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Stereodefined ring contraction-rearrangement of thiocoumarins to new fused benzo[*b*]thiophene derivatives

Massimiliano Cordaro [a], Giovanni Grassi [a,*], Antonio Rescifina [b], Ugo Chiacchio [b], Francesco Risitano [a], Angela Scala [a]

[a] *Dipartimento di Chimica Organica e Biologica, Università, Vill. S. Agata, I-98166 Messina, Italy*
[b] *Dipartimento di Scienze Chimiche, Università di Catania, I-95125 Catania, Italy*

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ABSTRACT

Mesoionic 1,3-oxazolium-5-olates (münchnones) react with thiocoumarins having an electron-withdrawing group at the 3-position to afford stereodefined fused polycyclic thienopyrroles. The reaction sequence seems to be triggered by a regiospecific dipolar cycloaddition followed by ring opening of the initial 1:1 cycloadduct and intramolecular rearrangement with an unusual ring contraction.

1. Introduction

1,3-Oxazolium-5-olates (münchnones) are the most extensively studied family of mesoionic compounds and their 1,3-dipolar cycloadditions are a powerful tool for the synthesis and decoration of *N*-heterocyclic scaffolds.[1] These mesoionic oxazoles act as masked cyclic azomethine ylides on reacting with a variety of dipolarophiles providing an initial cycloadduct that usually releases carbon dioxide. With olefins or acetylenes, the cycloaddition–extrusion sequence constitutes a general synthetic route to pyrrole derivatives.[2]

Recently we have reported an unusual behaviour of the mesoionic oxazole system towards selected coumarins.[3] The reaction proceeded differently from the standard decarboxylative cycloreversion depending on the stereochemical course of the initial cycloaddition step.

Prompted by the above results, we became interested in extending these studies to thioanalogues of coumarins as dienophiles.

2. Results and discussion

We describe herein our results on the reaction of thiocoumarins having an electron-withdrawing group at the 3-position with 3,4-dimethyl-2-phenyl-l,3-oxazolium-5-olate (DMPO) as an unsymmetrical münchnone template.

DMPO **2**, generated in situ from the appropriate *N*-methyl amino acid and acetic anhydride reacted in dioxane with thiocoumarins **1** to produce the stereodefined ring-fused derivatives **3** as indicated in Scheme 1.

When R=OH (entry 6, Table 1) rapid decarboxylation occurred leading to exclusive formation of **4**. When R=OMe and R=OEt (entries 1 and 2, Table 1) pyrrolothiocoumarins **5** were also isolated along with derivatives **3**.

Compounds **3**, **4** and **5** were identified on the basis of analytical and spectroscopic data. The *cis–syn–cis* configuration of **3**[4,5] and the stereochemistry of **5** (Fig. 1)[6] were assigned by X-ray crystallography. The *trans*-relationship between the substituents of the Δ^2-pyrroline ring of **5** was confirmed by a 1D NOESY experiment on **5a**.[7]

In light of these results, the isolated stereodefined polycyclic thienopyrrole derivatives **3** show that the relative cycloaddition reaction of the mesoionic oxazole proceeds primarily in an unusual way.

Indeed, only an unexpected domino process of cycloaddition and ring opening, followed by a further cyclization could satisfactorily explain the observed ring contraction-rearrangement of thiocoumarins.[8]

Thus, the pathway shown in Scheme 2 reasonably accounts for the formation of the above products.

The reaction sequence seems to be triggered by a preferential *endo* attack via the regiospecific 1,3-cycloaddition of the thiocoumarin to DMPO. The subsequent ring opening of the resulting

* Corresponding author. E-mail address: ggrassi@unime.it (G. Grassi).

