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PAPER

Gold(III) chloride catalysed synthesis of 5-alkylidene-dihydrothiazoles†

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A two step synthesis of dihydrothiazoles is presented. First, the previously unknown *N*-propargylic dithiocarboimidates are produced in good yields from easily available, cheap starting materials. The subsequent gold catalysed ring closure is fast and efficient, leading to dihydrothiazoles through a cascade of 5-*exo*-dig cyclisation and 1,3-alkyl migration. The yields range from 74% to 95%.

Introduction

Since the introduction of Epalrestat **1** in 1992 for the treatment of diabetic neuropathy (Fig. 1), rhodanines have emerged as a privileged substructure in medicinal chemistry.[1] More specifically, 5-alkylidene-rhodanines and 4-desoxy-5-alkylidene-rhodanines have been reported in the recent literature as antifungal,[2] antibacterial,[3] analgesic[4] and anticonvulsive[5] agents, as enzyme inhibitors of MurD ligase,[6] cell division cycle 7 kinase,[7] human arylamine N-acetyltransferase 1,[8] diaminopimelate aminotransferase[9] and HIV-1 integrase,[10] and as histamine H_3 receptor antagonists.[11]

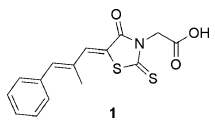

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Fig. 1 Epalrestat.

Hitherto, most of these bioactive molecules are *N*-alkylated rhodanines. Alkylation of sulphur, leading to the dithiocarboimidate isomeric form of rhodanine has been studied to a lesser extent. These molecules, however, do possess interesting biological properties, such as antimicrobial and antifungal activity.[12]

These *S*-alkylated rhodanines are synthesized mostly by an alkylation at the end of the total synthesis. However, this causes problems with functional group compatibility and alkylation site selectivity. To overcome these problems, a method involving *S*-alkylation in the early stages of the synthesis would provide much benefit. Therefore, we tried to expand our recently reported methodology for the construction of isoindoles[13] to the synthesis of 5-alkylidene-*S*-alkyl-rhodanines (Fig. 2).

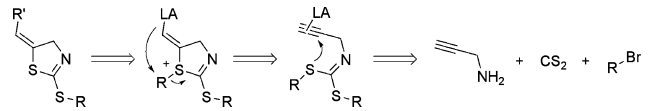
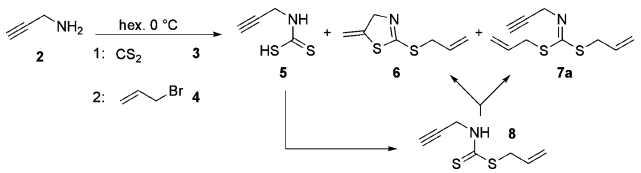


Fig. 2 Retrosynthetic analysis.

The projected synthesis proceeds through the 5-*exo*-dig cyclisation of Lewis acid activated *N*-propargylic dithiocarboimidates. Using allylic R groups, the thus formed zwitterionic intermediate undergoes a thio-Claisen type rearrangement, delivering the desired dihydrothiazoles. This methodology inherently introduces a 5-alkylidene substituent onto the thiazoline ring and is as such very well suited for the synthesis of bio-active rhodanine mimics. In analogy with literature reports, the dithiocarboimidate precursor should be easily obtained through a condensation of propargylamine, carbon disulfide and allylic bromides.[14]

Results and discussion

Our first attempts towards the construction of diallyl *N*-propargyl dithiocarboimidate **7a** showed the presence of three main components, which were identified as the intermediate **5**, side product **6** and the desired dithioimidate **7a** in a 23/23/54 ratio (Scheme 1).



Scheme 1 Synthesis of *N*-propargyl dithiocarboimidate **7a**.

Formation of the methylidene dihydrothiazole **6** is attributed to the spontaneous cyclisation of the monoalkylated **8**. This type of conversion has been reported before and has merit on its own,[15] but is undesirable in our case. Fortunately, the condensation product of propargylamine and CS_2 does not display this spontaneous ring closure. As such, it is possible to pre-form compound **5**, and subsequently quench it using an excess of allylic bromide. Using 6 equivalents of bromide, the product ratio is improved to 8/15/77,

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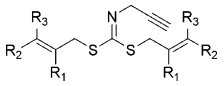
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c1ob05509g

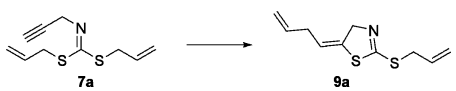
Table 1 Synthesis of compounds **7a–7f**



Entry	R_1	R_2	R_3	**7** (%)
a	H	H	H	78
b	Me	H	H	89
c	H	Me/H	Me/H	79[a]
d	H	Me	Me	88
e	Br	H	H	80
f	H	Ph	H	81
g	H	H	H	76[b]
h	H	H	H	0[c]

[a] Using a 4/1 *E*/*Z* mixture of bromide delivered a statistical 16/8/1 mixture of *EE*/*EZ*/*ZZ*. [b] Allyl iodide used. [c] Allyl chloride used, no conversion observed.

