UNICA UNIVERSITÀ DEGLI STUDI DI CAGLIARI

IRIS Università di Cagliari

UNICA IRIS Institutional Research Information System

This is the Author's manuscript version of the following contribution:

Stefano Barranco, Federico Cuccu, Federico Devoto, Régis Guillot, Pierluigi Caboni, David J. Aitken, Angelo Frongia, Synthesis of cyclobutane-fused oxazolidine-2-thione derivatives, Tetrahedron Letters 139 (2024) 155009.

The publisher's version is available at:

https://doi.org/10.1016/j.tetlet.2024.155009

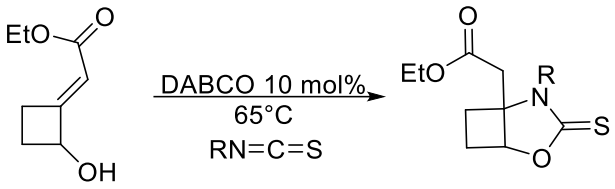
When citing, please refer to the published version.

This full text was downloaded from UNICA IRIS https://iris.unica.it/

Graphical Abstract

Synthesis of cyclobutane-fused oxazolidine-2-thione derivatives

Stefano Barranco, Federico Cuccu, Federico Devoto, Régis Guillot, Pierluigi Caboni, David J. Aitken and Angelo Frongia*



14 examples

up to 89% yield

no solvent

one-pot reaction

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of cyclobutane-fused oxazolidine-2-thione derivatives

Stefano Barranco,[a] Federico Cuccu,[a] Federico Devoto,[a] Régis Guillot,[b] Pierluigi Caboni,[c] David J. Aitken[b] and Angelo Frongia[a,*]

[a]*Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Complesso Universitario di Monserrato, S.S. 554, Bivio per Sestu, I-09042, Monserrato, Cagliari, Italy*
E-mail: afrongia@unica.it
[b]*Université Paris-Saclay, CNRS, ICMMO, Site Henri Moissan, 19 Avenue des Sciences, 91400 Orsay, France*
[c]*Dipartimento di Scienze della Vita e dell'Ambiente, Università degli Studi di Cagliari, Complesso Universitario di Monserrato-Blocco A, S.S. 554, Bivio per Sestu, I-09042, Monserrato, Cagliari, Italy.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Synthetic methods
Strained rings
Cyclobutanes
Heterocycles

ABSTRACT

An expedient, solvent-free, mild base catalyzed intermolecular cyclization reaction has been developed to enable the one-pot synthesis of fourteen examples of cyclobutane-fused oxazolidine-2-thiones in good to high yields. Bicyclic structures of this type have not previously been described in the literature; they have a *cis* ring junction with both rings deviating slightly from planarity.

2009 Elsevier Ltd. All rights reserved.

Introduction

Oxazolidine-2-thiones are an interesting class of heterocyclic molecules with a particular portfolio of chemical and biological activities. Some simple derivatives are present in foodstuffs known to cause hypothyroid effects [1], while others display antifertility activity [2] or have been proposed as plant growth regulators [3]. In a complementary yet distinct manner to the use of the related oxazolidine-2-ones, chiral oxazolidine-2-thiones have been widely employed as chiral auxiliaries in stereoselective synthesis strategies [4].

The bicyclic heteroaromatic benzoxazole-2-thione is tautomerized and *S*-functionalized derivatives thereof are of interest for their diverse biological activities [5]. In contrast, aliphatic ring-fused oxazolidine-2-thiones are a considerably less studied family (Figure 1). Most work has been done on combinations with 5- or 6-membered ring carbohydrate scaffolds [6] such as the pyranose derivatives **A-C** [7] and a nucleoside derivative **D** [8]; indeed, ribofuranosyl (and related pentofuranosyl) oxazolidinone-2-thiones such as **E** have been suggested as prebiotic precursors of ribonucleotides [9]. Other descriptions of alicyclic ring-fused oxazolidinone-2-thiones are rare: isolated examples are a cholestane derivative **F** [10], a putative unstable fullerene adduct (not shown) [11] and, recently from our group, a cyclohexane derivative **G** [12].

