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Synthesis of Thiomorpholin-3-ones by a Gold-Catalysed Oxidative Cyclisation-Rearrangement Cascade from Ynamides

Thomas Baker and Paul W. Davies*

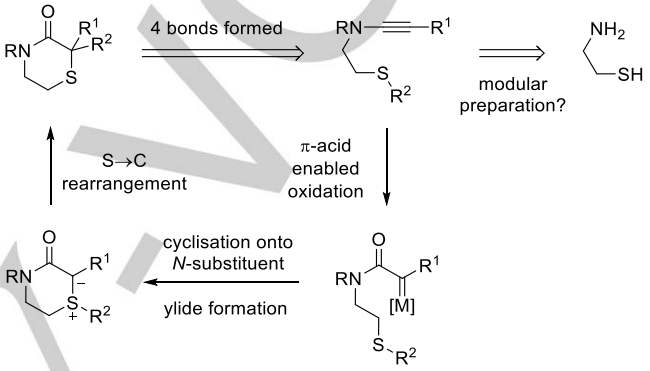
Abstract: A gold-catalyzed oxidative *N*-cyclisation strategy allows for the preparation of α-aryl thiomorpholin-3-ones from readily assembled ynamides bearing tethered thioethers. A cascade of oxidation, cyclisation and then [2,3]- or [1,2]-sigmatropic rearrangement of the resulting sulfonium ylide proceeds under mild reaction conditions. Cyclisation and intermolecular oxidation are in competition at two different stages of the reaction. The required switch in selectivity between these processes can be managed by combining pyridine *N*-oxide oxidant with an IPrAuCl-derived catalyst.

Introduction

ulfur heterocycles are of general interest, being found extensively within bioactive natural products[1] and drug molecules.[2] Within this area, the thiomorphilin-3-one motif has demonstrated broad biological potential, including antimycobacterial activity,[3] dual activity as norepinephrine reuptake inhibitors (NRI) and 5-HT1A partial agonists,[4] and antihypertensivity.[5] The motif is encountered widely across the patent literature[6] and is found in the natural product bafilomycin F.[7] New strategies to complement existing methods[8] with expedient syntheses of differently-elaborated thiomorphilin-3-one motifs can facilitate wider use of this motif and its derivatives. Here we describe a modular method to prepare the thiomorpholin-3-one scaffold from readily-assembled ynamides by a π-acid catalysed oxidative cyclisation-rearrangement cascade.

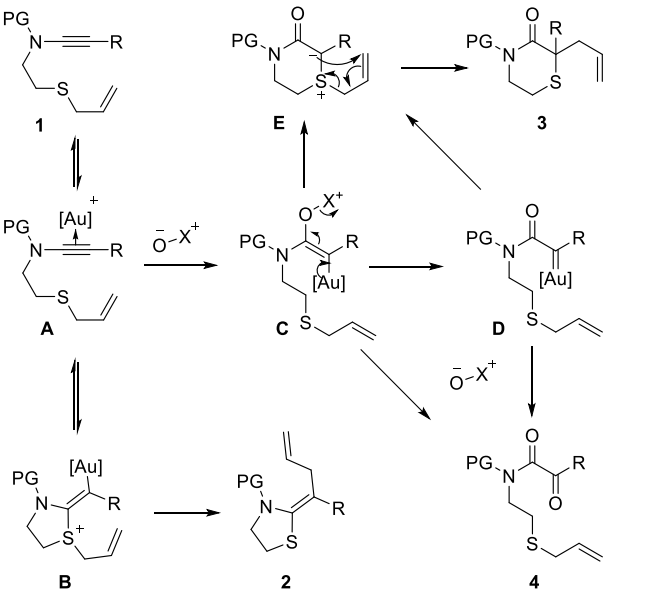
The formation and rearrangement of a cyclic sulfonium ylide provides a useful route into functionalized sulfur heterocycles.[9] This approach has not yet been exploited in thiomorpholin-3-one synthesis. The preparation of sulfonium ylides can be inefficient and limiting, requiring sulfonium salt formation and treatment with base, or the installation of sacrificial functionality such as diazomethane derivatives.[10] An alternative approach sees alkynes used as immediate precursors to sulfonium ylides in order to increase overall efficiency and widen the potential applicability of these reactive intermediates.[11]

