Heteroatom Chemistry
Volume 25, Number 1, 2014

A Novel Rearrangement Reaction of *N*-Acyliminium Ions Leading to Heterobicycles Arylated at Bridgehead Atom

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Received 7 August 2013; revised 7 October 2013

ABSTRACT: *Starting with thiazolines, an important class of heterocyclic imines, a novel rearrangement reaction of corresponding N-acyliminium ions is described. Furthermore, a new class of heterobicyclic compounds arylated at a single bridgehead atom is obtained diastereospecifically.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem. 25:20–27, 2014; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21131

INTRODUCTION

Five-membered heterocyclic compounds containing nitrogen, such as thiazolines, oxazolines, and imidazolines, can be found in a variety of natural compounds with many of them demonstrating interesting biochemical properties. Importantly, small chiral heterocyclic molecules find a wide use as chiral building blocks and ligands in asymmetric synthesis of many natural products, as well as in medicinal and agriculture applications [1]. Several methods for the synthesis of thiazolines have been reported, including acid-catalyzed condensation of amino derivatives with carboxylic acids, esters, nitriles, benzimidates, or intramolecular cyclization of carboxamide derivatives [2].

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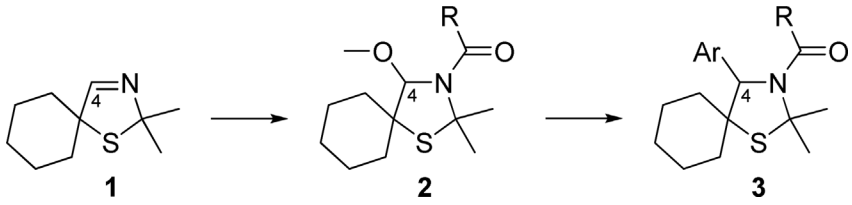
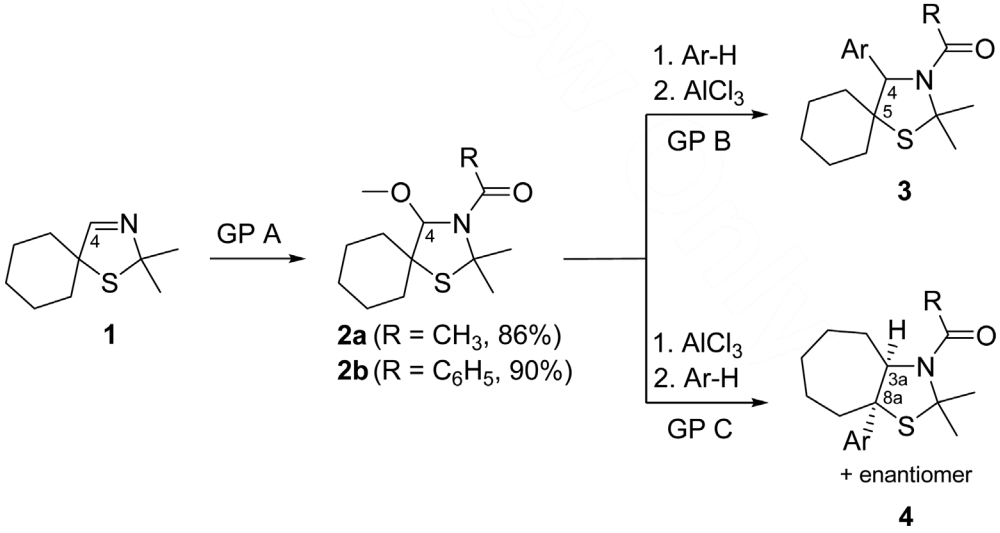
The Asinger reaction is a simple multicomponent reaction that allows the synthesis of 3–thiazolines with a variety of substituents [3–5]. Thiazolines and their derivatives are interesting substances on account of their similarity to thiazolidines, which are an important structural element in a variety of physiologically active substances commonly utilized as remedies [6]. One well-known example is penicillin [7], composed of a thiazoline- and a β–lactam ring, and other examples include remedies used to treat diabetes mellitus [8].

The primary aim of this work was to synthesize thiazolidines **3** with an aryl group attached to the carbon atom in 4-position next to the nitrogen, starting from thiazoline **1** by means of an intermolecular Friedel–Crafts reaction in the last step (Scheme 1). The imine **1** should therefore be *N*-acylated, followed by a trapping reaction of the resulting carbenium–iminium ion by MeOH to give methoxythiazolidines **2**. Finally, the methoxy group in 4–position should be substituted by an aryl group. Molecules similar to the target compounds could be regarded as privileged chiral auxiliaries in stereoselective operations [9]. Recently we presented an efficient approach to tricyclic lactams via intramolecular Friedel–Crafts cyclization with comparable methoxyamides (R = Ar; Scheme 1) as stable intermediates [10]. Herein, we wish to extend this methodology to the intermolecular type of Friedel–Crafts reactions. However, modifying the reaction conditions we were faced with surprising results.



SCHEME 1 Reaction pathway leading to 4-aryl substituted *N*-acyl *S*,*N*-heterocycles.