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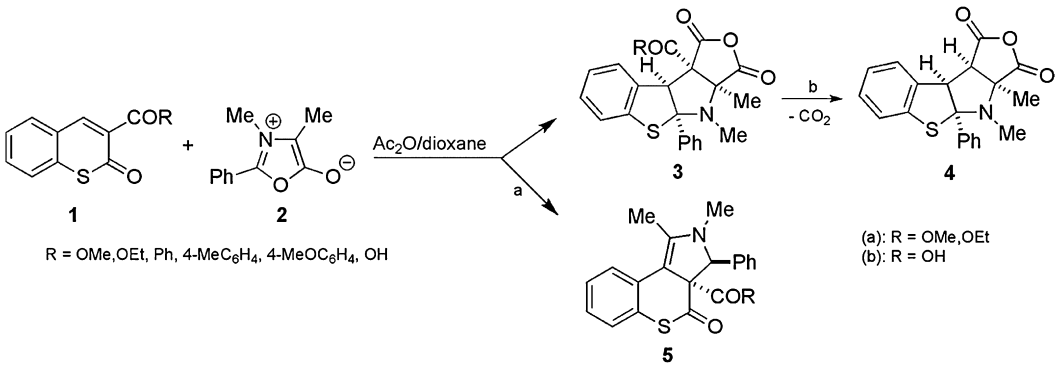


Scheme 1. Synthesis of compounds **3**–**5**.

Table 1
Yields and products from the domino cascade reaction

Entry	R	Reaction	Products (yield %)[a]
1	OMe	**3a** (45)	**5a** (37)
2	OEt	**3b** (40)	**5b** (35)
3	C_6H_5	**3c** (80)	
4	4-MeC_6H_4	**3d** (60)	
5	4-$MeOC_6H_4$	**3e** (75)	
6	OH	**4** (35)	

[a] Yield of pure isolated product.

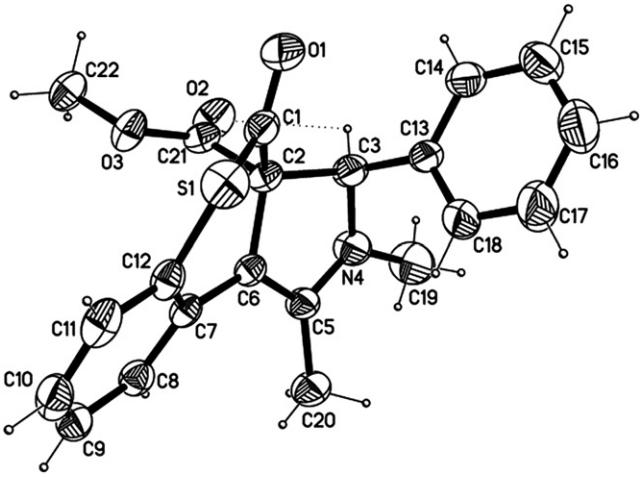
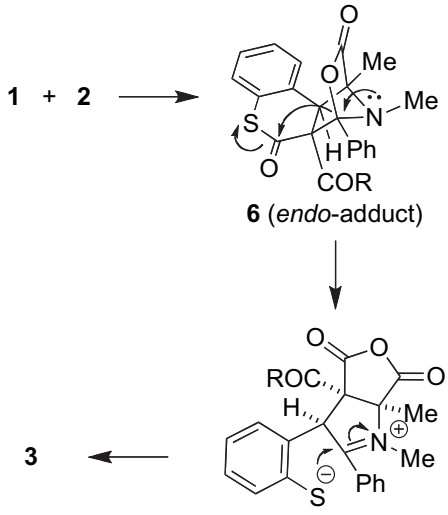


Fig. 1. Ortep drawing of **5a**.

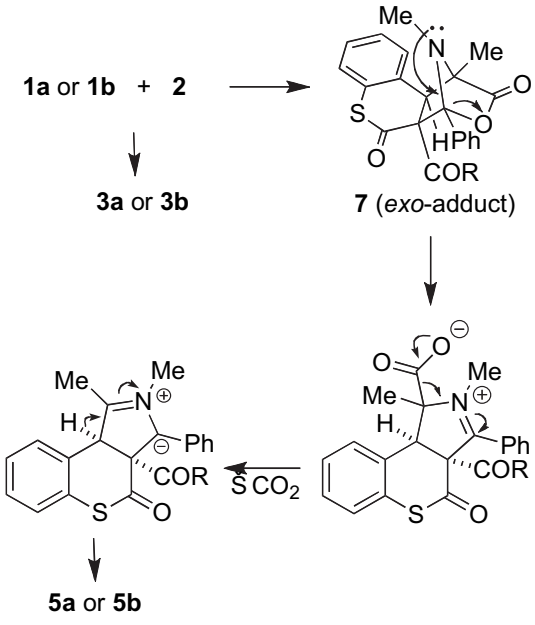


Scheme 2. Proposed mechanism for the formation of **3**.

endo cycloadduct **6** lead to a stable peripheral anhydride moiety and consequent fragmentation of the C–S bond followed by intramolecular sulfur atom transfer. The final ring contraction/rearrangement to **3** alleviates the strain of the polycyclic system.