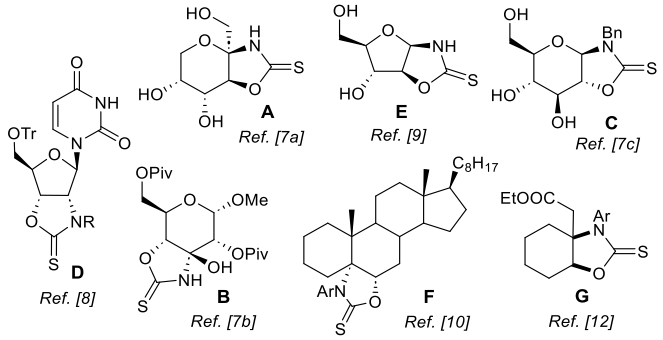
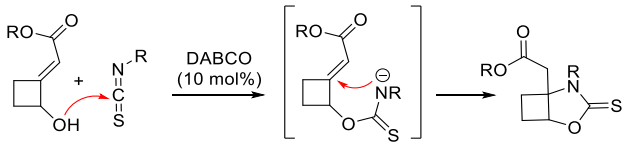


FIGURE 1. EXAMPLES OF PREVIOUSLY-DESCRIBED FUSED-RING OXAZOLIDINONE-2-THIONE SYSTEMS.

In order to expand the structural diversity of ring-fused oxazolidinone-2-thiones, we envisaged the preparation of derivatives fused to a 4-membered ring. The cyclobutane ring itself is hugely important in organic chemistry due to its particular geometry and its inherent ring strain [13], and numerous diversely-functionalized cyclobutanes of natural or synthetic origin are known to display a wide range of chemical and biological properties [14]. To the best of our knowledge however, no cyclobutane-fused oxazolidine-2-thiones have been reported to date. Such structures are expected to be quite strained and should only exist with a *cis* ring junction.

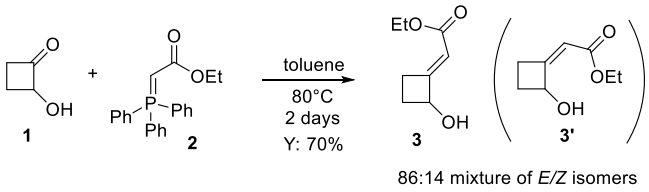
To provide a first entry to such compounds, we decided to investigate the reaction of isothiocyanates with a 2-hydroxycyclobutylidene ester. This strategy had proved successful in the recent preparation of simpler oxazolidine-2-thiones from acyclic α,β-unsaturated hydroxy esters [12]. The solvent-free DABCO-catalyzed protocol proceeds via the mechanism shown in Scheme 2.



SCHEME 2. PLANNED ACCESS TO CYCLOBUTANE-FUSED OXAZOLIDINE-2-THIONE DERIVATIVES.

Results and discussion

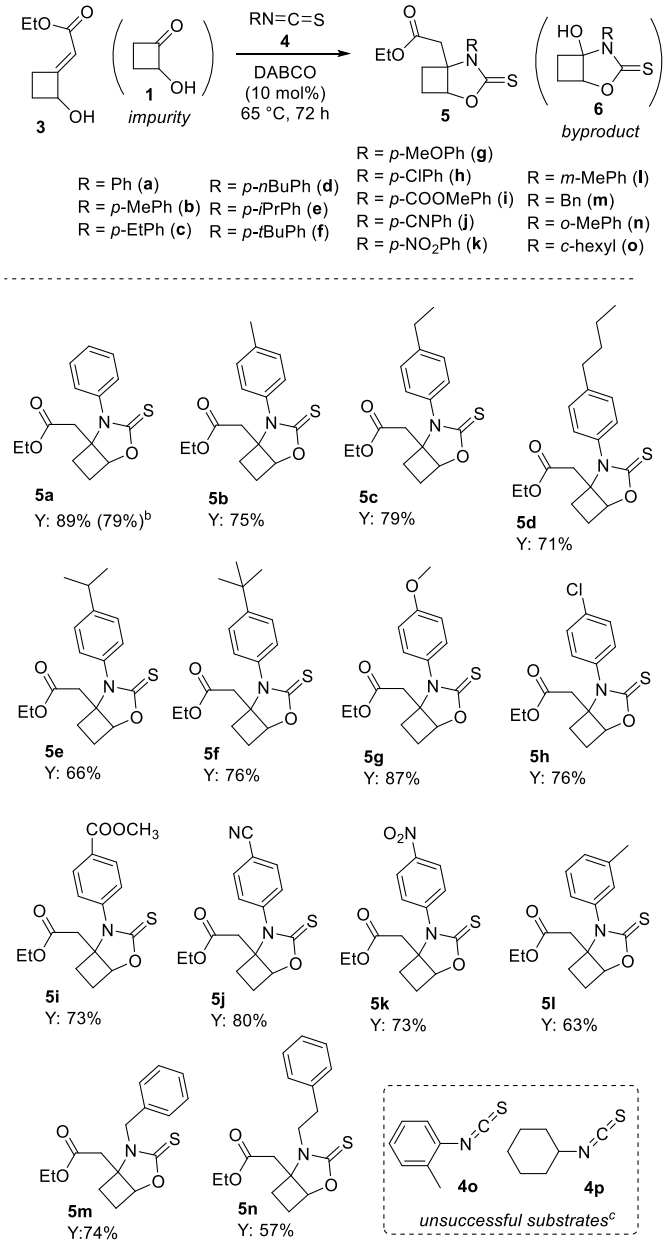
We selected the known ester **3** as the cyclobutane substrate, prepared by a Wittig reaction between 2-hydroxycyclobutanone **1** and ethyl 2-(triphenyl-λ^5-phosphanylidene)acetate **2** using the literature procedure [15] (Scheme 3). The required *E* isomer was separated from its *Z* isomer **3'** by chromatography [16].