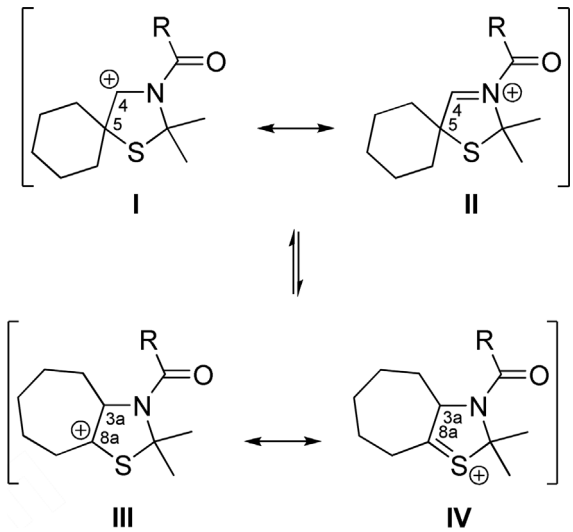


SCHEME 2 Reaction pathway leading to aryl substituted *N*-acyl *S*,*N*-heterocycles **3** and **4**. Reagents and conditions: GP A: (i) 1.1 equiv acyl chloride, CH_2Cl_2, 0°C—r.t., 2 h; (ii) 3.7 equiv MeOH, 1.1 equiv Et_3N, CH_2Cl_2, 0°C—r.t., overnight; GP B: 10 equiv Ar-H, 2.5 equiv $AlCl_3$, CH_2Cl_2, 0°C—r.t., 5 days; GP C: (i) 2.5 equiv $AlCl_3$, 0°C—r.t., CH_2Cl_2, 2 h; (ii) 10 equiv Ar-H, CH_2Cl_2, 0°C – r.t., 5 days.

RESULTS AND DISCUSSION

For the Asinger reaction, the corresponding α-chloroaldehyde, NaHS and aqueous NH_3 were utilized in CH_2Cl_2 to form thiazoline **1**, as described by us previously [11]. The intended reaction pathway based on 3-thiazoline **1** including all reagents and yields are shown in Scheme 2 (GP A and B).

Leuchs and co-workers described the addition of acid chlorides to linear imines by substituting the reactive chloride by a more resistant hydroxy or alkoxy group without isolating the addition product [12]. This reaction type was then applied to heterocyclic imines like **1** by Schwarze and co-workers [13]. By implementing Leuchs' and co-workers' method, compounds **2** were produced as substrates for the arylation and acetyl and benzoyl chloride were used. The methoxy-substituted *N*-acyl amines **2** are stable and can be stored over long periods of time. Starting from compounds **2**, the resonance-stabilized *N*-acyliminium ions **I** and **II** (Scheme 3) can be generated in situ by treatment with a Lewis acid like aluminum trichloride. These electrophilic ions **I** and **II** are investigated to react by nucleophilic partners



SCHEME 3 *N*-acyliminium ions **I**, **II** and proposed rearrangement to annulated heterocycles **III**, **IV**.

such as electron-rich arenes. The reaction conditions in this final step are similar to the Friedel–Crafts alkylation of arenes. The arylation was performed under cooling in an argon atmosphere. Adding

TABLE 1 Conversion of Methoxythiazolidine **2**. Residues, Conditions, and Yields

Entry	*Amide*	*R*	*Ar*	*GP*[a]	*Product (Yield)*[b]	*dr*[c]
1	**2a**	CH_3	4-Methoxyphenyl	B	**3a** (91%)	–
2	**2a**	CH_3	2,5–Dimethoxyphenyl	B	**3b** (83%)	–
3	**2a**	CH_3	2,4-Dimethoxyphenyl	B	**3c** (64%)	–
4	**2b**	C_6H_5	4-Methoxyphenyl	B	**3d** (87%)	–
5	**2a**	CH_3	4-Methoxyphenyl	C	**4a** (89%)	≥95:5
6	**2a**	CH_3	3,4-Dimethoxyphenyl	C	**4b** (59%)	≥95:5
7	**2a**	CH_3	2,4-Dimethoxyphenyl	C	**4c** (80%)	≥95:5
8	**2b**	C_6H_5	4-Methoxyphenyl	C	**4d** (48%)[d]	≥95:5

[a]GP = General Procedure (for details, see the Experimental section).
[b]Isolated yields.
[c]Diastereomeric ratio according to the ^{1}H NMR of the crude product.
[d]Cyclohexylidene **5** (see Scheme 4) was isolated as a by-product (26% yield).

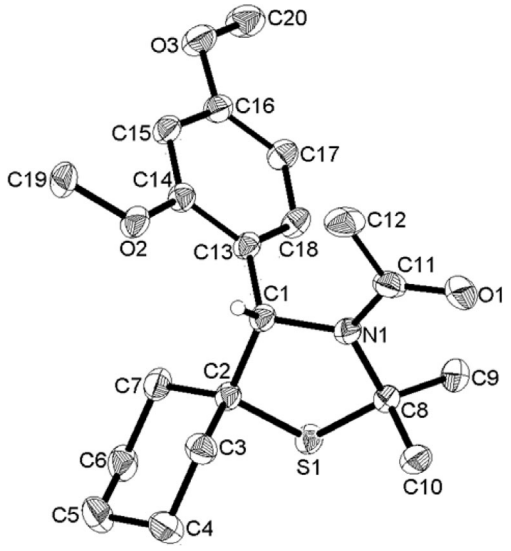


FIGURE 1 X-ray crystal structure of 4-arylthiazolidine **3c** (only one enantiomer is shown). The atom numbering does not follow the IUPAC nomenclature.

aluminum trichloride to a mixture of arene and 4-methoxythiazolidine **2** led to the desired final products **3a**–**d** in good yields of up to 91% (Table 1, entries 1–4). The constitution of 4-arylthiazolidines **3** could be unequivocally verified by single-crystal XRD analysis of compound **3c** (Fig. 1).