This rationale is consistent with our previous findings,[3] in which the initial 1:1 *endo* cycloadduct of 3-substituted coumarins and DMPO undergoes translactonization and decarboxylation. The different rearrangement pathway of the transient *S*-analogue **6** can be reasonably attributed to the greater nucleophilicity of the sulfur atom and its more readily ionization to a thiolate.

Regarding the formation of **5**, only the *exo*-cycloadduct **7** can be expected to evolve to these pyrrolothiocoumarin derivatives via decarboxylative cycloreversion as indicated in Scheme 3.



Scheme 3. Proposed mechanism for the formation of **5**.

Accordingly, *endo* and *exo* approaches in the initiating cycloaddition will dictate the reaction course leading to **3**/**4** and **5**, respectively.

The outcome of observed *endo*/*exo* selectivities can be rationalized on the basis of the proposed transition states geometries represented in Fig. 2.

Thus, the products **3a**,**b** and **5a**,**b** are both equally formed because the *endo*-TS and *exo*-TS are both likely. In fact the *exo*-TS is contemporaneously stabilized by a secondary orbital interaction between the nitrogen atom and the thioate moiety and destabilized by repulsive steric and electronic interactions,[9] while the *endo*-TS

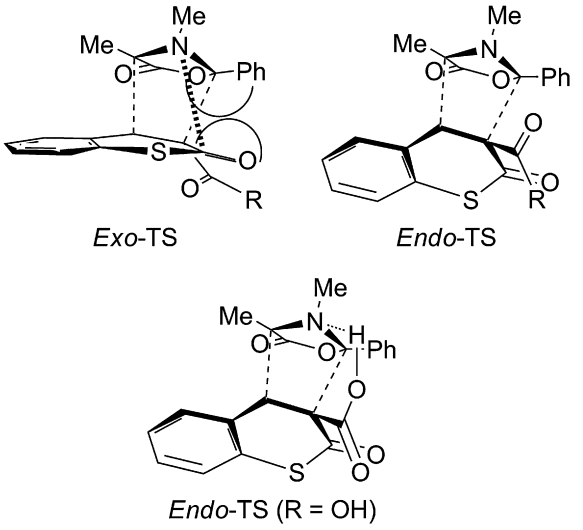


Fig. 2. Proposed transition states for cycloaddition of thiocoumarins **1** with münchnone **2**. Broken lines represent the new forming bonds, hashed line represents secondary orbital interaction, dotted line represents hydrogen bond and semi-circumferences represent repulsive destabilizing interactions.

lacks for both effects. However, the introduction of an aromatic ring (entries 3–5, Table 1) implies more steric and electronic demands that strongly penalize the *exo*-TS. In entry 6 (R=OH), the formation of a hydrogen bond in the *endo*-TS drives the reaction to the exclusive formation of **4** after unavoidable decarboxylation.

3. Conclusion

In summary, the reaction of mesoionic 1,3-oxazolium-5-olates (münchnones) with selected thiocoumarins gave stereodefined fused polycyclic thienopyrroles together with pyrrolothiocoumarin derivatives. The nature of the reaction products depends on the *exo/endo* stereochemistry of the initial 1:1 cycloadduct. Coupled with their intriguing mechanism of formation the 2-benzo[*b*]thieno[2,3-*b*]pyrrole derivatives **3** and **4** reveal an attractive *U-shaped* molecular architecture. Further studies towards exploring the usefulness of this new class of potential molecular hosts are currently in progress.

4. Experimental section

4.1. General method

Melting points were determined on a Kofler melting apparatus. IR spectra were recorded in Nujol with a Nicolet Impact 410D spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX R300 spectrometer. The chemical shifts (δ) and coupling constants (J) are expressed in parts per million and hertz, respectively. Mass spectrometry analyses and Microanalyses were carried out on a 3200 QTRAP (Applied Biosystems SCIEX) and on a Carlo Erba EA 1102, respectively. All solvents and reagents were obtained from commercial sources and purified before use if necessary. 3-Substituted thiocoumarins[10] and DMPO[11] were prepared according to literature methods. Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063–0.100 mm) for column chromatography.

