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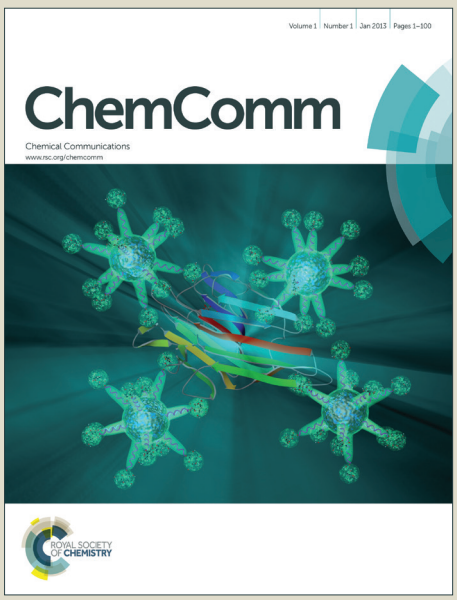

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Gold superacid-catalyzed preparation of benzo[*c*]thiophenes

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A three-step synthesis of benzo[*c*]thiophenes is presented in which the key transformation is the gold-catalyzed 5-*exo-dig* migratory cycloisomerization of a diallyl thioacetal. It was shown that a small amount of *in situ* generated $HAuCl_4$ from $AuCl_3$ is the active catalytic species. A mechanism was proposed.

Benzo[*c*]thiophenes or isothianaphthenes are of particular interest to material chemists. Most of their applications rely on their presence in oligomers or polymers, bestowing specific photochemical and –physical features on these materials.[1] They are used in the generation of organic light-emitting diodes (OLEDs),[2] as colorimetric fluoride anion chemosensors,[3] as chromophores for non-linear optics materials,[4] NIR contrast agents for biomedical applications[5] and in transistors.[5a] However, benzo[*c*]thiophene oligomers are mostly applied in organic photovoltaic cells (OPV) due to their small band gap, as a cheaper alternative to silicon based solar cells.[6] Hitherto, benzothiophene-based OPVs with efficiencies exceeding 7% have been reported.[7] Despite the wide applicability of benzo[*c*]thiophenes in material sciences, the scope of reactions to generate these remains relatively limited. It mostly relies on thionating agents such as Lawesson's reagent or P_2S_5, which display poor atom economy.[1,4,5b,6b,8] In other cases, the benzene ring is annulated onto a thiophene or the corresponding dihydroisothianaphthene is oxidized to the desired isothianaphthene.[2b-e, 6a,d-e,h-k,9]

Herein, we present a 3-step approach to widely substituted benzo[*c*]thiophenes starting from *ortho*-halobenzaldehydes, of which many derivatives are commercially available. Based on our previous experience in the synthesis of 1-phosphono- and 1-cyanoisoindoles and 5-alkylidene-dihydrothiazoles,[10] we envisioned an Au-catalyzed 5-*exo-dig* migratory cycloisomerization to form the thiophene moiety annulated to a benzene ring.[11]

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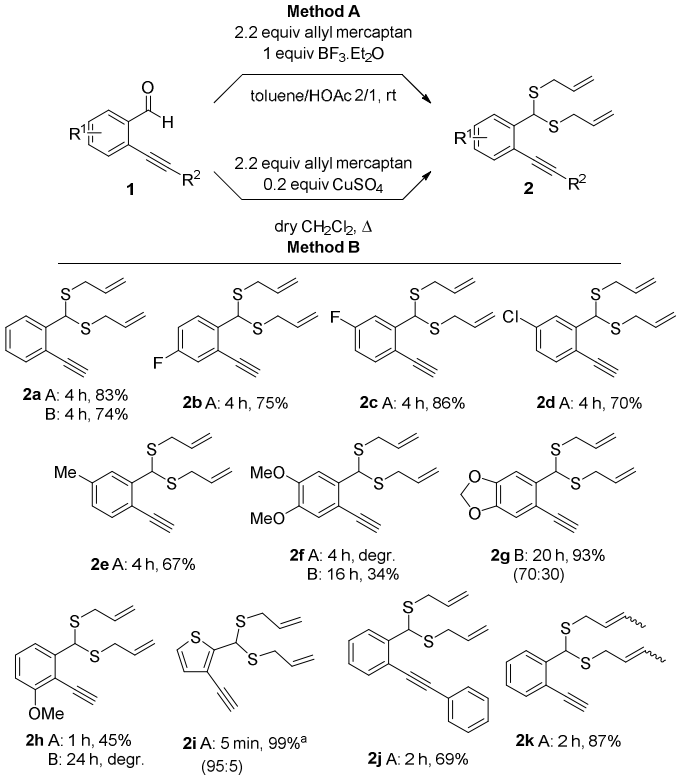
A number of aptly substituted *ortho*-ethynyl benzaldehydes **1** was purchased or prepared via Sonogashira coupling, according to literature procedures (see ESI). The substrate scope was further expanded using a heterocyclic core, a thiophene-2-carbaldehyde, and an internal alkyne instead of terminal ones. These substrates were converted into the corresponding diallyl thioacetals **2** with freshly distilled allyl mercaptan (CAUTION, see ESI for correct handling) or crotyl mercaptan (**2k**). Two literature protocols were applied, one using boron trifluoride in acetic acid and one using copper sulfate in dichloromethane (Scheme 1).[12] Electron rich substrates were more efficiently converted using the latter protocol (**1f-g**), whereas the other substrates gave satisfactory results using the boron trifluoride-mediated transformation. Some 30% formation of the corresponding benzo[*c*]thiophene was observed for **1g** and 5% for **1i**, according to ^{1}H-NMR integration. These mixtures were chromatographically inseparable, so the crude mixture was used as such in the following step.