In a fully intermolecular gold-catalyzed three-component coupling our group showed that ynamides[12] can be used as precursors to sulfonium ylides.[11g] We questioned whether such an approach could be adapted to ynamides bearing a thioether unit for a partially intramolecular manifold. The thiomorpholin-3-one scaffold would follow a controlled intermolecular oxidation, then cyclisation and rearrangement cascade (Scheme 1).[13]



Scheme 1. Proposed oxidative cyclisation-rearrangement cascade strategy to prepare thiomorphilin-3-ones.

Several powerful nitrogen heterocycle-forming transformations have been developed in recent years based on the oxidative *N*-cyclisation of ynamides under π-acid catalysis.[14] A common challenge lies in favouring cyclisation onto the *N*-substituent over a second oxidation process.[14a-h, 15] The proposed



Scheme 2. Outline of potential competing pathways in the oxidative *N*-cyclisation route to thiomorphilinones.

[a] Thomas Baker and Dr. Paul W. Davies
School of Chemistry,
University of Birmingham, Birmingham, UK
E-mail: p.w.davies@bham.ac.uk
Web: www.birmingham.ac.uk/daviesgroup

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thiomorphilinone synthesis appeared to offer a further level of complexity to this oxidative *N*-cyclisation strategy. Seemingly viable cyclisation and oxidation processes are in competition at two distinct stages of the reaction and a switch in selectivity between these processes must occur as the reaction proceeds (Scheme 2).

For the desired transformation to occur, intermolecular attack of the oxidant (**A**→**C**) must outperform intramolecular cyclisation (**A**→**B**), where a subsequent S→C 1,3-allyl migration or thio-Claisen rearrangement could deliver an ynamide carbothiolation product **2**. Though known with alkynes,[16] carbothiolation has not previously been reported on ynamides, but the closely related carboalkoxylation processes have been.[17],[18] Subsequently, cyclisation must outcompete oxidation to deliver ylide **E** to form **3** rather than oxo-compound **4**, whether directly from the vinyl gold carbenoid **C** or after elimination of the nucleofuge through the gold carbene **D**.

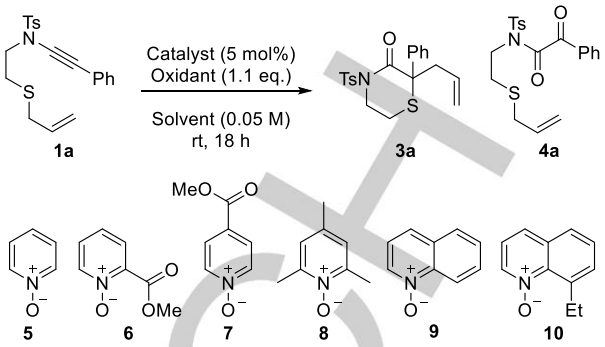
Results and Discussion

Our study commenced with ynamide **1a**. Initial investigations under gold catalysis employed diphenyl sulfoxide as oxidant.[19] Complex mixtures of isomeric products were observed that were consistent with an operative carbothiolation pathway. As the same products were formed when the reactions were run in the absence of oxidant, a more reactive oxidant was deemed necessary in order to initiate the desired cascade.

Thiomorpholin-3-one **3a** was seen along with the over-oxidation product **4a** and unreacted **1a** when pyridine *N*-oxides were employed (Table 1). Despite the presence of remaining ynamide, none of the isomerisation products were seen, which is consistent with pyridine *N*-oxide, or the released pyridine, attenuating the activity of the gold catalyst.

