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Unexpected regioselectivity in the reaction between cycloalkenyl-1-diazenes and thioamides: useful entry to fused cycloalkyl-thiazoline and cycloalkyl-thiazoline–pyrazole systems

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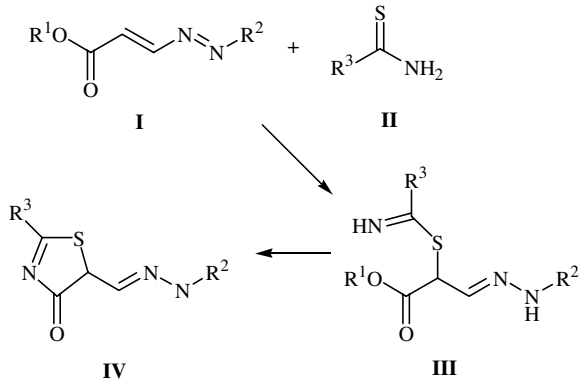
Abstract—New tetrahydro-3a*H*-cyclopenta[*d*][1,3]thiazolines and hexahydro-1,3-benzothiazolines were obtained in satisfactory yields by reaction of cycloalkenyl-1-diazenes with thioamides. These thiazolines were converted into unknown fused cycloalkyl-thiazoline–pyrazole systems.

In previous papers, we reported the reaction of 1,2-diaza-1,3-butadienes **I** with thioamides **II** to provide substituted 2-thiazolin-4-ones **IV** in high yields.[1] The mechanism involves a preliminary sulfur nucleophilic attack of compounds **II** at the azo-ene system with formation of hydrazones **III**[2] that spontaneously cyclize by nitrogen internal nucleophilic attack at the ester function leading to the final 2-thiazolin-4-ones **IV** (Scheme 1).

When this synthetic methodology was applied to the cycloalkenyl-1-diazenes,[3] some significant differences in the behaviour of these reactions were observed. In fact, cycloalkenyl-1-diazenes **1a–c** easily reacted with aryl thioamides **2a–i** in methanol at room temperature to give the exclusive formation of aryl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*][1,3]thiazolines **5a–d** or aryl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazolines **5e–m** in excellent yields (Scheme 2, Table 1).

The reaction pathway proceeds via SH nucleophilic attack of thioamides **2a–i** in its tautomeric thioloimido form at the carbon atom in position four of the azo-ene system of cycloalkenyl-1-diazenes **1a–c** with formation of cycloalkyl-hydrazones **3**. These intermediates immediately undergo the ring closure by regioselective internal nucleophilic attack of the nitrogen at the hydrazono moiety, producing the new fused cycloalkyl-thiazoline derivatives **5a–m**.[4] In these cases, no formation of spiro cycloalkyl-thiazolinones **4** by means of the nucleophilic attack at the ester function was observed, probably on account of the strong strain of these compounds (Scheme 2). Hence, cycloalkenyl-1-diazenes furnished new examples of aminothiazoline ring systems as supported by X-ray diffraction study



Scheme 1.