In contrast, stirring the thiazolidine **2** and aluminum trichloride for 2 h at room temperature (r.t.) before adding this mixture dropwise to the arene (Scheme 2, GP C) gives the bicyclic compounds **4a**–**d** in good yields of up to 89% (Table 1, entries 5–8) surprisingly. The annulated products **4** consist of a heterocyclic five-membered ring originating from the thiazolidine and a condensed seven-membered ring with a carbon–carbon connection to the arene on one of the bridgehead atoms.

This indicates that if sufficient time is provided prior to the addition of the arene, a rearrangement of the cyclohexyl group occurs, producing the ionic species **III** and **IV** (Scheme 3). There are very few substances described in the literature that resemble these rearranged bicyclic products, and yet they all exhibit hydrogen atoms attached to the bridgehead atoms [14]. The possibility of a carbon–carbon bond at a bridgehead atom of this kind of a ring system, as well as this special case of the rearrangement reaction for the applied heterocyclic iminium ions, is not described in the literature.

The annulated structure **4** was elucidated by one- and two-dimensional NMR spectroscopy. Although the ^{1}H NMR spectroscopic data for both the originally targeted products **3** and the corresponding rearranged compounds **4** are very similar, there exists a crucial difference. In the spectrum of **3a**, the peak for the single hydrogen atom is a singlet at 4.75 ppm; whereas in the spectrum for the corresponding rearranged product **4a**, there is instead a doublet for this hydrogen atom at 4.65 ppm. The usually expected doublet of doublets cannot be resolved as a result of the fact that the bonding angle between the regarded proton and a proton from the neighboring CH_2 group is nearly 90°. Thus, this bonding angle renders the vicinal coupling constant to approach zero, allowing only the interaction of the second proton of the CH_2 group to be visible in the ^{1}H NMR spectrum.

The proposed annulated structure was confirmed by single-crystal XRD analysis of **4a**, and the X-ray crystal structure is provided in Fig. 2. The single-crystal XRD analysis reveals that both bonds connecting the seven-membered ring to the thiazolidine cycle are positioned on one side of the five-membered heterocycle. During preparation of bicyclic compounds **4**, the two cis isomers were produced exclusively, as depicted by the high diasteromeric ratio of $dr \geq 95{:}5$ in the ^{1}H NMR spectroscopic data of the crude product. This fact can easily be explained as the nucleophile approaches the

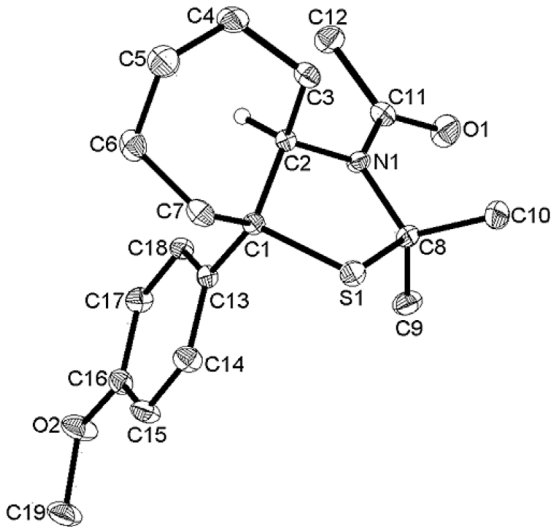
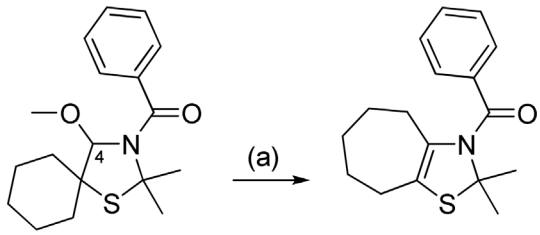


FIGURE 2 X-ray crystal structure of 5-arylthiazolidine **4a** (only one enantiomer is shown). The atom numbering does not follow the IUPAC nomenclature.

substrate from the sterically less hindered face forcing both alkyl groups to a cis-orientation. The relative configurations of all other compounds **4** were assigned by analogy.

To identify the driving force for the observed rearrangements, presumably the sec-carbon and tert-carbon atoms in the resonance structures of the *N*-acyliminium ion **I**, **II** and the thionium ion **III**, **IV** are responsible, respectively. The rearrangement of resonance structure **I** into **III** can be classified as a sigmatropic [1,2] rearrangement because a sigma bond is migrating to the neighboring atom. It shows similarities to the Wagner–Meerwein rearrangement, which is a known side reaction in the Friedel–Crafts alkylation. But by definition, there are no heteroatoms allowed as direct neighbors of the starting or ending point of the migrating bond. This special case is known in the semipinacol rearrangement [15] where an oxygen atom stabilizes the ionic intermediate. Therefore, the observed rearrangement resembles the semipinacol rearrangement, except for the fact that the involved heteroatom is not oxygen, but rather sulfur.

