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Gold(I)-Catalyzed Synthesis of 3-Sulfenyl Pyrroles and Indoles by a Regioselective Annulation of Alkynyl Thioethers

Peter E. Simm, Prakash Sekar, Jeffery Richardson, and Paul W. Davies*

ABSTRACT: The combination of nucleophilic nitrenoids and π-acid catalysis has emerged as a powerful tool in heterocycle synthesis. Accessing more varied heterocycle-substitution patterns by maintaining the same reaction pathways across different alkynes remains a challenge. Here we show that Au(I) catalysis of isoxazole-based nitrenoids with alkynyl thioethers provides controlled access to (3 + 2) annulation by a regioselective addition β to the sulfenyl group. The reaction with isoxazole-containing nitrenoids delivers sulfenylated pyrroles and indoles as single regioisomers bearing useful functional groups and structural variety.

KEYWORDS: gold, pyrroles, nitrenoid, annulation, thioether, indole

Nucleophilic nitrenoids have proved to be versatile surrogates for nitrene-containing 1,3-dipoles, providing modular and expedient access to a variety of densely functionalized N-heterocycles by a formal (3 + 2) cycloaddition to gold-activated alkynes.1 Most of these annulations were first realized with ynamides,2 and to date there are only a few specific instances where those same transformations have been achieved with other types of alkynes.3 As the alkynyl substitution pattern is directly translated into the product, retaining the same transformation across different alkynes would greatly expand the potential of these convergent annulation methods for complex molecule synthesis. A challenge lies in finding alkynes that are sufficiently reactive and do not change how the reaction pathway evolves while providing useful substitution patterns.

The use of isoxazole-based N-nucleophilic nitrenoids is illustrative: The groups of Ye2f and Hashmi2j demonstrated the potential of using isoxazoles and [2,1]benzisoxazoles, respectively, to assemble pyrroles and indoles through a formal (3 + 2) cycloaddition across C-aryl ynamides (Figure 1b). Several groups have subsequently established that a tremendous variety of heterocyclic structures can be formed when these nitrenoids are combined with differently substituted alkynes.4 Because the alkynyl structure affects the nature of the intermediate α-imino gold carbene B and the pathways through which it can evolve (Figure 1a), even relatively small changes can divert the pathway away from formal (3 + 2) cycloaddition (Figure 1c).

Few reports have addressed gold-catalyzed intermolecular reactions with alkynyl thioethers, and the majority have reported nucleophilic addition α to the sulfur,5 invoking a dominant gold ketenethionium character. However, a recent study from our group using N-acylpyridinium aminides showed that, in the presence of a Au(III) precatalyst, the outcomes matched selective attack at the β-position of alkynyl thioethers.6 We reasoned that if this latter route was generally accessible from other types of nitrenoids, especially those accessing using Au(I) catalysis, then a more generalized approach for (3 + 2)-type annulations with nitrenoids could be realized. Replicating this reactivity would ensure that the auroated carbon is substituted by the sulfenyl group throughout the reaction manifold, potentially facilitating a more consistent reactivity profile that tolerates modifications elsewhere. Sulfur-substituted heterocycles are desirable, not least in medicinal chemistry.6,7 The increasing number of C−S functionalization methods renders them potentially useful substrates for further elaboration.8 The prospective utility of sulfenylated pyrrole and indole products combined with the diversity of reaction pathways that can be accessed from (benz)isoxazoles identified them as ideal systems for probing the wider utility of alkynyl thioethers in nitrenoid-based annulations.

During our studies Ye and co-workers reported the Zn(II)-catalyzed reaction of alkynyl thioethers with isoxazoles, where
SbF₆ in a capped vial and no measures taken to exclude air and moisture (Scheme 1; see the Supporting Information for an alternative). Only a small reduction in yield is seen at lower temperatures or with a lower stoichiometry of SbF₆. The wider generality of alkynyl thioethers was established using anthranil 4 as the nitrenoid to deliver 3-sulfenyl-7-acyl indoles (3a−f). An aryl fluoride and an aniline derivative worked well, as did heteroaromatic groups such as indole and thiophene (3m−p). Alkyl-substituted alkynyl thioethers reacted sluggishly but did give the desired 3-sulfenylated pyrroles 3r,s in serviceable yields.

