Chemical Science

EDGE ARTICLE



Cite this: Chem. Sci., 2019, 10, 1201

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Gold-catalyzed (4+3)-annulations of 2-alkenyl-1alkynylbenzenes with anthranils with alkynedependent chemoselectivity: skeletal rearrangement *versus* non-rearrangement[†]

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Two distinct (4+3)-nitroxy annulations between 1,5-enynes and anthranils have been developed to access tetrahydro-1*H*-benzo[*b*]azepine derivatives; the chemoselectivity varies with the types of alkynes. Terminal alkyne substrates deliver benzo[*b*]azepine derivatives *via* a novel skeletal rearrangement while internal 1,5-enynes afford products without a rearrangement process. To elucidate the mechanism of rearrangement, we performed ¹³C- and ²H-labeling experiments to identify the gold-containing isobenzofulvene intermediates, but their formation relies on the presence of anthranils.

Received 14th August 2018 Accepted 11th November 2018

DOI: 10.1039/c8sc03619e

rsc.li/chemical-science

Introduction

Cyclic nitroxy species (N–O) are widespread functionalities in numerous bioactive molecules and natural products.¹ Tetrahydro-1*H*-benzo[*b*]azepines bearing a hydroxyl (I–IV) represent a family of privileged seven-membered azacycles,² possessing potent activities in antiparasitic disease, antidiuretic hormone receptors and β_2 adrenergic agonists.³ Synthetic procedures for compounds I–IV are generally long and tedious.² A short route to construct tetrahydrobenzo[*b*]azepine cores involves the development of stereoselective (4+3)-annulations between anthranils and allcarbon 1,3-dipoles (eqn (1)), but only donor–acceptor cyclopropanes were shown to be applicable substrates.⁴ We are aware of no π -bond motifs that can serve as effective 1,3-dipoles.⁵

Synthetic interest in isoxazoles and anthranils is rapidly growing in Au- and Pt-catalysis because of their various annulations with alkynes.^{6,7} Nevertheless, these hetero-aromatics serve as nucleophiles that attack π -alkynes *via* a N- or O-attack route, inevitably cleaving the N–O bonds; selected examples are provided in eqn (2) and (3). We sought the first (4+3)-nitroxy annulations using alkyne-based 1,3-dipoles and anthranils. This work reports two distinct (4+3)-annulations of 1,5-enynes with anthranils; interestingly, the chemoselectivity varies with the alkynes. Terminal 1,5-enynes **1** (R = H) afford seven-membered nitroxy

Fig. 1 Representative molecules and a postulated short route.

heterocycles 3 *via* an unprecedented rearrangement in gold catalysis;⁸ the mechanism of this novel rearrangement has been elucidated. Annulation products 5 derived from internal alkynes 4 are not skeletally rearranged, but are elaborated into various benzo[*b*]azepine frameworks (Fig. 1).

Annulations with N-O cleavages

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 [†] Electronic supplementary information (ESI) available. CCDC 1853703–1853706.
 For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc03619e

This work: (4+3)-nitroxy annulations



Results and discussion

We optimized the reactions of terminal 1,5-envne 1a with anthranil 2a (1.2 equiv.) using various gold catalysts; the results are shown in Table 1. Operations in dry dichloroethane (DCE, 25 °C) with L'AuCl/AgNTf₂ (L' = $P(t-Bu)_2(o-biphenyl)$, IPr, PPh₃) afforded seven-membered nitroxy product 3a in 8-68% yield (entries 1–3), with $P(t-Bu)_2(o-biphenyl)AuCl/AgNTf_2$ being the most effective. To our delight, (PhO)₃PAuCl/AgNTf₂ increased the yield of the desired 3a up to 73% (entry 4); different silver salts as those in $(PhO)_3AuCl/AgX$ (X = SbF₆ and OTf) delivered compound 3a in relatively low yields (35-42%, entries 5 and 6). With (PhO)₃PAuCl/AgNTf₂, the yields of compound 3a in different solvents were as follows: DCM (62%), acetonitrile (30%) and MeNO₂ (0%, entries 7-9). AgNTf₂ alone was completely inactive (entry 10). The molecular structure of compound 3a was characterized by X-ray diffraction9 to reveal a (4+3)-annulation with an intact N-O bond. In the absence of anthranil 2a, 1,5enyne 1a was isomerized by a gold catalyst to afford 1'-methylvinyl-1H-indene 1a', which was structurally unrelated to our target 3a. Anthranil 2a is obviously indispensable to enabling the (4+3)-annulations with structural rearrangement.