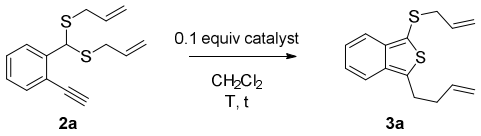
Sulfur containing compounds have a reputation of being difficult substrates for catalytic reactions as they can cause catalyst poisoning. Nevertheless, gold salts and thiols or thio-ethers have been shown to be compatible.[10c,13] Based on our previous work on 5-alkylidene-dihydrothiazoles, a gold catalyzed 5-*exo-dig* migratory cycloisomerization was envisioned, yet a selection of other catalytic systems was evaluated to ensure optimal reaction conditions (Table 1). No 6-*endo-dig* cyclization was encountered for any of the screened catalysts. Heating diallyl thioacetal **2a**, either conventionally or by microwave irradiation (60 min, 165 °C), did not deliver the desired benzo[*c*]thiophene (entries 1-2). The use of iron, copper, ammonium, nickel, palladium and silver salts resulted in no conversion after 3 hours of refluxing in dichloromethane (entries 3-8). Also, the use of some mild and very strong protic acids such as acetic acid, sulfuric acid and tetrafluoroboric acid as catalyst proved to be unsuccessful and resulted in full recovery of starting material (entry 9-13). Addition of $BF_3.Et_2O$ or $CuSO_4$ did not yield any benzo[*c*]thiophene, precluding them as ring-closure catalysts in the earlier dithioacetalization step (Scheme 1, **2g** and **2i**). When moving to the previously optimized conditions for the synthesis of 5-alkylidene-dihydrothiazoles, using $AuCl_3$ in dichloromethane, full consumption of the starting material was observed at room temperature within 15 minutes. $AuBr_3$ and AuCl performed well too, albeit with a drop in isolated yield or at a slower rate (entries 16-18).



Scheme 1: Formation of diallyl thioacetals **2**. Values between parentheses refer to the ratio of diallyl thioacetal/benzo[*c*]thiophene. [a] reaction at 0 °C.

However, when other monovalent Au catalysts were used we were surprised that no conversion took place at all. This led us to believe that small amounts of hydrochloric acid, released from the catalyst by moisture, played a key role in the conversion. The acidity of HCl can be increased in the presence of $AuCl_3$, by complexation of the chloride and formation of a $HAuCl_4$ superacid.[14] Indeed, when the substrate was treated with $HAuCl_4$, full conversion to the end product could be observed. However, these conditions were too harsh and the end product showed appreciable degradation, resulting in an isolated yield of 48%. Upon addition of 10 mol% 2,6-di-*tert*-butylpyridine as a sterically hindered base to a mixture of diallyl thioacetal **2c** (chosen for stability reasons) and 10 mol% $AuCl_3$ the reaction proceeded much slower, indicating that strongly acidic conditions are required. This was further supported by the fact that use of $KAuCl_4$ under anhydrous conditions did not result in any conversion (entry 22). It is known that alkynes can mediate the reduction of trivalent gold to a complex of monovalent gold and tetrachloroaurate.[15] Yet, this is unlikely to occur here as both AuCl and $KAuCl_4$ did not give better results than $AuCl_3$. Instead of $HAuCl_4$, TfOH was selected as another superacid to verify whether it could perform the desired transformation as well.