4.2. Reactions of DMPO 2 with thiocoumarins 1

3-Substituted thiocoumarin **1** (1.0 equiv) and *N*-methyl-*N*-benzoylalanine (1.5 equiv) were dissolved in dioxane and acetic anhydride (3.5 equiv). The resulting solution was heated at reflux for 3 h. The solvent was removed by vacuum evaporation and the residue was purified by column chromatography on silica gel (CH_2Cl_2) affording **3**, **4** and **5** as white or yellowish solids.

*4.2.1. Compound **3a** (Table 1; entry 1).* Yield: 45%; mp 171–173 °C; IR (Nujol, ν, cm^{-1}): 1847, 1780, 1752; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 3H), 2.47 (s, 3H), 3.90 (s, 3H), 4.76 (s, 1H), 7.04–7.10 (m, 2H), 7.21–7.34 (m, 5H), 7.69–7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 32.8, 53.8, 67.0, 68.5, 74.5, 100.7, 123.3, 125.2, 127.2, 127.5, 128.7, 128.9, 129.6, 133.7, 139.9, 140.5, 165.5, 166.9, 171.6; ESI-MS: m/z [M+H]$^+$ calcd: 410.1, obsd: 410.5. Elemental anal. Calcd for $C_{22}H_{19}NO_5S$: C 64.53, H 4.68, N 3.42; found: C 64.63, H 4.58, N 3.55.

*4.2.2. Compound **3b** (Table 1; entry 2).* Yield: 40%; mp 110–115 °C; IR (Nujol, ν, cm^{-1}): 1846, 1779, 1746; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J=6.9 Hz, 3H), 1.67 (s, 3H), 2.47 (s, 3H), 4.37 (q, J=6.9 Hz, 2H), 4.75 (s, 1H), 7.04–7.09 (m, 2H), 7.21–7.35 (m, 5H), 7.69–7.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 19.1, 32.8, 63.6, 67.0, 68.4, 74.4, 100.7, 123.3, 125.2, 127.2, 127.5, 128.5, 129.4, 133.8, 140.0, 140.5, 165.6, 166.3, 171.7; ESI-MS: m/z [M+H]$^+$ calcd: 424.1, obsd: 424.3. Elemental anal. Calcd for $C_{23}H_{21}NO_5S$: C 65.23, H 5.00, N 3.31; found: C 65.11, H 5.15, N 3.51.

*4.2.3. Compound **3c** (Table 1; entry 3).* Yield: 80%; mp 143–145 °C; IR (Nujol, ν, cm^{-1}): 1852, 1777, 1674; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 2.51 (s, 3H), 5.18 (s, 1H), 6.96–6.98 (m, 2H), 7.18 (m, 1H), 7.25–7.35 (m, 4H), 7.45–7.50 (m, 2H), 7.60 (m, 1H), 7.76–7.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 32.8, 68.7, 71.7, 74.8, 100.6, 123.3, 125.1, 127.4, 127.6, 128.7, 128.9, 129.0, 129.5, 134.0, 134.3, 135.3, 140.3, 140.6, 167.8, 172.1, 191.8; ESI-MS: m/z [M+H]$^+$ calcd: 456.1, obsd: 456.3. Elemental anal. Calcd for $C_{27}H_{21}NO_4S$: C 71.19, H 4.65, N 3.07; found: C 71.25, H 4.81, N 3.16.

*4.2.4. Compound **3d** (Table 1; entry 4).* Yield: 60%; mp 185–186 °C; IR (Nujol, ν, cm^{-1}): 1851, 1774, 1671; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 3H), 2.40 (s, 3H) 2.50 (s, 3H), 5.20 (s, 1H), 6.95–6.97 (s, 2H), 7.17 (m, 1H), 7.24–7.38 (m, 6H), 7.68 (d, 2H), 7.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 21.6, 32.8, 68.5, 71.6, 74.7, 100.7, 123.2, 125.1, 127.5, 127.6, 128.6, 128.7, 129.3, 129.4, 129.5, 129.6, 132.6, 134.4, 140.4, 140.6, 145.3, 168.0, 172.2, 190.9; ESI-MS: m/z [M+H]$^+$ calcd: 470.1, obsd: 470.3. Elemental anal. Calcd for $C_{28}H_{23}NO_4S$: C 71.62, H 4.94, N 2.98; found: C 71.55, H 4.81, N 3.06.