Under these optimized conditions, we assess the generality of these new annulations with various terminal 1,5-enynes and

anthranils. The results are provided in Table 2; only a single diastereomeric product was obtained for all instances. In several instances, vinyl-1*H*-indene **1a**' was present as





 a [1] 0.20 M. b Yields of the products were reported after isolation on a silica gel column.

Table 1	Optimized	conditions	over various	gold catal	vsts

+		(10 mol %) catalyst solvent, time		
1a	2a		3a	1a'

						Yields ^{b} (%)		
Entry	Catalyst ^a (mol %)	2 a <i>n</i> equiv.	Solvent	Time (h)	Temp (t °C)	1a	3a	1a'
1	LAuCl/AgNTf2	1.2	DCE	5	25	_	68	_
2	IPrAuCl/AgNtf ₂	1.2	DCE	15	25	25	8	
3	Ph ₃ PAuCl/AgNtf ₂	1.2	DCE	12	25	_	35	_
4	(PhO) ₃ PAuCl/AgNtf ₂	1.2	DCE	4	25	_	73	
5	(PhO) ₃ PAuCl/AgSbF ₆	1.2	DCE	10	25	10	35	_
6	(PhO) ₃ PAuCl/AgOTf	1.2	DCE	2	60	_	42	_
7	(PhO) ₃ PAuCl/AgNtf ₂	1.2	DCE	10	25	_	62	_
8	(PhO) ₃ PAuCl/AgNtf ₂	1.2	MeCN	10	25	_	30	_
9	(PhO) ₃ PAuCl/AgNtf ₂	1.2	MeNO ₂	20	25	80	_	
10	AgNtf ₂	1.2	DCE	24	25	85	>5	_
11	(PhO) ₃ PAuCl/AgNtf ₂	0	DCE	4	25	—	—	65

^{*a*} **1a** (0.20 M), **2a** (1.2 equiv.). ^{*b*} Product yields are given after purification on a silica gel column, $L = P(t-Bu)_2(o-biphenyl)$, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene).

a byproduct in a minor proportion (5-15%). The annulations of anthranil 2a (1.2 equiv.) with terminal 1,5-envnes 1b-1d bearing various 4-phenyl substituents (X = Me, Cl, and F) proceeded smoothly to yield 3b-3d in 68-77% yields (entries 2-4). For their 5-phenyl analogues 1e-1g, the resulting annulation products **3e-3g** (Y = Me, Cl and F) were obtained in 65–74% yields (entries 5-7). Variations of the olefin substituents as those in species 1h-1j (R, R = cyclopentyl, cyclohexyl and dipropyl) were still compatible with these new N-O annulations to afford compounds 3h-3j in 55-67% yields (entries 8-10). We have also prepared a terminal alkyne such as 1-ethynyl-2-styrylbenzene 1k that gave a recovery yield (>95%) of two reactants under the standard conditions.

We next examined anthranils 2b-2f bearing various C(5)substituents (X' = Me, Cl, Br, OMe and OCO₂Et), yielding cyclic nitroxy species 3k-3o in 48–77% yields, with X' = OMebecoming less efficient (entries 11-15). Methoxy-containing anthranil 2e renders the gold catalyst less reactive because of its high basicity. This gold catalysis worked well with additional anthranils 2g and 2h bearing C(6)-substituents (Y' = Br and Me), yielding the desired 3p and 3q in 41% and 70% yields, respectively (entries 15 and 16). We also varied the C(3)substituents of anthranils (R' = Ph 2i; Me 2j) to yield the desired 3r and 3s in 35% and 63% yields, respectively (entries 18 and 19). An effective range of alkynes and anthranils manifests the practicability of these new nitroxy annulations.

This gold-catalyzed reaction was also extensible to an internal alkyne 4a, but led to a distinct (4+3)-annulation reaction without a skeletal rearrangement. Among various gold catalysts, P(OPh)₃AuCl/AgSbF₆ was superior to its NTf₂ catalyst analogue, delivering a nitroxy product 5a with respective yields

> (10 mol %) (OPh)₃PAuCl / AgSbF₆

> > Dry DCE, 25 °C

4) 5e (Y = Me, 11 h, 74%)

Y = CI, 8 h, 70%)

Ó

CH3'H

11) 5I (X' = Me, 8 h, 75%)

12) 5m(X' = Br, 9 h, 59%)

13) 5n (X' = Cl. 8 h. 71%)

14) 50 (X' = OMe. 8 h. 55%)

15) 5p (X' = OCO₂Et, 8 h, 75%)

5) 5f (Y = F, 10 h, 65%)

6) 5g (

Ή

5^[b]

0

0

7) **5h** (n = 1, 10 h, 71%)

8) 5i (n = 2, 10 h, 72%)