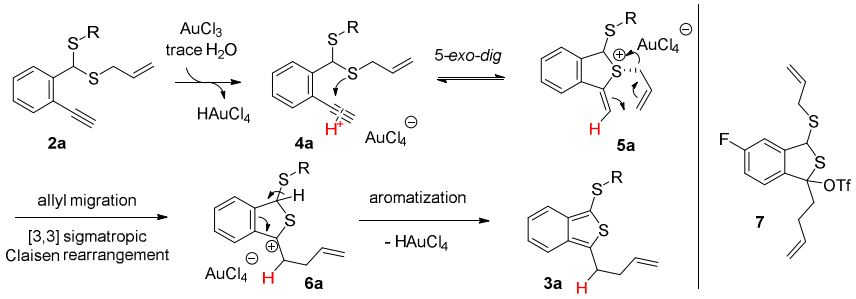
Table 1: Screening of different catalysts.



Entry	Catalyst	Temp (°C)	Time (min)	Yield (%)
1	-	40	1 d	-
2	-[a]	165	60	-
3	$Fe_2(acac)_3$	40	120	-
4	CuI	40	120	-
5	TBAB	40	120	-
6	$Ni(cod)_2$	40	180	-
7	$PdCl_2$	40	180	-
8	AgOTf	40	120	-
9	*p*-TsOH	40	180	-
10	HOAc	20	180	-
11	H_2SO_4	20	180	-
12	$HClO_4$	20	180	-
13	HBF_4	20	180	-
14	$BF_3.Et_2O$	20	180	-
15	$CuSO_4$	20	180	-
16	$AuCl_3$	20	15	65
17	$AuBr_3$	20	15	37
18	AuCl	20	60	60
19	AuOTf	20	180	-
20	$AuClPPh_3$	20	180	-
21	$HAuCl_4$	20	60	48
22	$KAuCl_4$[b]	20	180	-

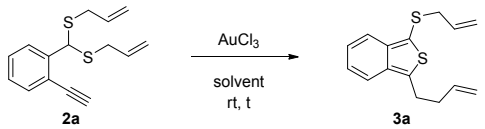
[a] microwave heating; [b] anhydrous conditions.

Curiously, the use of 10 mol% TfOH resulted in precisely 10% conversion to the desired benzo[*c*]thiophene. Repeating the reaction with a quantitative amount of TfOH in $CDCl_3$ to allow direct NMR-analysis revealed the formation of an intermediate product, which could be converted to the corresponding benzo[*c*]thiophene by addition of Cs_2CO_3 or by aqueous work-up. Based on the crude ^1H, ^{13}C, ^{19}F, COSY and HSQC NMR data, we postulate having trapped an intermediate as a covalently bound triflate (Scheme 2, compound **7**). This suggests that both the strongly acidic conditions as well as the counterion play a key role in the transformation. A sufficiently strong acid is able to execute the migratory cycloisomerization but cannot catalytically form the desired benzo[*c*]thiophene, as the intermediate is trapped by the counteranion. As such, the use of a catalytic amount of $AuCl_3$ under non-anhydrous conditions was selected as the best option. Due to its highly hygroscopic nature, simply weighing the catalyst in open air introduced enough moisture for the reaction to proceed swiftly.



Scheme 2. Proposed mechanism of the migratory cycloisomerization.

Table 2: Screening of different solvents.