An unsymmetrical acetylene disulfide reacted to give the 2,3-bis-sulfenyl pyrroles as a mixture of regioisomers 3t−u. The regioselective preference correlates to the relative reactivity seen on changing the sulfenyl group in alkynyl thioethers (cf. Scheme 1, 1a−g). The major product arising from C−N bond formation β to the smaller sulfenyl group, although the regioisomer 3′t was formed despite the recalcitrance of 1b.

Neither triisopropylsilane nor terminal alkynyl thioethers gave productive reactions (1u,v, see Supporting Information). A variety of differently substituted isoxazoles proved to be compatible with the reaction. 3-Sulfenylated pyrroles can be prepared with alky1, aryl, and vinyl groups at the 4-position (3u−3zf), and with aldehydes (3x), amides (3y,z), and aryl- and alkyl-substituted carbonyl groups at the 4-position (3z−w,ac−af). No reaction was seen with the electronically deactivated 3-(perfluorophenyl)-S-phenylisoxazole and 3-phenyl-5-(trifluoromethyl)isoxazole (not shown). The use of isoxazol-5-aminos had not previously been reported under gold catalysis, while Liu reported non-pyrrole-forming pathways (Scheme 2). The reaction was largely invariant to steric bulk at the C-terminus of the alkynyl thioether, allowing ortho and diortho substitution (3h−j). A single-crystal X-ray diffraction analysis confirmed the structure of 3j. Electron-donating substituents on the aryl group are beneficial but not required (3k−q). An aryl fluoride and an aniline derivative worked well, as did heteroaromatic groups such as indole and thiophene (3m−p). Alkyl-substituted alkynyl thioethers reacted sluggishly but did give the desired 3-sulfenylated pyrroles 3r,s in serviceable yields.

The wider generality of alkynyl thioethers was established using anthranil 4 as the nitrenoid to deliver 3-sulfenyl-7-acyl indole motifs 5a−f by the formal (3 + 2) cycloaddition pathway. 3-Sulfenyl indoles have shown some medicinal potential with activity against HIV and inhibition of tubulin polymerization. As anthranil and the products coeluted, the alkynyl thioether was used in excess (see the Supporting Information for an optimization survey). No reaction was seen in the absence of catalyst or on replacing it with a strong Bronsted acid, while gold(I) and gold(III) catalysts with other ligand combinations were less effective. The noncoordinating counterions tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate and hexafluoroantimoniate were optimal in comparison to weakly coordinating alternatives. Only a small reduction in yield is seen at lower temperatures or with a lower stoichiometry of 2a.

The effects of different S-substituents on the annihilation were tested (Scheme 1). While an S-phenyl substituent stalled the process, presumably due to its rigid steric bulk, S-benzylated systems were reactive (3c,d). 1,5-Enynyl thioether 1e gave solely the pyrrole (3e), despite the potential for intramolecular cyclopropanation at an intermediate α-imino gold carben. The S-alkynyl thioester 1f degraded under the reaction conditions, but the 2-(ethynylthio)acetate derivative 1g afforded pyrrole 3g.

Figure 1. Divergent outcomes for the reaction of alkynes and isoxazoles under α-acid catalysis.

Scheme 1. Pyrrole Formation from Alkynyl Thioethers: S-Substituent
Information). A competition experiment showed that anthranil 4 is less reactive than isoxazole 2a (see the Supporting Information).

Reactions with 3,4,5-trisubstituted isoxazoles 6a,b were investigated (Scheme 3). Reactions with isoxazoles 6a,b saw formation of the N-acylated pyrrole 7 and deacylatative annulation product 9, respectively, as has been precedented in ynamide reactions. Reactivity unique to alkynyl thioethers was also elucidated with the formation of desulfenylated 3-acylated pyrroles 8a,b.