16) 5q (Y' = Br, 8 h, 48%)

17) 5r (Y' = Me, 8 h, 68%)

Table 3 Reactions with internal 1,5-enynes and anthranils

^a 4/2 = 1 : 2.1, [4] 0.20 M. ^b Yields of the products were reported after isolation on a silica gel column.

of 78% and 68%; a molar ratio of 4a/2a = 1 : 2.1 was the optimized condition. The molecular structure of 5a was inferred from its 5b analogue (Table 3, entry 1).9



We assess the scope of these nitroxy annulations with various internal 1,5-envnes 4 and anthranils 2; only one diastereomeric product was obtained without exception. Entries 1-6 show the compatibility of these reactions with 1,5-enynes 4b-4d and 4e-4g bearing 4- and 5-phenyl substituents (X = Me, F and Cl or Y = Me, F and Cl), delivering compounds **5b–5d** and 5e-5g in 65-75% yields (entries 1-6). An X-ray diffraction study⁹ confirms the molecular structure of compound 5b showing no skeletal rearrangement. 1,5-Enynes 4h and 4i bearing varied trisubstituted alkenes were also suitable for the reactions, affording the desired nitroxy species 5h and 5i in 71-72% yields (entries 7 and 8). When the alkyl substituents R were a cyclopropyl or CH2OTBS group, the corresponding compounds 5j and 5k were obtained in 56% and 53% yields, respectively (entries 9 and 10). We tested the reactions of various anthranils 2b-2f bearing various C(5)-substituents (X' = Me, Br, Cl, OMe and OCO₂Et), giving the expected products 5l-5p in 55-75% yields with the methoxy substituent being less efficient (entries 11-15). For additional anthranils 2g and 2h bearing 6-substituents (Y' = Br and Me), the resulting products 5q and 5r were obtained in 48% and 68% yields, respectively (entries 16 and 17).

We performed the reductive N–O cleavage of compounds 3a and 5a to manifest their synthetic utility. Treatment of species 3a with Zn in AcOH/MeOH/H₂O¹⁰ gave compound 6a in 89% yield while the reaction with Pd/H₂ gave compound 6b efficiently. Alternatively, compound 5a was hydrolyzed with HCl/ water to yield ketone derivative 7b that was convertible to 1amino-5-ol 7c with Zn/AcOH reduction, and to the diol derivative 7d with Pd/H₂ reduction. An imine reduction of species 5a was achieved with Pd/H2 to afford species 7a. Unexpectedly, Znreduction of species 5a in HOAc/MeOH/water led to a structural rearrangement to form compound 7e in 81% yield. The imine moiety of the initial 5a was incorporated into the structural skeleton of product 7e, but the mechanism is not clear at this stage. Molecular structures of compounds 7a and 7e were verified by X-ray diffraction.9 The mechanism for the transformation of 5a into 7e will be elucidated in a future study (Scheme 1).

Among the two nitroxy annulations, the mechanism for terminal 1,5-enynes 1a is difficult to deduce because its cycloisomerization product 1a' is not skeletally rearranged. We prepared ¹³C-1a containing 12% ¹³C at only the =C-H carbon, and its resulting product 3a contained the ¹³C-content only at

1) 5b (X = Me, 12 h, 75%, X-ray)

2) 5c (X = F, 10 h, 68%)

o

9) **5i** (16 h. 56%)

R = cyclopropyl

= CH₂OTBS

10) 5k (10 h. 53%)

3) 5d (X = Cl. 8 h. 71%)



Scheme 1 Reductive cleavage of the N–O bonds.

the alkyl C–H carbon (eqn (6)). Isobenzofulvene species **In 1** was unlikely to occur here although it was observed in a rutheniumcatalyzed cycloisomerization.¹¹ In the presence of D₂O, we found that the resulting **d**₁-3a contained deuterium (X = 0.29D) only at its alkenyl C–H moiety (eqn (7)). Accordingly, goldcontaining isobenzofulvene **In 2** is compatible with these ¹³C and ²H-labeling experiments.



Scheme 2 depicts the mechanisms of the two annulations. Internal 1,5-enynes 4 react with LAu⁺ to form cyclopropyl gold carbenes **B** (or **B**') in two resonance forms; *exo*-(4+3)-



Scheme 2 Plausible mechanisms for rearrangement and non-rearrangement.