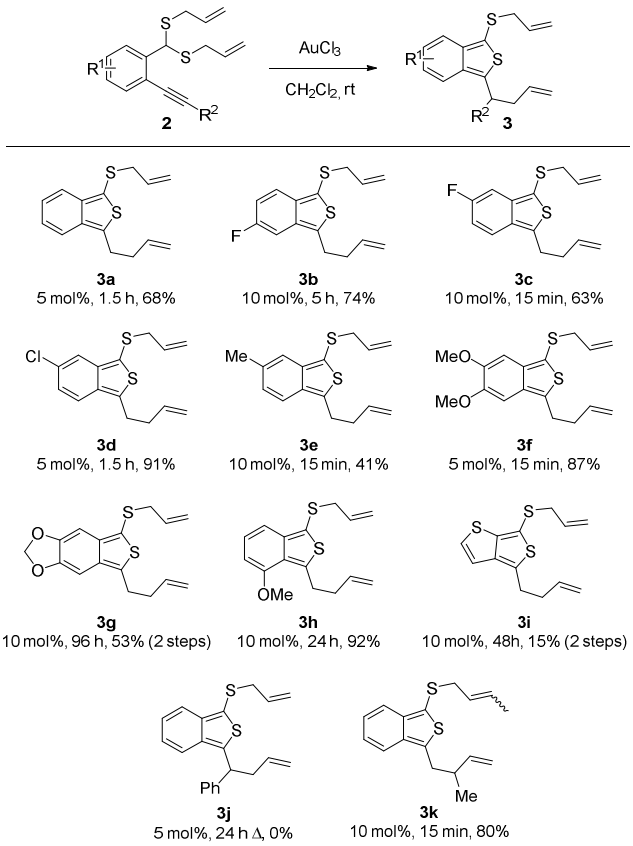


Entry	Loading (equiv)	Solvent	Time (min)	Yield (%)
1	0.1	Hexane	2 d	-
2	0.1	Toluene	1.5 d	56
3	0.1	EtOAc	180	40
4	0.1	DME	180	40
5	0.1	DCE	30	43
6	0.1	Acetone	180	45
7	0.1	DMF	2.5 d	23
8	0.1	CH_3CN	180	35
9	0.1	1-Pentanol	2.5 d	25
10	0.1	MeOH	2.5 d	7
11	0.1	CH_2Cl_2	15	65
12	0.01	CH_2Cl_2	180	65
13	0.05	CH_2Cl_2	15	68

The proposed mechanism for benzo[*c*]thiophene formation is depicted in Scheme 2. After acidic alkyne activation by *in situ* formed $HAuCl_4$, a 5-*exo*-*dig* cyclization takes place, furnishing intermediate **5a** which readily undergoes a Claisen rearrangement to **6a**. Instead of trapping **6a**, as was the case for the TfOH-mediated transformation, the $AuCl_4^-$ counteranion does not covalently bind to **6a**. This allows for consecutive aromatization to yield the desired benzo[*c*]thiophene **3a** by elimination of a proton, thus regenerating the catalyst. The concerted nature of this Claisen-type rearrangement was confirmed by transformation of **2k** to branched **3k**, ruling out a fragmentative allyl shift.

Next, a solvent screen was performed to verify whether CH_2Cl_2 indeed gave the best results in this case. Using strongly apolar solvents (Table 2, entries 1-2) resulted in very long reaction times, as did the use of highly polar solvents (entries 7-10). Solvents of intermediate polarity gave more valuable results, with yields around 40% and reaction times of 3 hours (entries 3-6). In dichloroethane (entry 5) the reaction was almost equally fast as in dichloromethane, however, product degradation occurred (which was clearly visible upon TLC analysis), resulting in an isolated yield of only 43%. These observations established dichloromethane as the solvent of choice. The catalyst loading could be lowered to 1 mol%, maintaining an isolated yield of 65%, while lengthening the reaction time to 3 hours (entry 12). As a compromise, a catalyst loading of 5-10 mol% was applied, depending on how fast the transformation proceeded (Scheme 3). As product stability was clearly a determining factor in order to obtain good yields, an experiment was performed using 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenging additive. This attempt to further stabilize the end product proved to be unsuccessful and the reaction yield was unchanged. For all derivatives **2**, except **2j**, a conversion of ≥ 98% was achieved based on HPLC, though poor product stability led to losses during work-up and purification.

The influence of electron-withdrawing groups on the migratory cycloisomerization is mainly reflected in the improved stability of the formed benzo[*c*]thiophenes. As for electron-donating groups there is a large discrepancy in reaction time between **2f** and **2g** for no apparent reason, while the 4-methoxybenzo[*c*]thiophene **3h** is obtained in excellent yield but only after 24 hours, possibly due to steric hindrance. Thieno[3,4-*b*]thiophene **3i** was obtained in 15% yield over 2 steps. Non-terminal alkyne **2j** could not be cyclized, not



Scheme 3. Ring closure of diallyl thioacetals **2**. Catalyst loading, reaction time and yield are indicated.

even after 48 hours of reflux with 5 mol% $AuCl_3$ in toluene, and only starting material was recovered.

In conclusion, we have developed a 3-step approach to benzo[*c*]thiophenes from commercially available *ortho*-halo aromatic aldehydes. Sonogashira coupling and generation of diallyl thioacetals **2** yielded suitable substrates for ring closure. It was proven that a sufficiently strong acid can perform the migratory cycloisomerization, but the consecutive benzo[*c*]thiophene formation depends on the nature of the counteranion. Use of $AuCl_3$ led to the *in situ* formation of $HAuCl_4$ which efficiently catalyzed the desired transformation. While it is often unclear whether similar cycloisomerizations are proton- or metal-catalyzed, we have clearly demonstrated that, in our case, a proton is the catalytic species. However, the importance of the gold counteranion cannot be neglected. This approach has led to the desired products **3** in 15-92% yields. A catalyst loading of 5-10 mol% was considered optimal as a compromise between reaction time and product stability. This approach could be applied to widely substituted *ortho*-halobenzaldehydes and to heterocyclic cores as well, however it is restricted to terminal alkynes. The obtained benzo[*c*]thiophenes are mainly of interest as oligomers in organic photovoltaic cells (OPV), along with a number of other earlier discussed applications.

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