Scheme 2. Synthesis of the starting material **3**.

Compound **3** was reacted with a panel of aryl isothiocyanates **4** using similar reaction conditions to those that had been established in previous syntheses of simple oxazolidine-2-thiones (1 equiv. of each reagent; 10 mol% DABCO; 65 °C; 72 h). In this way, we successfully prepared the small library of cyclobutane-fused oxazolidine-2-thiones **5** shown in Scheme 3.

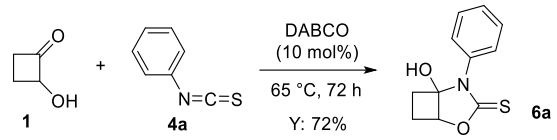
The first isothiocyanate tested was the phenyl derivative **4a** which gave the target compound **5a** as the only product in an encouraging 89% yield. For this first example, the reaction progress was monitored periodically (see supporting information) and the transformation appeared to be largely complete within 36 h. No depletion of the yield was observed over the following 36 h period so the 72h reaction time was retained for all subsequent reactions. Isothiocyanates **4b-f** with alkyl substituents at the *p*-position of the aromatic ring performed well, giving **5b-f** in good yields (66-79%). Satisfyingly, isothiocyanates **4g-k** bearing either electron-donating or electron-withdrawing substituents at the *p*-position were accommodated in the reaction, affording the products **5g-k** in uniformly good yields (73-87% yield). The *m*-substituted isothiocyanate **4l** led to the adduct **5l** (63% yield) but the reaction with the *o*-substituted isothiocyanate **4o** was unsuccessful, presumably due to steric hindrance. We examined three aliphatic isothiocyanates: pleasingly, the benzyl and phenethyl substrates **4m-n** were converted smoothly into the corresponding derivatives **5m-n** in moderate to good yield (57-74%), whereas the cyclohexyl substrate **4p** failed to react. To demonstrate the preparative applicability of the methodology, a five-fold scale-up synthesis of compound **5a** was performed. The reaction of **3** with **4a** on a 1.36 mmol scale gave the product **5a** in only slightly reduced yield (79%). The reactivity of the (*Z*)-2-hydroxycyclobutylidene ester **3'** with **4a** was also examined in the standard conditions: in this case, compound **5a** was obtained in only 11% yield, possibly due to increased steric hindrance prevailing in the substrate.



Scheme 3. Synthesis of cyclobutane-fused oxazolidine-2-thione derivatives.[a,b,c]

[a]Reaction conditions: **3** (0.272 mmol), **4** (0.272 mmol), DABCO (0.0272 mmol), 65 °C, 72 h. Isolated yields are indicated. [b]In parentheses, the yield of a scale-up reaction (1.36 mmol of **3**). [c]The starting materials were recovered.

All the new compounds presented in Scheme 3 were isolated in the indicated yields after purification by column chromatography and were characterized spectroscopically (see supporting information). On some occasions we detected (using ^{1}H NMR) the presence of a by-product (up to 5%) in crude product mixtures. We assigned its structure as that of **6** displaying a hemi-aminal-type function. This by-product might arise from the reaction between isothiocyanate **4** and small amounts of 2-hydroxycyclobutanone **1**, present as an inseparable contaminant of the starting material **3**. To confirm this postulate, **1** was reacted with isothiocyanate **4a** in the standard reaction conditions, leading to the formation of **6a** in good isolated yield (72%) (Scheme 4). This observation underlined the advantage of using a clean sample of the substrate **3**, even though the requisite compounds **5** in Scheme 3 could be obtained pure (devoid of **6**) by careful chromatography.