Gold salts such as Au(I) chloride and picolinate gold(III) chloride were superior to a triphenylphosphine ligated gold(I) system, which favoured the formation of **3a**, but were less effective than an NHC ligated gold(I) species (Table 1, entries 1-4). Simple pyridine *N*-oxide **5** proved superior to the other oxidants screened, including the methyl picolinate *N*-oxide **6** that we have found to be effective in other ynamide reactions,[11g, 14c] and the ethylquinoline *N*-oxide **10** widely used in other oxidations (Entries 4-9).[20] Using acetonitrile as the solvent saw further improvement (Entry 10). In addition to aiding catalyst longevity and turnover, the positive impact of the IPr ligand and acetonitrile solvent could be ascribed to greater solvation of the oxidant slowing down the second oxidation event, while the cationic nature of the organogold species is attenuated to favour reaction with neutral and more polarisable sulfide. Use of silver tosylate proved more efficient than other commonly used silver salts (Entries 10-12). Increasing temperature was not beneficial, while halving the catalyst loading saw reduction in recovery and yields (Entries 13-14). Ynamide was recovered in the absence of gold catalyst, while decomposition was seen using tosic acid (Entries 15-16).

Table 1. Screen of reaction conditions with pyridine *N*-oxides



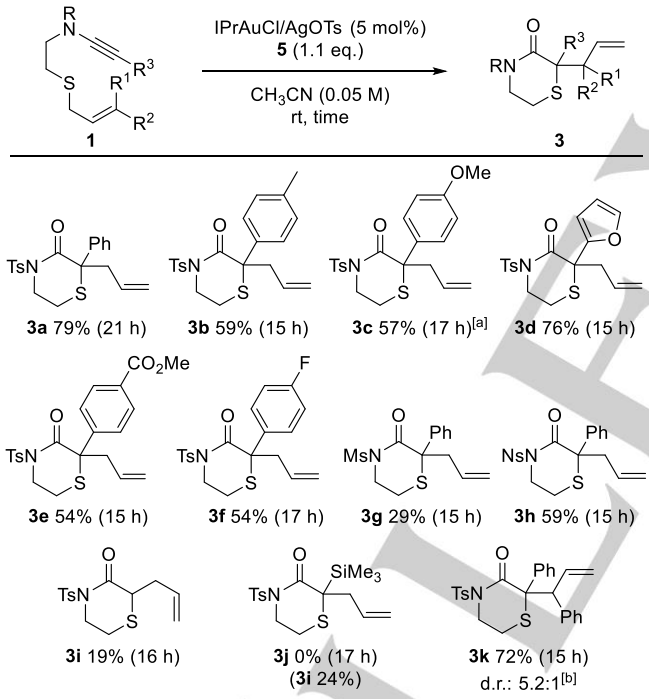
Entry	Catalyst	Solvent	Oxidant	Yields (%)[a]		
				3a	**4a**	**1**
1	$PicAuCl_2$	CH_2Cl_2	**5**	44	28	14
2	AuCl	CH_2Cl_2	**5**	40	25	22
3	PPh_3AuCl /AgOTs	CH_2Cl_2	**5**	17	39	31
4	IPrAuCl /AgOTs	CH_2Cl_2	**5**	56	18	13
5	IPrAuCl /AgOTs	CH_2Cl_2	**6**	17	34	<5
6	IPrAuCl /AgOTs	CH_2Cl_2	**7**	-	18	<5
7	IPrAuCl /AgOTs	CH_2Cl_2	**8**	5	7	76
8	IPrAuCl /AgOTs	CH_2Cl_2	**9**	22	34	30
9	IPrAuCl /AgOTs	CH_2Cl_2	**10**	45	42	9
10	IPrAuCl /AgOTs	CH_3CN	**5**	83	12	<5
11	IPrAuCl /$AgNTf_2$	CH_3CN	**5**	74	20	6
12	IPrAuCl /$AgSbF_6$	CH_3CN	**5**	70	26	10
13	IPrAuCl /AgOTs[b]	CH_3CN	**5**	65	13	5
14	IPrAuCl /AgOTs[c]	CH_3CN	**5**	66	14	12
15	AgOTs	CH_3CN	**5**	<5	<5	>95
16	$TsOH.H_2O$	CH_3CN	**5**	-	-	-

[a] Yields determined by NMR spectroscopy against a known quantity of tetramethylbenzene. [b] Reaction performed at 40 °C. [c] Reaction performed with 2.5 mol% of catalyst..

