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Gold-Catalysed Formal Cyclisation/Dimerization of Thiophene-Tethered Diynes

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Abstract

A new pathway in dual gold-catalysed reaction of thiophene-tethered diynes has been identified. *t* series of fully conjugated alkynyl-substituted benzothiophenes and benzofurans was obtained by formal cyclisation/dimerization sequence. All the products are fluorescent, owing to their extende conjugation. The mechanistic studies have been carried out, suggesting that gold acetylides take pai in this transformation.

Introduction

Gold catalysis has received considerable attention in the last decades.^[1] A new reactivity pattern i the gold catalysed cycloisomerisation of diynes was recently identified by the group of Zhang an ours.^[2] It was entitled dual activation, since two gold centers activate one single molecule of the substrate simultaneously – one via σ -bonding to a terminal alkyne and another via π -complexation to the second alkyne group. This double activation leads to the formation of highly reactive species – mono aurated gold vinylidene or diaurated arene cation derivatives are obtained (Scheme 1).



Scheme 1. Differerent cyclisation modes for dual gold catalysed diyne reactions.

Different initial cyclisation modes were observed for diynes incorporated into varying aromati backbones: benzenes^[3] and 3,4-diethynylthiophenes as backbones^[4] followed a 5-*endo* cyclisatio pathway forming aurated gold vinylidene intermediates (Scheme 1, A-type intermediate), 2,3 diethynylthiophenes^[5] and vinyl bound diynes^[6] initiate 6-*endo* cyclisations (Scheme 1, B). Both type of intermediates are reacting rapidly *via* C-H insertion reactions in an intramolecular manner or wit the solvent.^[7]

Among the dialkynylthiophene cyclisations, we already explored C-H activations for differer substituents on the internal alkynes. As can be seen from Scheme 2, formation of 5 membered ring in the second step of the cyclisations are preferred but a cyclobutene formation was also possible i special cases if no C-H group suitably situated to obtain 5-membered ring is available (Scheme 2, d) In continuation of these studies we considered aryl groups at the internal alkyne as well. The potentia intermediates also lack the possibility of γ -insertion which might contribute to the discovery of new reaction pathways (Scheme 2, f). This contribution summarizes the chemistry of these startin materials in dual gold catalysis.



Scheme 2. Reported thiophene and furan cyclisation pathways and the potential intermediates addresed in this contribution.

Results and Discussion

Initial experiments were conducted with aryl substituted compound (1a) in the presence of a dua activation catalyst.^[8] Indeed the clean formation of one major product was detectable by TLC. Full characterisation of the isolated product based on 2D-NMR data revealed the formation of a no symmetric cyclisation/dimerisation product 2. While one of the diyne systems rearranged to th aromatic core a second starting molecule is connected *via* the former terminal alkyne without a furthe cyclization (Scheme 3).



Scheme 3. Initial observation.

An optimization of the reaction conditions revealed DAC NTf₂ in toluene at 80°C being the best catalyst system (see ESI). Under these conditions we explored the scope of the transformation by variations of the aryl substituent as well as the heterocyclic backbone (Table 1). Thiophenes, bearing electron-donating groups on the phenyl moiety gave better results than the phenylacetylene derivative (Entries 1 and 3 vs. 2). In agreement with this behavior, the reaction of *para*-fluoro-substituted compound **1d** was less clean, furnishing the product in only 25% yield (Entry 4). Furan backbones were well tolerated and both applied substrates for this transformation led to the formation of cyclised dimers in good yields (Entries 5-6). For benzothiophenes overall faster conversions were obtained and in all cases the products were obtained in high yields (Entries 7-9). All of the obtained products show fluorescence in solution. The absorption and emission spectra of two representative compounds (**2** and **2h**) are depicted in Figure 1. The compounds show an emission maximum at 388 and 412 nr with a determined quantum yields of 11.4% and 23.1% respectively.