Cyclohexylidene **5** was isolated as a by-product in the conversion of **2b** to give rearranged 5-arylthiazolidine **4d** (see Scheme 2) (26% yield). Knowing the possibility of elimination, the specific formation of **5** was intended to realize without using an aromatic component (Scheme 4). This goal was successfully gained in moderate yield of 35%. Considering a possible mechanism, intermediate **III** (Scheme 3) could easily eliminate a proton to form an endocyclic C-C double bond. This assumption is



SCHEME 4 Cyclohexylidene **5** formed by elimination; (a) 1.1 equiv $AlCl_3$, CH_2Cl_2, 0°C—r.t., 5 days.

in perfect accordance with reports of similar eliminations after rearrangement [16].

CONCLUSIONS

It can be assessed that based on heterocyclic imines as a starting material, 4-arylthiazolidines can be prepared in good yields by the addition of acyl chlorides to the C=N double bond and then substituting the group in 4-position with various arenes. By changing the reaction conditions of the last step, a novel rearrangement reaction resembling the semipinacol rearrangement can be realized. This reaction is highly diastereoselective and leads to a class of new arylated bicyclic heterocycles in good yields.

EXPERIMENTAL

Synthetic procedures under argon atmosphere were performed on a vacuum line using standard Schlenk techniques. Preparative column chromatography was carried out using Grace SiO_2 (0.035–0.070 mm, type KG 60) with *n*-hexane and EtOAc as eluents. TLC was performed on Machery–Nagel SiO_2 F254 plates on aluminum sheets. Melting points were obtained on a melting point apparatus of Laboratory Devices and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX R 500 (measuring frequency: ^1H NMR = 500.1 MHz, ^{13}C NMR = 125.8 MHz) or a Bruker Avance III 500 (measuring frequency: ^1H NMR = 499.9 MHz, ^{13}C NMR = 125.7 MHz) spectrometer in the $CDCl_3$ solution. Chemical shifts are referenced to tetramethylsilane (0.00 ppm). Assignments of the signals were supported by measurements applying DEPT and COSY techniques. Mass spectra (CI-MS, EI-MS, HRMS) were obtained with a Finnigan-MAT 95. The IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "golden gate" diamond ATR (attenuated total reflection) unit. 2,2-Dimethyl-1-thia-3-azaspiro[4.5]dec-3-ene (**1**) was prepared according to a published procedure [11]. CH_2Cl_2 was refluxed with calcium hydride

and freshly distilled prior to use. MeOH was refluxed with Mg and freshly distilled prior to use. Et_3N was dried over molecular sieves and freshly distilled prior to use.

General Procedure A (GP A) for Preparation of Methoxythiazolidines **2a–b**

Under argon atmosphere, 1 equiv of imine **1**, dissolved in anhydrous CH_2Cl_2 (0.5 mL per mmol imine), was cooled down to 0–5°C. 1.1 equiv of the respective acyl chloride was added dropwise. After stirring for 2 h at r.t., 7.4 equiv of anhydrous MeOH were added dropwise at 0–5°C. Thereupon, the solution was stirred for 10 min at r.t., before 1.1 equiv of anhydrous Et_3N, dissolved in anhydrous CH_2Cl_2 (0.2 mL per mmol imine) was added dropwise at 0–5°C. After having been stirred overnight at r.t., the solution was poured into ice water (0.7 mL per mmol imine). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (0.2 mL per mmol imine). The recombined organic phases were washed with saturated $NaHCO_3$ solution (1 × 0.5 mL per mmol imine), HCl solution (1 × 0.5 mL per mmol imine, 4%), water (2 × 0.5 mL per mmol imine) and dried with $MgSO_4$. The solvent was removed on a rotary evaporator. The purification of the crude product is described in the experiments.

*(RS)-3-Acetyl-2,2-dimethyl-4-methoxy-1-thia-3-aza-spiro[4.5]decane (***2a***).* Following GP A, 2,5-dihydrothiazole **1** (4.59 g, 0.025 mol), acetyl chloride (2.17 g, 0.028 mol), anhydrous MeOH (7.0 mL, 0.173 mol), and anhydrous Et_3N (4.0 mL, 0.028 mol) were used. The crude product was crystallized from *n*–hexane to give product **2a** as a colorless solid. Yield: 5.53 g, 86%. mp: 58°C. IR (ATR): 2972, 2931, 2854, 1647, 1446, 1379, 1076 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.21–1.34 (m, 2H, C^8H_2), 1.55–2.01 (m, 8H, $C^{6,7,9,10}H_2$), 1.80 (s, 3H, C^2CH_3), 1.90 (s, 3H, C^2CH_3), 2.24 (s, 3H, $NCOCH_3$), 3.45 (s, 3H, OCH_3), 4.91 (s, 1H, C^4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 22.15, 24.17, 25.14, 25.43, 30.70, 32.20, 32.97, 37.65, 55.53, 58.66, 71.12, 99.36, 169.37. MS (CI, isobutane): *m/z* (%) = 258.0 (58) $[MH]^+$, 226.0 (100) $[MH - CH_4O]^+$. HRMS (CI, isobutane): *m/z* calcd. for $[C_{13}H_{24}NO_2S]^+$: 258.1527; found: 258.1526.