The scope of this reaction was then investigated across ynamides bearing a range of substituents on the ynamide and sulfide substituents. These were prepared from cysteamine hydrochloride by a straightforward and modular approach. Allylation, followed by immediate sulfonylation of the resulting residue precedes copper-catalysed ynamide formation using the

methods developed by the groups of Hsung or Evano (See ESI).[21]

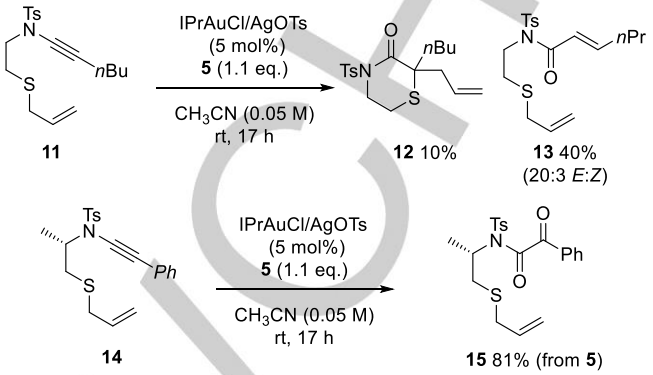
Under the standard conditions, the reaction accommodates a selection of (hetero)aromatic groups on the alkyne (Scheme 3). Over-oxidation pathways have completely dominated in a number of oxidative *N*-cyclisation reactions when the ynamide bears electron-donating groups.[14f, 14g] However, they are tolerated here (**3b**-**d**), as are electron-withdrawing substituents (**3e**-**f**). The mesyl-protected ynamide **1g** was less stable, and afforded **3g** in poor yield alongside over-oxidised material and recovered **1g** in approximately equal quantities. However, the nosyl protecting group afforded **3h** in reasonable yield, providing the potential for complementary deprotection strategies to the reducing metals commonly used for *N*-tosyl amides.[14c, 22][23] Use of a terminal ynamide led to low yield of mono α-substituted compound **3i**, with the ynamide proving unstable. The trimethylsilyl protected ynamide **1j** gave none of the silylated thiomorpholin-3-one **3j** with a small quantity of **3i** formed instead. A substituted allyl group also migrates allowing the ready assembly of a congested system (**3k**). A regiospecific allylic inversion was observed, matching a sigmatropic rearrangement of the sulfonium ylide rather than an allyl cation migration mechanism.[11c]



Scheme 3. The effect of modifying the substitution pattern around ynamides for the formation of thiomorpholin-3-ones. [a] Inseparable from overoxidised product, yield determined by ^{1}H NMR spectroscopy against a known quantity of tetramethylbenzene. [b] Ratio determined by ^{1}H NMR spectroscopy.

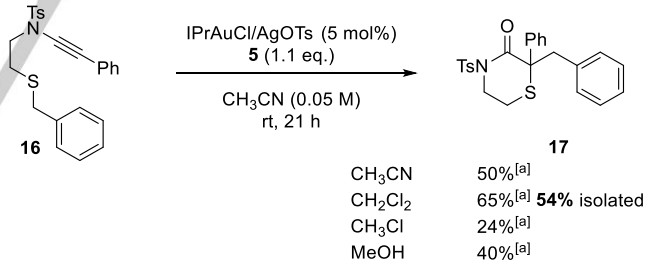
The presence of alkyl groups adjacent to the forming carbenoid centre is often not compatible with an oxidative cyclisation approach as it introduces a fast competing 1,2-CH insertion process that diverts the reaction outcome.[14a-h, 15a] Reaction of **11** shows that, while this pathway does dominate to give the α,β-unsaturated *N*-tosyl amide **13**, some of the thiomorpholin-3-one **12** was obtained (Scheme 4).

An attempt to extend this method to more substituted thiomorpholines through the use of an L-alanine derived analogue **14** was unsuccessful (Scheme 4). The over-oxidation product **15** was favoured, presumably due to increased steric impedance at the conformation required for cyclisation.



Scheme 4. Competing processes outperforming the oxidative *N*-cyclisation pathway.