Keywords: Cycloalkenyl-1-diazenes; Michael additions; Thioamides; Thiazolines.
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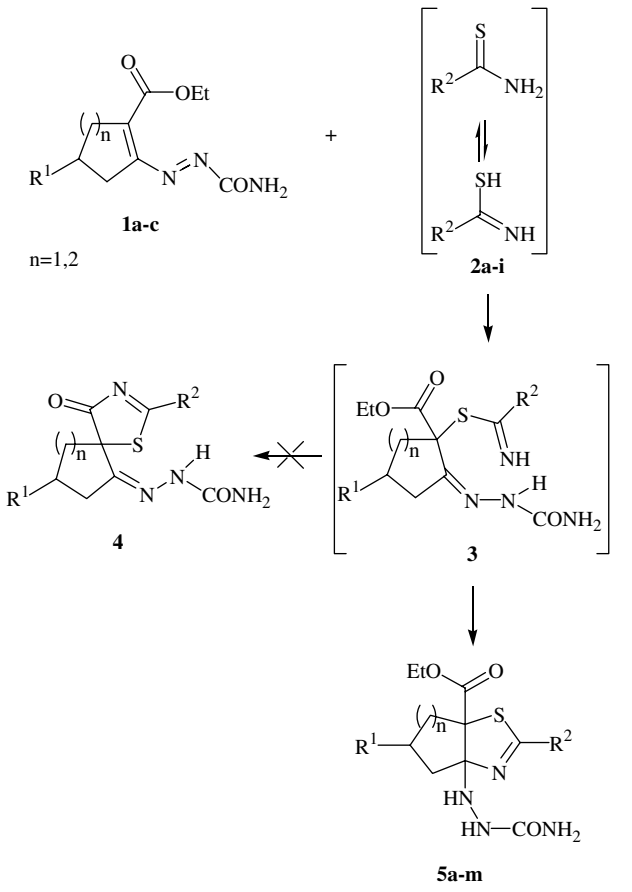


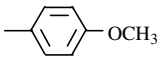
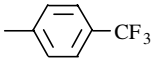
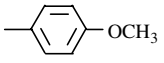
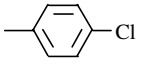
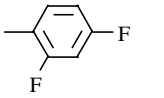
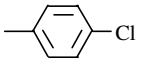
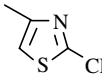
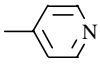
Scheme 2. Reagent and condition: (i) MeOH, rt.

of compound **5k** (Fig. 1).[5] It is known that this latter class of compounds find applications for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial and HIV infections.[6]

The contemporary presence of both ester and hydrazine functions makes compounds **5** able to give further transformations. In fact, by treatment of compounds **5c**–**h**,**j** in THF at room temperature in the presence of a stoichiometric amount of sodium hydride, the internal nucleophilic attack of the hydrazine nitrogen at the carbonyl group determined the second ring closure to obtain intermediates **6** (Scheme 3). The spontaneous loss of carbamic residue produced the new and interesting 6-thia-2,3,8-triaza-tricyclo[3.3.3.0^{1,5}]undec-7-en-4-ones **7a**,**b** and 10-thia-7,8,12-triaza-tricyclo[4.3.3.0^{1,6}]dodec-11-en-9-ones **7c**–**g** in good yields (Scheme 3, Table 1).[7]

In conclusion, this Letter shows a different behaviour between 1,2-diaza-1,3-butadienes and cycloalkenyl-1-diazenes in the reaction with aryl-thioamides. In this way, it is possible to obtain new aryl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*][1,3]thiazolines and aryl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazolines that are valuable derivatives in consideration of their potential pharmacological and biological activities. In addition, by a simple workup procedure, these cycloalkyl-thiazolines can be used in the construction of attractive and unknown fused cycloalkyl-thiazoline–pyrazoles, which are not easy to obtain by other methods.

Table 1. Yields of aryl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*][1,3]-thiazolines **5a**–**d**, aryl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazolines **5e**–**m**, 6-thia-2,3,8-triaza-tricyclo[3.3.3.0^{1,5}]undec-7-en-4-ones **7a**,**b** and 10-thia-7,8,12-triaza-tricyclo[4.3.3.0^{1,6}]dodec-11-en-9-ones **7c**–**g**

1	*n*	R^1	2	R^2	5	Yield[a] (%)	7	Yield[b] (%)
1a	1	H	**2a**		**5a**	68		
1a	1	H	**2b**		**5b**	59		
1a	1	H	**2c**		**5c**	91	**7a**	54
1a	1	H	**2d**		**5d**	86	**7b**	44
1b	2	H	**2a**		**5e**	93	**7c**	63
1b	2	H	**2c**		**5f**	97	**7d**	56
1b	2	H	**2e**		**5g**	64	**7e**	59
1b	2	H	**2f**		**5h**	96	**7f**	63
1b	2	H	**2g**		**5i**	92		
1c	2	Me	**2a**		**5j**	92	**7g**	62
1c	2	Me	**2e**		**5k**	69		
1c	2	Me	**2h**		**5l**	84		
1c	2	Me	**2i**		**5m**	77		

[a] Yield of pure isolated products **5a**–**m** based on cycloalkenyl-1-diazenes **1a**–**c**.

