis of the crude reaction mixtures.

10 Diastereomeric products were not evident by ^{1}H NMR analysis of crude reaction mixtures.

11 The structure of [D_1]**11** was determined by 2DNMR (DEPT 135, COSY, NOESY, HMQC, HMBC) and HRMS (ESI). **7a** was first converted into a pair of isomers with similar structures to [D_1]**11**, and that these isomers could be transformed into **9a** by neutral Al_2O_3 exclusively, see ESI†.

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