Previous studies into the rearrangement chemistry of sulfonium ylides generated from gold carbenes and carbenoids have been limited to allylic systems. The *S*-benzyl ynamide **16**[24] reacted to give thiomorpholine **17** resulting from a Stevens (1,2-) rearrangement pathway, with no Sommerlet-Hauser (2,3-) rearrangement product observed (Scheme 5). Dichloromethane was a superior solvent in this case to acetonitrile, methanol or chloroform, permitting carbenoid and ylide formation while providing a suitable solvent cage for the migration.



Scheme 5. Oxidative cyclisations of ynamides featuring Stevens rearrangement. [a] Yields determined by ^{1}H NMR spectroscopy against a known quantity of tetramethylbenzene

Conclusions

An oxidation-cyclisation-sigmatropic rearrangement cascade sequence affords α-disubstituted or α-monosubstituted α-aryl thiomorpholin-3-ones under mild reaction conditions. Four bonds and a sulfur substituted quaternary centre are generated from a triple bond in a single step. A modular synthesis of the starting ynamides enables straightforward access into the heterocyclic motif in four steps from cysteamine. Modified allyl units and electronically-diverse groups at the C-terminus are tolerated in the process, but an additional substituent adjacent to nitrogen is not.

Despite the presence of competing cycloisomerisation and oxidation processes, effective control over the course of the reaction can be achieved using an efficient near-stoichiometric amount of pyridine-*N*-oxide as oxidant alongside an IPrAuCl/AgOTs catalyst system. Under these conditions, oxidation is initially favoured over an intramolecular cyclization process at the gold-ynamide complex, but then disfavoured relative to cyclisation in the next step at the carbenoid. As shown by the reactions with ynamides bearing electron-rich aromatic or alkyl C-substituents, cyclisation to form the sulfonium ylide after oxidation is relatively fast compared to other cyclisation modes employed in oxidative *N*-cyclisation reactions. The reactivity of sulfonium ylides generated from alkynes under gold catalysis has been expanded to include 1,2-rearrangements alongside 2,3-rearrangements. Further investigations into the reactivity of sulfur bearing ynamides under gold catalysis are ongoing.

Experimental Section

Ynamide (1.0 eq.), CH_3CN (0.2 M), pyridine *N*-oxide (1.1 eq.), AgOTs (0.05 eq.) and then IPrAuCl (0.05 eq.) are added to a Schlenk tube under argon and then stirred at room temperature. On completion, the solution is filtered through a small plug of silica, eluting with ethyl acetate, concentrated *in vacuo* and the residue purified by flash column chromatography.

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Keywords: ynamide • gold • oxidation • cyclisation • nitrogen heterocycles

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[1] K. L. Dunbar, D. H. Scharf, A. Litomska, C. Hertweck, *Chem. Rev.* **2017**, *117*, 5521-5577.

[2] M. Feng, B. Tang, S. H. Liang, X. Jiang, *Curr. Top. Med. Chem.* **2016**, *16*, 1200-1216.

[3] M. Biava, G. C. Porretta, G. Poce, C. Battilocchio, S. Alfonso, A. D. Logu, N. Serra, F. Manetti, M. Botta, *Biorg. Med. Chem.* **2010**, *18*, 8076-8084.

[4] D. L. Gray, W. Xu, B. M. Campbell, A. B. Dounay, N. Barta, S. Boroski, L. Denny, L. Evans, N. Stratman, A. Probert, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6604-6607.

[5] A. M. Velázquez, L. Martínez, V. Abrego, M. A. Balboa, L. A. Torres, B. Camacho, S. Díaz-Barriga, A. Romero, R. López-Castañares, E. Angeles, *Eur. J. Med. Chem.* **2008**, *43*, 486-500.

[6] a) R. Duggal, W. Hao, K. J. Herlihy, W. Liu, A. K. Patick, E. Sha (Agouron Pharma), US2004229817, **1999**; b) M. L. Phillips, J. A. Panetta (Eli Lilly co), US5981523, **1999**.

[7] G. Carr, D. E. Williams, A. R. Díaz-Marrero, B. O. Patrick, H. Bottriell, A. D. Balgi, E. Donohue, M. Roberge, R. J. Andersen, *J. Nat. Prod.* **2009**, *73*, 422-427.