[b] Yield of pure isolated products **7a**–**g** based on thiazolines **5c**–**h**,**j**.

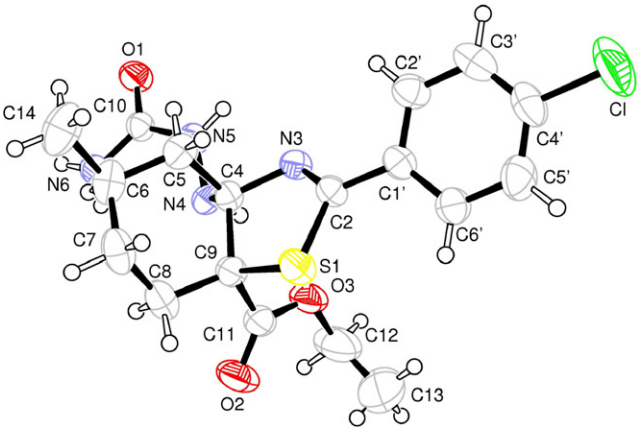
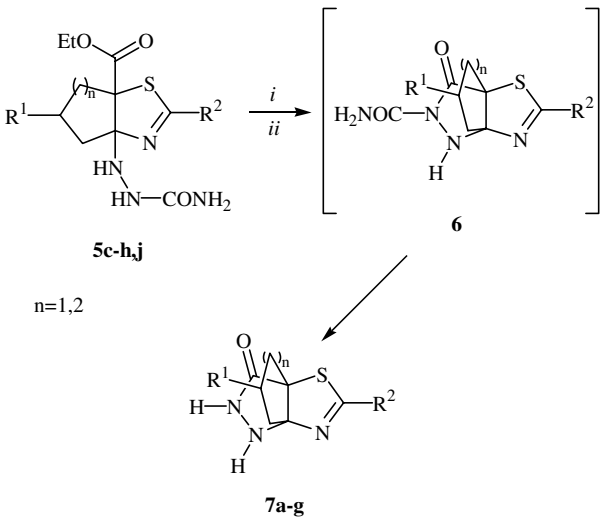


Figure 1. Crystal structure of compound **5k**. Ellipsoids enclose 50% probability.



Scheme 3. Reagents and conditions: (i) NaH (1 equiv), MeOH, rt; (ii) Amberlyst 15H, MeOH, rt.