*(RS)-3-Benzoyl-2,2-dimethyl-4-methoxy-1-thia-3-azaspiro[4.5]decane (***2b***).* Following GP A, 2,5-dihydrothiazole **1** (15.87 g, 0.087 mol), benzoyl chloride (13.50 g, 0.095 mol), anhydrous MeOH (25.0 mL, 0.616 mol), and anhydrous Et_3N (13.5 mL, 0.095 mol) were used. The crude product was purified by column chromatography (silica gel; *n*–hexane/EtOAc, 4:1; R_f = 0.56) and finally by crystallization from *n*–hexane to give product **2b** as a colorless solid. Yield: 24.92 g, 90%. Mp: 68°C. IR (ATR): 3062, 2971, 2928, 2857, 2827, 1644, 1609, 1581, 1446, 1357, 1073, 736, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.21–1.33 (m, 2H, C^8H_2), 1.49–1.69 (m, 4H, $C^{7,9}H_2$), 1.72–2.06 (m, 4H, $C^{6,10}H_2$), 1.97 (s, 3H, C^2CH_3), 2.00 (s, 3H, C^2CH_3), 3.08 (s, 3H, OCH_3), 4.99 (s, 1H, C^4H), 7.38–7.49 (m, 5H, 5×ArCH). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 22.60, 24.30, 25.47, 31.29, 31.70, 33.10, 38.78, 55.26, 58.86, 71.09, 99.84, 127.57, 128.50, 130.07, 138.09, 171.05. MS (CI, isobutane): *m/z* (%) = 320.1 (17) $[MH]^+$, 288.0 (100) $[MH - CH_4O]^+$. HRMS (CI, isobutane): *m/z* calcd. for $[C_{18}H_{26}NO_2S]^+$: 320.1684; found: 320.1684.

General Procedure (GP B) for Preparation of Arylthiazolidines **3a–d**

Under argon atmosphere, 2.5 equiv of aluminum trichloride was added in a period of 1 h to a solution of 1 equiv of the respective methoxythiazolidine **2**, dissolved in anhydrous CH_2Cl_2 (6 mL per mmol thiazolidine), and 10 equiv of the respective aromatic component at 0–5°C. After stirring for 5 days at r.t., the solution was poured into ice (10 g per mmol thiazolidine) and stirred fiercely until the ice was totally melted. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL per mmol thiazolidine). The recombined organic phases were washed with NaOH solution (1 × 2 mL per mmol thiazolidine, 2%), water (2 × 2 mL per mmol thiazolidine) and dried with $MgSO_4$. The solvent was removed on a rotary evaporator. The purification of the crude product is described in the experiments.

*(RS)-3-Acetyl-4-(4-methoxyphenyl)-2,2-dimethyl-1-thia-3-azaspiro[4.5]decane (***3a***).* Following GP B, methoxythiazolidine **2a** (5.00 g, 0.019 mol), methoxybenzene (21.01 g, 0.194 mol), and aluminum trichloride (6.48 g, 0.049 mol) were used. The crude product was crystallized from *n*–hexane to give product **3a** as a colorless solid. Yield: 5.89 g, 91%. mp 109°C. IR (ATR): 3003, 2929, 2855, 1639, 1608, 1511, 1452, 1375, 1244, 1031, 832 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.91–2.36 (m, 10H, 5×CH_2), 1.91 (s, 3H, $NCOCH_3$), 2.00 (s, 3H, CCH_3CH_3), 2.01 (s, 3H, CCH_3CH_3), 3.81 (s, 3H, OCH_3), 4.75 (s, 1H, C^4H), 6.88 (d, ^3J = 8.02 Hz, 2H, $C^{3',5'}H$), 7.35 (d, ^3J = 8.02 Hz, 2H, $C^{2',6'}H$). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 22.88, 24.46, 25.53, 25.95, 29.02, 32.26, 36.19, 41.12, 55.17, 58.29, 71.76, 79.42, 113.51, 129.44, 131.32,

159.11, 169.77. MS (CI, isobutane): *m/z* (%) = 334.0 (100) $[MH]^+$. HRMS (CI, isobutane): *m/z* calcd. for $[C_{19}H_{28}NO_2S]^+$: 334.1841; found: 334.1841.