Scheme 4. Control experiment: preparation of derivative **6a**.

Compound **5f** furnished crystals that were suitable for single crystal X-ray diffraction analysis [17]. The molecular structure is illustrated in Figure 2, confirming the expected *cis* ring junction. The cyclobutane ring was considerably flattened, with a puckering angle of only 12° while the oxazolidinone-2-thione ring was nearly planar, with C5 being 10° out of the plane of the other four atoms to accommodate the cyclobutane ring puckering.

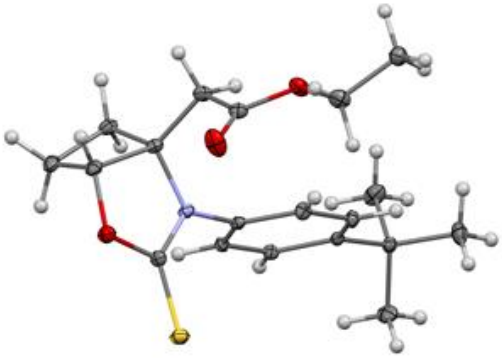
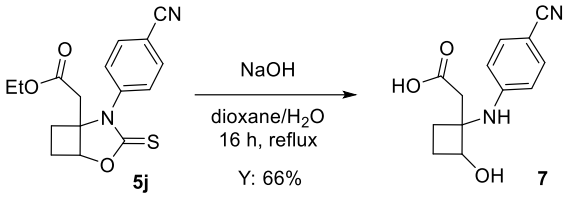


Figure 2. X-ray crystal structure of **5f**.

We examined the reaction of compound **5j** in basic conditions (NaOH, dioxane/H_2O, reflux). Hydrolysis of both the ester and the heterocycle was observed, leading to monocyclic product **7** in 66% yield. This result contrasted with the behaviour of a monocyclic analogue (with Ar = Ph) reported in our previous work [12], which undergoes hydrolysis of only an ester function in the same conditions. The heterocyclic ring-opening of **5j** may be due to the added strain imparted by the fused four-membered ring. A further indication of the exalted reactivity was the observation that the attempted ammonolysis (2 M NH_3/EtOH, 110 °C 16 h, sealed tube) of ester **5j** led to a complex product mixture.



Scheme 6. Preparation of cyclobutane compound **7**.

Conclusion

In summary, the procedure described in this paper provides a practical, solvent-free, mild base catalyzed protocol for the one-pot preparation of cyclobutane-fused oxazolidine-2-thiones for the first time. Both rings in the new bicyclic system are near to planar. Further applications of this strategy in synthetic methodology are currently underway in our laboratory.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Financial support from the MUR (PNRR 2022, Spoke VS4, WP4.5 Task 4.5.1–RETURN) is acknowledged. C.I.N.M.P.I.S. "Consorzio Interuniversitario Nazionale di Ricerca in Metodologie e Processi Innovativi di Sintesi" is acknowledged. We acknowledge the CeSAR (Centro Servizi Ricerca d'Ateneo) core facility of the University of Cagliari and Dr. Sandrina Lampis for assistance with the generation of NMR data.