Acknowledgements

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3. Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F. *Synlett* **2006**, 2735.
4. *General procedure for the synthesis of 2-aryl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,3]thiazolines* **5a**–**d** *or 2-aryl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazolines* **5e**–**m**. Aryl thioamides **2a**–**i** (1 mmol) were added to a magnetically stirred solution of cycloalkenyl-1-diazenes **1a**–**c**[1] (1 mmol) in methanol (10 mL). The reaction was allowed to stand at room temperature until the disappearance of the reagents (0.5–1.5 h). Compounds **5c**–**e**,**g**,**k**,**l** crystallized directly from the reaction medium. They were collected as pure products by filtration. In the other cases, the reaction solvent was evaporated under reduced pressure and the final aryl thiazolines **5a**,**b**,**h**–**j**,**m** were purified by chromatography on silica column (elution mixtures: ethyl acetate–cyclohexane) and crystallized from ethyl acetate–cyclohexane. *Spectral data for* **5e**: *ethyl 3a-[2-(aminocarbonyl)hydrazino]-2-phenyl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazoline-7a-carboxylate*. White powder, mp 152–154 °C. IR (Nujol): $\nu_{max} = 3473$, 3256, 3156, 1732, 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, $J = 6.8$ Hz), 1.40–1.52 (m, 1H), 1.53–1.56 (m, 1H), 1.59–1.66 (m, 2H), 1.90–1.98 (m, 1H), 2.07–2.11 (m, 1H), 2.18–2.26 (m, 2H), 4.17 (q, 2H, $J = 6.8$ Hz), 5.18 (br s, 1H), 5.72 (br s, 2H), 6.56 (br s, 1H), 7.36 (dt, 2H, $J^1 = 6.8$ Hz, $J^2 = 1.2$ Hz), 7.43 (dt, 2H, $J^1 = 7.2$ Hz, $J^2 = 1.2$ Hz), 7.76 (dt, 2H, $J^1 = 7.2$ Hz, $J^2 = 1.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (q), 20.3 (t), 20.9 (t), 29.0 (t), 35.3 (t), 61.9 (t), 68.1 (s), 93.5 (s), 128.0 (d), 128.4 (d), 131.8 (d), 132.7 (s), 161.2 (s), 167.4 (s), 170.4 (s). MS: m/z (%) = 362 (M^+, 1), 317 (2), 288 (65), 273 (67), 244 (42), 216 (46), 170 (100). Anal. Calcd for $C_{17}H_{22}N_4O_3S$: C, 56.33; H, 6.12; N, 15.46. Found: C, 56.38; H, 6.16; N, 15.38.
5. Crystallographic data (excluding structure factors) for compound **5k** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 636093. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].
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7. *General procedure for the synthesis of 6-thia-2,3,8-triaza-tricyclo[3.3.3.0^{1,5}]undec-7-en-4-ones* **7a**,**b** *and 10-thia-7,8,12-triaza-tricyclo[4.3.3.0^{1,6}]dodec-11-en-9-ones* **7c**–**g**. To a magnetically stirred solution of aryl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*][1,3]thiazolines **5a**–**d** or aryl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazolines **5e**–**m** in tetrahydrofuran (30 mL) a stoichiometric amount of sodium hydride (0.1 equiv) was added. The reaction easily took place (0.5–1 min.) at room temperature. Then, at the disappearance of **5** 2 equiv of Amberlyst 15H were added under magnetic stirring to the crude and the reaction was allowed to stand under this condition for 10 min. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. Products **7a**–**g** were obtained pure by chromatography on silica column (elution mixtures: ethyl acetate–cyclohexane).
Spectral data for 11-phenyl-10-thia-7,8,12-triaza-tricyclo[4.3.3.0^{1,6}]dodec-11-en-9-one **7c**: colourless oil, IR (Nujol): $\nu_{max} = 3428$, 3219, 3160, 1687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32–1.56 (m, 3H), 1.59–1.66 (m, 1H), 1.86–1.93 (m, 1H), 1.98–2.04 (m, 1H), 2.06–2.22 (m, 2H), 5.92 (br s, 1H), 6.21 (br s, 1H), 7.47 (dt, 2H, $J^1 = 7.2$ Hz, $J^2 = 1.6$ Hz), 7.51 (dt, 2H, $J^1 = 7.2$ Hz, $J^2 = 1.4$ Hz), 7.84 (dt, 2H, $J^1 = 7.2$ Hz, $J^2 = 1.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 (t), 20.5 (t), 28.7 (t), 31.0 (t), 63.7 (s), 99.0 (s), 128.6 (d), 129.0 (d), 131.8 (d), 132.4 (s), 169.4 (s), 175.3 (s). MS: m/z (%) = 273 (M^+, 100). Anal. Calcd for $C_{14}H_{15}N_3OS$: C, 61.51; H, 5.53; N, 15.37. Found: C, 61.59; H, 6.44; N, 15.29.