*4.2.5. Compound **3e** (Table 1; entry 5).* Yield: 75%; mp 169–170 °C; IR (Nujol, ν, cm^{-1}): 1848, 1778, 1669; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 3H), 2.49 (s, 3H), 3.86 (s, 3H), 5.26 (s, 1H), 6.92–6.97 (m, 4H), 7.16 (m, 1H), 7.25–7.37 (m, 4H), 7.75–7.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 32.8, 55.5, 68.4, 71.3, 74.8, 100.7, 114.2, 123.1, 123.4, 127.6, 127.8, 128.5, 128.8, 131.7, 131.9, 134.5, 140.5, 140.7, 164.2, 168.2, 172.3, 189.1; ESI-MS: m/z [M+H]$^+$ calcd: 486.1, obsd: 486.2. Elemental anal. Calcd for $C_{28}H_{23}NO_5S$: C 69.26, H 4.77, N 2.88; found: C 69.33, H 4.81, N 2.98.

*4.2.6. Compound **4** (Table 1; entry 6).* Yield: 35%; mp 189–192 °C.; IR (Nujol, ν, cm^{-1}): 1844, 1776; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 3H), 2.51 (s, 3H), 3.54 (d, J=11.5 Hz, 1H), 4.01 (d, J=11.5 Hz, 1H), 7.03–7.18 (m, 2H), 7.21–7.35 (m, 5H), 7.64–7.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 31.9, 55.2, 63.1, 71.5, 102.0, 123.3, 125.1, 127.6, 128.6, 128.7, 129.0, 129.5, 134.3, 140.1, 140.7, 168.4, 172.3; ESI-MS: m/z [M+H]$^+$ calcd: 352.1, obsd: 352.3. Elemental anal. Calcd for $C_{20}H_{17}NO_3S$: C 68.36, H 4.88, N 3.99; found: C 68.25, H 4.81, N 3.81.

*4.2.7. Compound **5a** (Table 1; entry 1).* Yield: 37%; mp 155–157 °C; IR (Nujol, ν, cm^{-1}): 1737, 1677; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19

(s, 3H), 2.67 (s, 3H), 3.55 (s, 3H), 5.24 (s, 1H), 7.07–7.36 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3, 32.8, 52.8, 70.1, 74.4, 100.7, 124.7, 125.7, 126.8, 127.0, 127.7, 128.1, 128.3, 128.5, 129.2, 130.1, 130.4, 136.3, 150.4, 169.9, 185.1; ESI-MS: m/z $[M+H]^+$ calcd: 366.1, obsd: 366.4. Elemental anal. Calcd for $C_{21}H_{19}NO_3S$: C 69.02, H 5.24, N 3.83; found: C 69.16, H 5.10, N 3.76.

4.2.8. Compound ***5b*** *(Table 1; entry 2).* Yield: 35%; mp 135–138 °C; IR (Nujol, ν, cm^{-1}): 1738, 1677; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J=6.9 Hz, 3H), 2.18 (s, 3H), 2.67 (s, 3H), 3.89–4.09 (q, J=6.9 Hz, 2H), 5.25 (s, 1H), 7.06–7.39 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9, 13.3, 34.9, 48.1, 68.9, 87.3, 110.7, 124.2, 125.8, 126.6, 127.3, 127.4, 128.8, 129.1, 131.2, 136.3, 136.6, 138.0, 168.4, 187.5; ESI-MS: m/z $[M+H]^+$ calcd: 380.1, obsd: 380.3. Elemental anal. Calcd for $C_{22}H_{21}NO_3S$: C 69.63, H 5.58, N 3.69; found: C 69.75, H 5.51, N 3.76.

Supplementary data

Supplementary data associated with this article can be found on line version, at doi:10.1016/j.tet.2010.11.061. These data include MOL files and InChIKeys of the most important compounds described in this article.

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