[8] a) M. H. Keylor, J. E. Park, C.-J. Wallentin, C. R. J. Stephenson, *Tetrahedron* **2014**, *70*, 4264-4269; b) S. Marcaccini, R. Pepino, T. Torroba, D. Miguel, M. a. García-Valverde, *Tetrahedron Lett.* **2002**, *43*, 8591-8593; c) A. J. Williams, S. Chakthong, D. Gray, R. M. Lawrence, T. Gallagher, *Org. Lett.* **2003**, *5*, 811-814; d) S. Indumathi, S. Perumal, J. C. Menéndez, *Tetrahedron* **2011**, *67*, 7101-7105; e) Z. Liu, A. Nefzi, *Tetrahedron Lett.* **2012**, *53*, 1013-1014; f) A. Otto, J. Liebscher, *Synthesis* **2003**, *2003*, 1209-1214.

[9] For examples: a) C. J. Moody, R. J. Taylor, *Tetrahedron* **1990**, *46*, 6501-6524; b) A. J. P. Mortimer, A. E. Aliev, D. A. Tocher, M. J. Porter, *Org. Lett.* **2008**, *10*, 5477-5480; Reviews: c) S. N. Lakeev, I. O. Maydanova, F. Z. Galin, G. A. Tolstikov, *Russ. Chem. Rev.* **2001**, *70*, 655-672; d) J. B. Sweeney, *Chem. Soc. Rev.* **2009**, *38*, 1027-1038.

[10] a) C.-Y. Zhou, W.-Y. Yu, P. W. H. Chan, C.-M. Che, *J. Org. Chem.* **2004**, *69*, 7072-7082; b) V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J.-L. Vasse, C. L. Winn, *J. Am. Chem. Soc.* **2003**, *125*, 10926-10940.

[11] a) Y. Kato, K. Miki, F. Nishino, K. Ohe, S. Uemura, *Org. Lett.* **2003**, *5*, 2619-2621; b) P. W. Davies, S. J. C. Albrecht, *Chem. Commun.* **2008**, 238-240; c) P. W. Davies, S. J. Albrecht, *Angew. Chem. Int. Ed.* **2009**, *48*, 8372-8375; *Angew. Chem.* **2009**, *121*, 8522; d) P. W. Davies, S. J. C. Albrecht, *Synlett* **2012**, *23*, 70-73; e) D. Yadagiri, P. Anbarasan, *Chem. Eur. J.* **2013**, *19*, 15115-15119; f) J. Li, K. Ji, R. Zheng, J. Nelson, L. Zhang, *Chem. Commun.* **2014**, *50*, 4130-4133; g) M. Dos Santos, P. W. Davies, *Chem. Commun.* **2014**, *50*, 6001-6004.

[12] a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064-5106; b) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2840-2859; *Angew. Chem.* **2010**, *122*, 2902; c) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560-578; d) G. Evano, C. Theunissen, M. Lecomte, *Aldrichimica Acta* **2015**, *48*, 59-70; e) F. Pan, C. Shu, L. W. Ye, *Org. Biomol. Chem.* **2016**, *14*, 9456-9465.

[13] For a review on cascade methods to access sulfur heterocycles, see: P. Przybylski, K. Pyta-Klich, K. Pyta, A. Janas, *Tetrahedron* **2018**, *74*, 6335-6365.