Scheme 3 Four possible paths for the $D \rightarrow G$ transformation.

annulations of species \mathbf{B}' with anthranils $2\mathbf{a}$ likely yield goldcarbene species C that subsequently capture a second anthranil to yield products 5. This mechanism is essentially the same as that of their annulations with nitrosoarenes.12 Herein, a stepwise mechanism for the annulation of anthranils with 1,3dipoles \mathbf{B}/\mathbf{B}' is also likely to occur. Terminal 1,5-envne 1a also generates cyclopropylgold carbene E because its cycloisomerization product 1a' is also a 1-vinylindene derivative. We envisage that the cyclopropyl C-H proton of gold carbene E is acidic because of its proximity to the gold carbene functionality; the deprotonation with anthranil 2a generates cyclopropylidenylgold species F that undergoes a "methylenecyclopropane-trimethylenemethane" rearrangement,13 further generating gold-containing isobenzofulvene species In 2. An exo-(3+4)-annulation between fulvene In 2 and anthranil 2a affords the observed product 3a. The intermediacy of organogold species G is supported by ²H and ¹³C-labeling experiments.

Density functional theory calculations were then performed to investigate the feasibility for the key steps $\mathbf{D} \rightarrow \mathbf{G}$. Four possible paths 1–4 are considered; Path 1 is our proposed mechanism in Scheme 2. The energy profile is provided in Scheme 4. The formation of cyclopropylgold carbenes \mathbf{E} from π alkyne \mathbf{D} has a low barrier of 9.1 kcal mol⁻¹; the anionpromoted deprotonation of gold carbene \mathbf{E} to form



Scheme 4 DFT calculation and energy profiles of Path 1.



Scheme 5 DFT calculation and energy profiles of Path 2.

cyclopropylidenylgold species **F** is operable as the enthalpy cost is 16.9 kcal mol⁻¹; the energy of species **F** is slightly higher than that of π -alkyne **D** by only 6.6 kcal mol⁻¹. The remaining steps **F** \rightarrow **In 2** and **In 2** \rightarrow **G** are also operable as the transition states **TS-F-In2** and **TS-In2-G** are close to π -alkyne **D** energy levels. One notable feature is that the enthalpy of transition state **TS-F-In2** is surprisingly smaller than that of species **F** by -0.3 kcal. This atypical case has similar precedents in the literature.¹⁴ This is because **TS-F-In2** has less zero-point vibration energy than **F**, due to the loss of one degree of freedom in the transition state. This also means that **F** \rightarrow **In2** is a barrierless process.

We next examined the energy profiles in the (4+3) annulations (Path 2) between cyclopropyl gold carbenes **E** and anthranil **2a**. The reaction proceeds in a stepwise manner. As shown in Scheme 5, the N-attack of anthranil **2a** at gold carbene **E** produces species **E**_{step} by an endothermic process (H =13.6 kcal mol⁻¹); its activation energy is as high as 25.4 kcal mol⁻¹. In the next step involving **E**_{step} \rightarrow **GH**, the energy level of **TS-E**_{step}-**GH** is higher than that of 1,5-enyne **D** by 18.1 kcal mol⁻¹. We conclude that Path 2 is not as feasible as Path 1 according to Scheme 5.

We also considered the remaining Paths 3 and 4, as depicted in Scheme 3. In Path 3, the deprotonation and ring rearrangement take place simultaneously ($\mathbf{E} \rightarrow \mathbf{In2}$), in contrast to a stepwise process in Path 1 ($\mathbf{E} \rightarrow \mathbf{F} \rightarrow \mathbf{In2}$). Despite multiple attempts, we were unable to locate the transition state for the direct $\mathbf{E} \rightarrow \mathbf{In2}$ step, suggesting that Path 3 probably does not exist. In Path 4, a ring opening takes place initially ($\mathbf{E} \rightarrow \mathbf{In2}$ -H), followed by deprotonation ($\mathbf{In2}$ -H \rightarrow In2). However, our calculations show that this pathway is unlikely to occur as we are unable to locate In2-H; all geometry optimizations lead to E.

Conclusions

Before this work, Au- and Pt-catalyzed annulations of anthranils with alkynes typically produced azacyclic products that cleaved the N–O bonds. To develop new (4+3)-annulations of alkyne-

derived 1,3-dipoles¹⁵ with anthranils, we achieve stereoselective synthesis of two classes of tetrahydrobenzo[*b*]azepines using 1,5enynes, anthranils and a gold catalyst. Internal 1,5-enynes deliver these cyclic nitroxy species without skeletal rearrangement while their terminal alkyne analogues afford distinct annulation products with skeletal rearrangement. To elucidate the mechanism of this rearrangement, ²H and ¹³C-labeling experiments were performed to identify the intermediates of gold-containing isobenzofulvene species, the formation of which is dependent on the presence of anthranils.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We thank the Ministry of Education (MOE 106N506CE1) and Ministry of Science and Technology (MOST 107-3017-F-007-002), Taiwan, for financial support of this work.

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