The practicality of the annulation protocol is demonstrated by its ready upscaling, which proceeded smoothly under noninert conditions to give 3a on a gram scale (Scheme 4).

Selective oxidations of the resulting pyrrole 3a into its sulfonyl and sulfanyl forms (10 and 11) were effective. Treating 11 with triflic anhydride in the presence of base led to protodesulfenylation and the formation of trisubstituted pyrrole 12. The direct use of triflic acid gave a dirtier reaction and only traces of 12. However, bronsted acid mediated desulfenylation of the sulfide 3d also gave 12. Such acid-mediated desulfuration reactions permit chemoselective reduction of the sulfenyl group in the presence of the ketone.
and enable the nitrenoid chemistry to be used to access non-heteroatom-substituted pyrroles. Initial attempts to achieve metal-catalyzed C−S activation for cross-coupling have so far been unsuccessful with these elaborated pyrroles.

The isotopically labeled substrate $^{13}$C-$^{1}$l was prepared in order to determine whether there was any skeletal rearrangement of the alkynyl thioether backbone during or after annulation. $^{1,2}$-Sulfenyl migrations have been reported in π-acid mediated reactions that invoke carbenoid character, while methylthio-substituted pyrroles have been shown to undergo Brønsted acid mediated isomerization. The single pyrrole isotopomer $^{13}$C-$^{3}$l was formed under the standard conditions. A combination of HMBC and NOESY experiments was used to confirm the regiochemical outcome on $^{3}$l and that the connectivity of the alkynyl thioether was maintained (Scheme 5). A small amount of the enriched β-keto enamide $^{13}$C-$^{13}$ was also isolated. This outcome is in concordance with the pathway reported by Ye under Zn(II) catalysis and provides labeling evidence for the $^{1,2}$-S-migration step.

A general mechanism is proposed on the basis of these observations and literature precedent (Scheme 5). The $^{13}$C-labeling experiment is consistent with slippage to either end of the triple bond being energetically accessible: α-addition, matching a gold ketenethionium type activation A1 invoked in the majority of Au(I)-catalyzed reactions of alkynyl thioethers, is the minor pathway and is not viable for the formation of pyrrole. This pathway leads to β-ketoenamide D. The β-addition pathway is more productive (A $\rightarrow$ E), and we postulate that a stabilizing S–Au interaction17 promotes irreversible gold carbene formation. This pathway is aided by, but not dependent upon, the presence of more electron rich alkyne substituents (Scheme 2), which would further distort the π-complex toward a nascent Au–S interaction A2. The resulting α-imino α′-sulfenyl gold carbene F undergoes cyclization and aromatization to pyrrole I. When C-4-substituted isoxazoles are used, in addition to established deacetylation mechanisms (H $\rightarrow$ J/K), an unprecedented desulfenylation can follow 1,5-acyl migration, leading to all-carbon substituted pyrroles (H $\rightarrow$ M).

In conclusion, alkynyl thioethers react with isoxazoles and anthranils under gold catalysis and provide selective access to the formal (3 + 2) cycloaddition pathway. This pathway is maintained across reactants with broad structural and functional group changes. As a result, these readily accessed substrates can be used to deliver convergent and modular access to sulfenylated pyrroles and indoles. The practical and straightforward protocol has been demonstrated on a multimillimole scale. Initial investigations into the annulation with trisubstituted isoxazoles also reveal reactivity unique to alkynyl thioethers. One-step access to all-carbon-substituted pyrroles establishes the intriguing potential of using a sulfenyl moiety as a traceless directing and alkyne-activating group for heterocycle synthesis.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01457. Experimental details, compound characterization data, crystallographic data, and NMR spectra (PDF) Crystallographic data for 3j (CIF)
Crystallographic data for 8a (CIF)

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All authors contributed to the preparation of the manuscript and have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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References

(18) Even without an aryl substituent on the alkyne, the β-keto enamide product from the α-addition pathway was only observed in small amounts (<10%) in the 1H NMR spectra of the crude reaction mixture for the formation of 3r.