Table 1. Scope	of the	dimerization	reaction of	of substrates 1	1
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Entry	Diyne 1		X	R	Time	Pro	duct
5						2	Yield
1		1a	S	Me	4 h	2a	62 %
2	R	1b	S	Н	5.5 h	2b	48 %
3		1c	S	OMe	6 h	2c	71 %
4		1d	S	F	18 h	2d	25 %
5		1e	0	Н	4 h	2e	52 %
6		1f	0	Me	6 h	2f	75 %
7		1g	S	Н	2.5 h	2g	81 %

8	R	1h	S	Me	2 h	2h	70 %
9		1i	S	OMe	2.5 h	2i	56 %





Figure 1. UV spectra of compounds 2a and 2h

Fortunately, crystals suitable for X-ray analysis were obtained by slow diffusion of pentane into a solution of 2h in CD₂Cl₂. The result further verifies the right assigned connectivity. Interestingly, the

solid-state molecular structure of compound **2h** shows a nearly perfect planar orientation of the fluorenothiophene-alkyne-benzothiophene moieties with optimal overlap for π -conjugation (only the *p*-tolyl moieties are slightly twisted out of plane). As depicted in Figure 2, a cyclisation/dimerisation product **2h** was obtained as single product.^[9]



Figure 2. Molecular structure of 2h in the solid state.

The very high substrate sensitivity of this transformation was even more pronounced after swappin the terminal and non-terminal alkyne substituents in the starting materials. While several of th inversely substituted thiophenes were screened, the reaction only occurred with fluoro substitute starting material **3a** leading to an isolable product in low yield (Entry 1, Table 2). The correspondin furan substrates **3b-3d** showed clean reactions again, yielding the desired cyclisation-dimerisatio products in good yields (Entries 2-4). Both general motifs **2** and **4** might be useful structural units fc the application in molecular electronics such as semiconductors.^[10]

Table 2. Scope of the dimerization of substrates 3



Entry	Starting material			Time	Product		
Linuy	3	Х	R		4	Yield	
1	3 a	S	F	18 h	4a	15 %	
2	3b	0	Н	3 h	4 b	75 %	
3	3c	0	OMe	3 h	4c	65 %	
4	3d	0	F	3 h	4d	73 %	

With one experiment we addressed a possible synthesis of hetero-dimers. An equimolar mixture of **1** and **1c** was treated with gold catalyst under standard reaction conditions. As a result, 13% of **2a**, 25% of **2c** and an inseparable mixture of two compounds (25% combined) was isolated. The mass spectrur indicated that this mixture is composed of the two conceivable hetero-dimers, the ration of the tw dimers was estimated to be 3:2 from the ¹H NMR integrals.

Based on the connectivity of the product, one could compare the formation of the cyclisation dimerisation products with the previously reported hydroarylating cyclisation of phenyl diyne bearing two terminal alkynes (Scheme 4).^[2a]



Scheme 4. Relationship between observed cyclisation and previously reported one.

In that case the addition of a solvent molecule took place ether in α - or β -position of the formed naphthalene systems dependent on the mode of activation of the diyne: while π -activation by one gold center delivered the α product, dual σ , π -activation led to the formation of the β -product. Based on the relationship of the products a π -activation of the terminal alkyne in the applied thiophene diyne substrate with cationic gold could initiate the cyclisation under formation of an intermediate aryl cation **A**, which could be attacked by either a σ -activated gold acetylide or a terminal alkyne unit from the starting material, giving rise to **B** and the product after protodeauration (Scheme 5, path 1). While one cannot exclude this pathway, our studies on the use of dual activation catalysts imply that acetylid initiated cyclizations are highly favored for this catalysts.^[8] Thus the formation of a diaurated specie **A**' followed by addition of an alkyne/ acetylide must be considered as well (Scheme 5, path 2) Alternatively, according to a report by Zhang and coworkers, first a gold catalysed head-to-ta coupling of the terminal alkynes of two starting materials^[11] might occur under formation of enyne **C** A subsequent cyclisation of the obtained vinyl gold intermediate could also give rise to the fina product after deauration (Scheme 5, path 3).



Scheme 5. Plausible mechanistic pathways.