[14] a) M. Lin, L. Zhu, J. Xia, Y. Yu, J. Chen, Z. Mao, X. Huang, *Adv. Synth. Catal.* **2018**, *360*, 2280-2284; b) C.-M. Wang, L.-J. Qi, Q. Sun, B. Zhou, Z.-X. Zhang, Z.-F. Shi, S.-C. Lin, X. Lu, L. Gong, L.-W. Ye, *Green Chem.* **2018**, *20*, 3271-3278; c) F. Sánchez-Cantalejo, J. D. Priest, P. W. Davies, *Chem. Eur. J.* **2018**, *24*, 17215-17219; d) M. Ito, R. Kawasaki, K. S. Kanyiva, T. Shibata, *Chem. Eur. J.* **2018**, *24*, 3721-3724; e) L. Li, B. Zhou, Y.-H. Wang, C. Shu, Y.-F. Pan, X. Lu, L.-W. Ye, *Angew. Chem. Int. Ed.* **2015**, *54*, 8245-8249; *Angew. Chem.* **2015**, *127*, 8363; f) L.-Q. Yang, K.-B. Wang, C.-Y. Li, *Eur. J. Org. Chem.* **2013**, 2775-2779; g) K.-B. Wang, R.-Q. Ran, S.-D. Xiu, C.-Y. Li, *Org. Lett.* **2013**, *15*, 2374-2377; h) R. Liu, G. N. Winston-McPherson, Z. Y. Yang, X. Zhou, W. Song, I. A. Guzei, X. Xu, W. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 8201-8204; i) B.-H. Zhu, C.-M. Wang, H.-Y. Su, L.-W. Ye, *Chin. J. Chem .* **2019**, *37*, 58-62; j) W.-B. Shen, Q. Sun, L. Li, X. Liu, B. Zhou, J.-Z. Yan, X. Lu, L.-W. Ye, *Nature Commun.* **2017**, *8*, 1748.

[15] a) P. W. Davies, A. Cremonesi, N. Martin, *Chem. Commun.* **2011**, *47*, 379-381; b) C.-F. Xu, M. Xu, Y.-X. Jia, C.-Y. Li, *Org. Lett.* **2011**, *13*, 1556-1559.

[16] I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 4473-4475; *Angew. Chem.* **2006**, *118*, 4585.

[17] a) M. C. Blanco Jaimes, V. Weingand, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 12504-12511; b) H. V. Adcock, T. Langer, P. W. Davies, *Chem. Eur. J.* **2014**, *20*, 7262-7266.

[18] For a review of related reactions, see: H. V. Adcock, P. W. Davies, *Synthesis* **2012**, *44*, 3401-3420.

[19] C.-W. Li, K. Pati, G.-Y. Lin, S. M. A. Sohel, H.-H. Hung, R.-S. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 9891-9894; *Angew. Chem.* **2010**, *122*, 10087.

[20] D. B. Huple, S. Ghorpade, R.-S. Liu, *Chem. Eur. J.* **2013**, *19*, 12965-12969.

[21] a) A. Coste, G. Karthikeyan, F. Couty, G. Evano, *Angew. Chem. Int. Ed.* **2009**, *48*, 4381-4385; *Angew. Chem.* **2009**, *121*, 4445; b) A. Coste, F. Couty, G. Evano, *Org. Synth.* **2010**, *87*, 231-244; c) X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen, M. R. Tracey, *J. Org. Chem.* **2006**, *71*, 4170-4177.

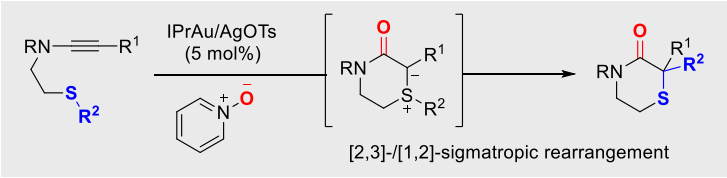
[22] C. P. Seath, J. W. B. Fyfe, J. J. Molloy, A. J. B. Watson, *Synthesis* **2017**, *49*, 891-898.

[23] Sulfonamide protected thiomorpholin-3-ones are of interest having been patented for multiple sclerosis treatment: See ref 6b.

[24] C. J. Moody, R. J. Taylor, *Tetrahedron* **1990**, *46*, 6501-6524.

Entry for the Table of Contents

COMMUNICATION



A cascade oxidation, sulfonium-ylide forming cyclisation, and sigmatropic rearrangement has been developed for the expedient synthesis of α,α' disubstituted thiomorpholin-3-ones. The gold-catalysed reaction proceeds effectively despite the presence of competing cycloisomerisation and over-oxidation pathways.

Heterocycle Synthesis

*Thomas Baker, Paul W. Davies**

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Synthesis of Thiomorpholin-3-ones by a Gold-Catalysed Oxidative Cyclisation-Rearrangement Cascade from Ynamides