Appendix A. Supplementary data

References

1 For leading references, see: (a) N. S. Radulović, M. M. Todorovskaa, D. B. Zlatković, N. M. Stojanović, P. J. Randjelović, Food Chem. Toxicol. 110 (2017) 94–108. (b) N. Agerbirk, C. E. Olsen, Phytochemistry 115 (2015) 143–151.
2 D. Lednicer, D. E. Emmert, J. Med. Chem. 11 (1968) 1258-1262.
3 R. W. Lang, G. Ramos, European Patent EP0417044A2 (1991).
4 Reviews: (a) E. Sansinenea, A. Ortiz, P. Rollin, S. Silva, Curr. Org. Synth. 14 (2017) 1109-1131. (b) M. Shamszad, M. T. Crimmins, Comprehensive Chirality 3 (2012) 19-41. (c) A. Ortiz, E. Sansinenea, J. Sulfur Chem. 28 (2007) 109–147. (d) F. Velázquez, H. F. Olivo, Curr. Org. Chem. 6 (2002) 303-340.
5 Recent examples: (a) B. T. Ramanjaneyulu, S. Vidyacharan, G.-N. Ahn, D.-P. Kim, **React. Chem. Eng.** 5 (2020) 849-852. (b) Y. Xiao, B. Jing, X. Liu, H. Xue, Y. Liu, Beilstein J. Org. Chem. 15 (2019) 279–284. (c) T. Tankam, J. Srisa, M. Sukwattanasinitt, S. Wacharasindhu, J. Org. Chem. 83 (2018) 11936–11943. (d) S. Kakkar, S. Tahlan, S. M. Lim, K. Ramasamy, V. Mani, S. Adnan A. Shah, B. Narasimhan, Chem. Cent. J. 12 (2018) 92. (e) P. Kohli, S. D. Srivastava and S. K. Srivastava, J. Chin. Chem. Soc. 54 (2007) 1003-1010.
6 Review: A. C. Simão, J. Rousseau, S. Silva, A. P. Rauter, A. Tatibouët, P. Rollin, Carbohydr. Chem. 35 (2009) 127–172.
7 For examples, see: (a) J. C. Jochims, A. Seeliger, G. Taigel, Chem. Ber. 100 (1967) 845-854. (b) S. Silva A. C. Simão, A. Tatibouët, P. Rolli, A. P. Rauter, Tetrahedron Lett. 49 (2008) 682–686. (c) H.-P. Kruse, M. Heydenreich, W. Engst, U. Schilde, J. Kroll, Carbohydr. Res. 340 (2005) 203-210.
8 A. Gondela, M. D. Tomczyk, Ł. Przypis, K. Z. Walczak, Tetrahedron 72 (2016) 5626-5632.
9 S. Stairs, A. Nikmal, D.-K. Bučar, S.-L. Zheng, J. W. Szostak, M. W. Powner, Nat. Commun. 8 (2017) 15270.
10 M. Mushfiq, T. Manuel, R. Rehman, Synth. Commun. 34 (2004) 3989-3996.
11 X. Yang, S. Huang, Z. Jia, Z. Xiao, Z. Jiang, Q. Zhang, L. Gan, B. Zheng, G. Yuan, S. Zhang, J. Org. Chem. 78 (2008) 2518-2526.
12 F. Soddu, F. Devoto, V. Marras, P. Caboni, F. Secci, D. J. Aitken, A. Frongia, Eur. J. Org. Chem. 2022 (2022) e202201115.
13 For selected reviews on cyclobutane preparation and reactivity, see: (a) J. C. Namsylo, D. E. Kaufmann, Chem. Rev. 103 (2003) 1485-1538. (b) E. Lee-Ruff, G. Mladenova, Chem. Rev. 103 (2003) 1449-1484. (c) N.-Y. Fu, S.-H. Chan, in The Chemistry of Cyclobutanes, eds. Z. Rappoport, J. F. Liebman, Wiley, Chichester, 2005, pp. 357–440. (d) E. Lee-Ruff, in The Chemistry of Cyclobutanes, eds. Z. Rappoport, J. F. Liebman, Wiley, Chichester, 2005, pp. 281–355.
14 For selected reviews on cyclobutanes in biologically active and/or natural products, see: (a) Yang, Q. Jia, S. S. Song, X. Huang, Nat. Prod. Rep. 40 (2023) 1094–1129. (b) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes, D. Blanco-Ania, ChemMedChem 17 (2022) e202200020. (c) J. Li, K. Gao, M. Ming Bian, H. Ding, Org. Chem. Front. 7 (2020) 136–154. (d) V. M. Dembitsky, J. Nat. Med. 62 (2008) 1-33. (e) R. M. Ortuño, A. G. Moglioni, G. Y. Moltrasio, Curr. Org. Chem. 9 (2005) 237-259.
15 F. Cuccu, L. Serusi, A. Luridiana, F. Secci, P. Caboni, D. J. Aitken, A. Frongia, Org. Lett. 21 (2019) 7755–7758.
16 For confirmation of the E configuration, see the supporting information for: V. Marras, P. Caboni, F. Secci, R. Guillot, D. J. Aitken, A. Frongia, Org. Biomol. Chem. 19 (2021) 8912–8916.
17 Crystallographic data for compound **5f** have been deposited at the CCDC in file number 2314381 (see supporting information for details).