*(RS)-3-Acetyl-4-(2,5-dimethoxyphenyl)-2,2-dimethyl-1-thia-3-azaspiro[4.5]decane (***3b***).* Following GP B, methoxythiazolidine **2a** (1.00 g, 0.004 mol), 1,4-dimethoxybenzene (5.25 g, 0.038 mol), and aluminum trichloride (1.33 g, 0.001 mol) were used. The crude product was crystallized from *n*–hexane to give product **3b** as a colorless solid. Yield: 1.09 g, 83%. mp 132°C. IR (ATR): 3055, 2968, 2928, 2855, 2826, 1646, 1497, 1446, 1384, 1211, 1046, 821 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.96–1.30 (m, 4H, 2×CH_2), 1.38–1.45 (m, 1H, C<u>H</u>H), 1.55–1.93 (m, 4H, 2×CH_2), 1.78 (s, 3H, NCOC<u>H</u>$_3$), 1.96 (s, 3H, CC<u>H</u>$_3$CH$_3$), 2.01 (s, 3H, CCH$_3$C<u>H</u>$_3$), 2.25–2.31 (m, 1H, CH<u>H</u>), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.44 (s, 1H, C^4H), 6.76 (s, 2H, 2×ArCH), 7.15 (s, 1H, ArCH). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 22.75, 24.48, 25.05, 25.51, 28.88, 32.23, 34.40, 40.75, 55.50, 55.77, 58.57, 71.36, 71.63, 110.67, 113.38, 114.36, 128.98, 150.42, 153.62, 169.81. MS (CI, isobutane): *m/z* (%) = 364.0 (100) $[MH]^+$. HRMS (CI, isobutane): *m/z* calcd. for $[C_{20}H_{30}NO_3S]^+$: 364.1946; found: 364.1947.

*(RS)-3-Acetyl-4-(1,3-dimethoxyphenyl)-2,2-dimethyl-1-thia-3-azaspiro[4.5]decane (***3c***).* Following GP B, methoxythiazolidine **2a** (2.00 g, 0.008 mol), 1,3-dimethoxybenzene (5.37 g, 0.039 mol), and aluminum trichloride (2.59 g, 0.019 mol) were used. The crude product was crystallized from *n*–hexane to give product **3c** as a colorless solid. Yield: 1.81 g, 64%. mp 124°C. IR (ATR): 3001, 2928, 2852, 1650, 1589, 1441, 1373, 1206, 1030, 708 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.99–1.31, 1.44–1.50, 1.60–1.80, 1.87–1.97, 2.29–2.35 (5m, 10H, $C^{6,7,8,9,10}H_2$), 1.83 (s, 3H, $COCH_3$), 2.01, 2.04 (2s, 6H, $C(CH_3)_2$), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.43 (s, 1H, C^4H), 6.46 (d, ^4J = 2.13 Hz, 1H, $C^{2'}H$), 6.54 (dd, ^3J = 8.54 Hz, ^4J = 2.13 Hz, 1H, $C^{6'}H$), 7.51 (d, ^3J = 8.54 Hz, 1H, $C^{5'}H$). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 22.81, 24.51, 25.10, 25.57, 28.83, 32.24, 34.55, 40.67, 55.25, 55.43, 58.76, 71.07, 71.50, 97.76, 104.33, 120.66, 129.31, 157.18, 160.06, 169.83. MS (CI, isobutane): *m/z* (%) = 364.6 (100) $[MH]^+$. HRMS (CI, isobutane): *m/z* calcd. for $[C_{20}H_{30}NO_3S]^+$: 364.1946; found: 364.1942.

*(RS)-3-Benzoyl-4-(4-methoxyphenyl)-2,2-dimethyl-1-thia-3-azaspiro[4.5]decane (***3d***).* Following GP B, methoxythiazolidine **2b** (3.07 g, 0.010 mol), methoxybenzene (10.38 g, 0.096 mol), and aluminum trichloride (3.20 g, 0.024 mol) were used. The crude product was crystallized from *n*–hexane to give product **3d** as a colorless solid. Yield: 3.29 g, 87%. mp 122°C. IR (ATR): 3065, 2979, 2937, 2851, 1645, 1610, 1583, 1514, 1445, 1368, 1246, 1029, 841, 738, 706 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.94–1.20 (m, 4H, 2×CH_2), 1.30–1.39 (m, 1H, C<u>H</u>H), 1.50–1.94 (m, 4H, 2×CH_2), 2.11 (s, 3H, CC<u>H</u>$_3$CH$_3$), 2.13 (s, 3H, CCH$_3$C<u>H</u>$_3$), 2.27–2.35 (m, 1H, CH<u>H</u>), 3.75 (s, 3H, OCH_3), 4.84 (s, 1H, C^4H), 6.63–6.69 (m, 2H, 2×ArCH), 6.81–6.98 (m, 4H, 4×ArCH), 7.19–7.31 (m, 3H, 3×ArCH). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 23.05, 24.20, 25.37, 29.38, 32.32, 35.34, 40.81, 55.03, 57.99, 71.62, 79.18, 112.90, 125.60, 127.95, 128.44, 129.90, 131.21, 139.34, 158.84, 170.61. MS (CI, isobutane): *m/z* (%) = 396.0 (100) $[MH]^+$. HRMS (EI): *m/z* calcd. for $[C_{24}H_{29}NO_2S]^+$: 395.1919; found: 395.1918.

General Procedure (GP C) for Preparation of Rearranged Arylthiazolidines **4a–d**

Under argon atmosphere, 1 equiv of the respective methoxythiazolidine **2**, dissolved in anhydrous CH_2Cl_2 (1.5 mL per mmol thiazolidine), was added dropwise to a suspension of 2.5 equiv of aluminum trichloride in anhydrous CH_2Cl_2 (1 mL per mmol thiazolidinethione) at 0–5°C. After stirring for 2 h at r.t., the solution was added to 10 equiv of the respective aromatic component, dissolved in anhydrous CH_2Cl_2 (1.5 mL per mmol thiazolidine), at 0–5°C. After stirring for 5 days at r.t., the solution was poured into ice (5 g per mmol thiazolidine) and stirred fiercely until the ice was totally melted. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 1 mL per mmol thiazolidine). The recombined organic phases were washed with NaOH solution (1 × 2 mL per mmol thiazolidine, 2%), water (2 × 2 mL per mmol thiazolidine), and dried with $MgSO_4$. The solvent was removed on a rotary evaporator. The purification of the crude product is described in the experiments.