This formation of an alkynyl-arene bond progresses via the electrophilic attack of a gold-generated aryl cation at either the alkyne or the aurated alkyne. Thus it is redox neutral and nicely complements the oxidative methods reported by the groups of Waser^[12a] and Nevado.^[12b]

To obtain further insight into the complex mechanistic puzzle, several experiments were conducted next. An attempt to trap the aryl-cation A/A' from pathway 1 or 2 by performing the reaction in the presence of three equivalents of methanol failed. Only the hydration of the terminal alkyne (proceeding probably via acetal formation with successive hydrolysis) occurred in this reaction giving rise to 5 (Scheme 6, eq. 1). When the reaction was performed in the presence of heptyne (5 eq.), th product of the addition of heptyne to the terminal triple bond of the substrate was isolated, whic would be in accordance to pathway 3. However it is noteworthy that no further cyclisation of enyne was observed, neither when the reaction time was extended, nor when 6 was resubjected to the gol catalyst (Scheme 6, eq. 2). To test further if pathway 3 represents a plausible reaction mechanism, th postulated intermediate 7 (which was prepared by an addition/elimimination sequence of the lithiate alkyne to the furyl ketone) was independently prepared. To our surprise not even a trace of conversio was monitored for compound 7 under the normal conditions (Scheme 6, entry 3). Even mor unexpected is the fact, that in the presence of even small amounts of 7, the conversion of 1a to 2a wa inhibited. Only when the gold loading was higher than the loading of 7, 1a was transferred to th product (Scheme 6, entry 4). This indicates that envne 7 is not an intermediate of the reactio mechanism. This might be attributed to the ability of enyne 7 to function as ligand for cationic gol to act as a sort of "gold sponge" to absorb the catalytically active free cationic gold species. Despit this fact still a cyclization might occur directly from the aurated intermediate, but outcome of th crossover experiment from eq. 2 makes this unlikely as in this case a further cyclization should als be monitored.



Scheme 6. Mechanistic experiments.



Figure 3. Molecular structure of 8 in the solid state.

When a mixture of substrate **1a** and its corresponding gold-acetylide **8** (Figure 3)^[9] (4:1) was subjecte to standard catalytic conditions, product **2a** was formed smoothly. The yield was comparable to tha of the standard experiment. The same reaction in the absence of cationic gold did not proceed (Schem 6, eq. 5). However, when acetylide **9** was used, only an equilibration of acetylides occurred (Schem 6, eq. 6). The formation of traces of enyne products might in this case contribute to the catalys deactivation again. The transformation of **1a** into **2a** in the presence of 5 mol% of IPr*AuCl/AgNTf as a catalyst, the reaction did not proceed. However, when **1a** as treated with IPr*AuCl/AgNTf2 in th presence of **8**, the product formation could be observed. Taking into account that IPr* ligated gold i less prone to the formation of gold acetylides (IPr*AuCl and **1a** yielded in only 16% of the corresponding acetylide), we can suggest that gold acetylides take part in the catalytic cycle.

The results of the deuterium labeling experiments are shown in the Scheme 7. When a deuteriur labeled starting material **1a** was used in the reaction, 94% deuterium incorporation at the position of the benzothiophene scaffold was observed. Position 4 suffered more from scrambling. I accordance with that, the conversion of unlabeled **1a** with DAC NTf₂ in the presence of D₂O led to deuterium incorporation of 80% in position 4 and 21% in the position 6. The unreacted startin material contained 54% D. The results of the labeling experiments are not easy to interpret but th difference between the two newly formed protons gives a hint that while the 4 position is most likel transferred by the common catalyst transfer from a substrate molecule onto the aurated intermediate due to the high degree of deuterium incorporated alkyne. Thus a direct 1,2-addition of a deuterate alkyne onto the aurated phenyl cation intermediate is more likely than the addition of an acetylide. I this case exchange processes with the acetylide should at least reduce the labeling degree Unfortunately the labeling experiments cannot completely rule out that pathway 1 operates, as in this case also a high degree of deuterium would be expected for the position next to the alkyne.



Scheme 7. Deuterium labeling experiments.

Conclusion

In conclusion, we have further explored the reactivity of thiophene-based diynes under dual gol catalyzed conditions. Thiophenes with aryl alkynes as starting materials give rise to highly interestin fluorescent dimers in a yet unknown pathway for this activation mode. Despite intense efforts, th mechanistic picture is still vage, but from the results of earlier studies and the mechanisti investigations herein, most possible a pathway initiated by a 6-*endo*-cyclization followed by a direc addition of the alkyne to the aryl cation takes place.

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[9] CCDC 1525756 (**2h**) and 1525757 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data request/cif

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