(3aS,8aS*)-3-Acetyl-8a-(4-methoxyphenyl)-2,2-dimethyloctahydro-2H-cyclohepta[d][1,3]thiazole (***4a***).* Following GP C, methoxythiazolidine **2a** (5.00 g, 0.019 mol), methoxybenzene (21.01 g, 0.194 mol), and aluminum trichloride (6.48 g, 0.049 mol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed a single diastereomer, indicating a *dr* ≥ 95:5. The crude product was crystallized from *n*–hexane to give product **4a** as a colorless solid. Yield: 5.79 g, 89%. mp 146°C. IR (ATR): 3003, 2965, 2917, 2854, 2830, 1650, 1604, 1508, 1447, 1387, 1258, 1035, 834 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.06–2.58 (m, 10H, 5×CH_2), 1.32 (s, 3H,

C^2CH_3), 1.75 (s, 3H, C^2CH_3), 2.24 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 4.65 (d, ^3J = 10.33 Hz, 1H, $C^{3a}H$), 6.86 (d, ^3J = 7.89 Hz, 2H, $C^{3',5'}H$), 7.50 (d, ^3J = 7.89 Hz, 2H, $C^{2',6'}H$). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 22.55, 28.26, 29.99, 33.90, 41.31, 25.42, 29.17, 29.77, 55.22, 61.97, 71.44, 72.38, 113.50, 128.01, 138.20, 158.30, 167.81. MS (CI, isobutane): *m/z* (%) = 334.0 (100) $[MH]^+$. HRMS (CI, isobutane): *m/z* calcd. for $[C_{19}H_{28}NO_2S]^+$: 334.1841; found: 334.1842.

(3aS,8aS*)-3-Acetyl-8a-(3,4-dimethoxyphenyl)-2,2-dimethyloctahydro-2H-cyclohepta[d][1,3]thiazole (***4b***).* Following **GP C**, methoxythiazolidine **2a** (5.00 g, 0.019 mol), 1,2-dimethoxybenzene (26.84 g, 0.194 mol), and aluminum trichloride (6.48 g, 0.049 mol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed a single diastereomer, indicating a *dr* ≥ 95:5. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:2; R_f = 0.2) to obtain product **4b** as a colorless solid. Yield: 4.17 g, 59%. mp 96°C. IR (ATR): 3005, 2953, 2935, 2857, 2841, 1636, 1603, 1589, 1514, 1444, 1385, 1264, 1024, 828 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.11–2.58 (m, 10H, 5×CH_2), 1.34 (s, 3H, C^2CH_3), 1.75 (s, 3H, C^2CH_3), 2.23 (s, 3H, $COCH_3$), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.64 (d, ^3J = 10.31 Hz, 1H, $C^{3a}H$), 6.78 (d, ^3J = 8.35 Hz, 1H, $C^{5'}H$), 7.00 (d, ^3J = 8.35 Hz, 1H, $C^{6'}H$), 7.28 (s, 1H, $C^{2'}H$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.64, 28.23, 29.98, 33.98, 41.15, 25.40, 29.13, 29.72, 55.78, 55.87, 62.36, 71.40, 72.31, 109.96, 112.01, 117.46, 138.70, 147.93, 148.83, 167.64. MS (CI, isobutane): *m/z* (%) = 364.0 (100) $[MH]^+$. HRMS (EI): *m/z* calcd. for $[C_{20}H_{29}NO_3S]^+$: 363.1868; found: 363.1868.

(3aS,8aS*)-3-Acetyl-8a-(2,4-dimethoxyphenyl)-2,2-dimethyloctahydro-2H-cyclohepta[d][1,3]thiazole (***4c***).* Following GP C, methoxythiazolidine **2a** (5.00 g, 0.019 mol), 1,3-dimethoxybenzene (26.84 g, 0.194 mol), and aluminum trichloride (6.48 g, 0.049 mol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed a single diastereomer, indicating a *dr* ≥ 95:5. The crude product was crystallized from *n*–hexane to give the product **4c** as a colorless solid. Yield: 5.63 g, 80%. mp 108°C. IR (ATR): 3000, 2967, 2933, 2862, 1650, 1501, 1441, 1392, 1211, 1029, 829 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.07–2.62 (m, 10H, 5×CH_2), 1.36 (s, 3H, C^2CH_3), 1.73 (s, 3H, C^2CH_3), 2.24 (s, 3H, $COCH_3$), 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.77–4.98 (m, 1H, $C^{3a}H$), 6.43 (d, ^3J = 8.75 Hz, 1H, $C^{5'}H$), 6.52 (s, 1H, $C^{3'}H$), 7.22–7.40 (m, 1H, $C^{6'}H$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.73, 29.54, 33.53, 35.48, 36.30, 25.39, 29.65, 29.94, 55.21, 55.49, 68.25, 71.26, 71.47, 100.73, 103.36, 103.44, 125.77, 158.39, 159.80, 167.94. MS (CI, isobutane): *m/z* (%) = 364.1 (100) $[MH]^+$. HRMS (CI, isobutane): *m/z* calcd. for $[C_{20}H_{30}NO_3S]^+$: 364.1946; found: 364.1947.

(3aS,8aS*)-3-Benzoyl-8a-(4-methoxyphenyl)-2,2-dimethyloctahydro-2H-cyclohepta[d][1,3]thiazole (***4d***).* Following GP C, methoxythiazolidine **2b** (4.00 g, 0.013 mol), methoxybenzene (13.52 g, 0.125 mol), and aluminum trichloride (4.17 g, 0.031 mol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed a single diastereomer, indicating a *dr* ≥ 95:5. The crude product was purified by column chromatography (silica gel; *n*–hexane/EtOAc, 7:3; R_f = 0.59) and finally by crystallization from *n*–hexane to give product **4d** as a colorless solid. Yield: 2.36 g, 48%. mp 140°C. IR (ATR): 2935, 2854, 1636, 1606, 1579, 1508, 1443, 1375, 1282, 826 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.62–0.78, 0.93–1.04, 1.12–1.25, 1.34–1.42, 1.55–1.64, 1.66–1.82, 1.84–1.98, 2.42–2.51 (m, 10H, 5×CH_2), 1.52 (s, 3H, C^2CH_3), 1.88 (s, 3H, C^2CH_3), 3.81 (s, 3H, OCH_3), 4.34–4.44 (m, 1H, $C^{3a}H$), 6.86 (m, ^3J = 8.86 Hz, 2H, $C^{2'',6''}H$), 7.24–7.27 (m, 2H, $C^{3'',5''}H$), 7.39–7.43 (m, 3H, $C^{2'',4'',6''}H$), 7.46 (m, ^3J = 8.86 Hz, 2H, $C^{3'',5''}H$). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 22.49, 27.33, 29.76, 34.70, 41.52, 29.45, 30.15, 55.29, 63.35, 71.94, 72.58, 113.35, 125.20, 128.42, 128.53, 128.73, 137.88, 139.67, 158.54, 169.02. MS (CI, isobutane): *m/z* (%) = 396.6 (100) $[MH]^+$. HRMS (EI): *m/z* calcd. for $[C_{24}H_{29}NO_2S]^+$: 395.1919; found: 395.1911.

*3-Benzoyl-2,2-dimethyl-3,4,5,6,7,8-hexahydro-2H-cyclohepta[d][1,3]thiazole (***5***).* *Method A*: **8** results as a by-product in the synthesis of **4d** (R_f = 0.78; *n*–hexane/EtOAc, 9:1). Yield: 0.96 g, 26%. mp 78°C. IR (ATR): 3061, 2978, 2922, 2851, 1646, 1628, 1599, 1578, 1492, 1445, 1362, 715, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.33–1.38 (m, 2H, C^6H_2), 1.59–1.68 (m, 4H, $^{C5,7}H_2$), 1.77–1.81 (m, 2H, $C^{4,8}$HH), 1.94 (s, 6H, $C(CH_3)_2$), 2.29–2.32 (m, 2H, $C^{4,8}$HH), 7.39–7.43 (m, 2H, $C^{3'',5''}H$), 7.45–7.49 (m, 1H, $C^{4''}H$), 7.61–7.64 (m, 2H, $C^{2'',6''}H$). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 26.02, 26.40, 28.49, 27.77, 30.27, 32.16, 78.83, 121.23, 128.38, 128.53, 131.23, 132.82, 138.01, 168.29. MS (CI, isobutane): *m/z* (%) = 288.4 (100) $[MH]^+$. HRMS (EI): *m/z* calcd. for $[C_{17}H_{21}NOS]^+$: 287.1344; found: 287.1340. *Method B*: Under argon atmosphere, methoxythiazolidine **2b** (0.92 g, 2.8 mmol), dissolved in anhydrous CH_2Cl_2 (9 mL), was added dropwise to a suspension

of aluminum trichloride (0.42 g, 3.2 mmol) in anhydrous CH_2Cl_2 (9 mL) at 0–5°C. After stirring for 5 days at r.t., the solution was poured into ice (10 g) and stirred fiercely until the ice was totally melted. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The recombined organic phases were washed with NaOH solution (1 × 10 mL per mmol thiazolidine, 2%), water (2 × 10 mL per mmol thiazolidine), and dried with $MgSO_4$. The solvent was removed on a rotary evaporator. The crude product was crystallized from *n*–hexane to give the product **8** as a colorless solid. Yield: 0.29 g, 35%.

Crystallographic Data

CCDC–954337 contains the supplementary crystallographic data for **3c** and CCDC–863381 for **4a**. These data can be obtained free of charge from the Cambridge Crystallographic data center via www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic data center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

ACKNOWLEDGMENTS

The silica gel was generously supplied to us by Grace GmbH & Co. KG. T. S. gratefully acknowledges the Heinz-Neumüller-Stiftung for a doctoral fellowship.

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