Table 2 Evaluation of reaction conditions



Entry	Solvent	*T*/°C	Catalyst	Time/min	**9a** (%)
1	THF	66	—	1260	0
2	THF	66	*p*-TsOH	150	0
3	CH_2Cl_2	20	*p*-TsOH	90	0
4	CH_2Cl_2	40	*p*-TsOH	180	0
5	CH_2Cl_2	20	10% $AuCl_3$	180	—[a]
6	CH_2Cl_2	20	10% $AuCl_3$	15	92
7	CH_2Cl_2	20	5% $AuCl_3$	15	90
8	CH_2Cl_2	20	1% $AuCl_3$	15	50[b]
9	CH_2Cl_2	20	1% $AuCl_3$	180	—[a]
10	CH_2Cl_2	20	5% AuCl	180	35[b]
11	CH_2Cl_2	20	5% $KAuCl_4$	180	44[b]
12	CH_2Cl_2	20	5% *p*-TsOH. AuCl	180	28[b]

[a] Heavy degradation, not isolated. [b] ^{1}H NMR conversion.

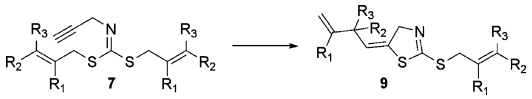
and when using 8 equivalents of bromide, conversion to **7a** is increased to 98%.

Using this optimized method, several dialkyl *N*-propargyl dithiocarboimidates were synthesized. As shown in Table 1, all yields are higher than 76%. Conversions were complete in all cases; however, column chromatography used to separate the excess of allylic bromide accounts for the observed product loss. Allylic iodides (entry g) showed a similar reactivity to their bromide counterparts, but allylic chlorides (entry h) were unreactive under these conditions.

Moving on to the ring closure of these products (Table 2), both heat and acid catalysis were evaluated. After simple heating of the compounds in THF, only trace amounts of the ring-closed product could be observed after 21 h. Furthermore, some product degradation had occurred. Also the use of *p*-TsOH in THF (entry 2) or dichloromethane (entries 3 and 4) proved to be unsuccessful. After 3 h of reflux no conversion could be detected.

Switching to the conditions previously optimized for the synthesis of 1-cyanoisoindoles, we were pleased to find that 1 mol% of $AuCl_3$ in dichloromethane readily catalyzed the envisioned ring closure.[16] After 15 min at room temperature, 50% conversion was observed. However, as the reaction continued, product degradation started to occur. This specific problem was encountered with

Table 3 Synthesis of compounds **9a–9f**



Entry	R_1	R_2	R_3	**9** (%)
a	H	H	H	90
b	Me	H	H	93
c	H	Me/H	Me/H	95[a]
d	H	Me	Me	92
e	Br	H	H	85[b]
f	H	Ph	H	74[c]

[a] No preference in terms of the migration of the *E* or *Z* alkene was observed, the 16/8/1 mixture of *EE*/*EZ*/*ZZ* reverts to a 4/1 *E*/*Z* mixture. [b] Quantitative, 85% pure by LC. [c] Column chromatography performed.

all derivatives: keeping these thiazolines at room temperature for periods exceeding 30 min causes significant product loss. As a result, we were forced to increase the catalyst loading in order to shorten reaction times. Both 10 and 5 mol% mediated full conversion in less than 15 min for all derivatives. As such, 5 mol% seems to be the ideal compromise between catalyst loading and reaction speed.

Since it is known that alkynes mediate the reduction of trivalent gold to a complex of monovalent gold and tetrachloroaurate,[17] these species must be considered as possible catalysts. Consequently, the reactions were run in the presence of AuCl (entries 10 and 12) and KAuCl4 (entry 11). In both cases the reaction occurred only very slowly, resulting in conversions of 28 to 45% after three hours. Comparing this to the high reactivity of $AuCl_3$, it seems unlikely that the active catalyst is formed by a reduction to AuCl. Some degree of co-catalysis, however, cannot be excluded.[18]

Continuing with 5 mol% $AuCl_3$ as the catalyst, all derivatives could be transformed in good to excellent yields, as shown in Table 3. The compounds are pure after work-up, which consists of filtration over a small plug of silica gel. Compound **9f** displays a lower yield: in this case column chromatography was performed to obtain an analytically pure product. Notably, bromide-containing thiazoline **9e** was obtained quantitatively, but showed more product degradation than the other derivatives. Its purity after reaction was approximately 85% (by LC analysis). Due to its inherent instability, an analytically pure sample of **9e** was obtained only after 3 chromatographic steps, resulting in significant product loss and a yield of 51%.

Some mechanistic aspects of this reaction are worth discussing. First, NOESY spectroscopy of the dihydrothiazoles shows that the exocyclic double bond is formed exclusively in the *E*-configuration (Fig. 3).

As shown in Scheme 2, the initial attack of sulphur on the alkyne leads to a non-isomerisable gold-stabilized *E*-carbanion in the intermediate species **10**. The trivalent gold species completes its coordination sphere by complexation of the allylic double bond, similar to previous reports in the literature.[13,19]

This *E*-configuration is maintained in the end product. Since there is no conceivable steric- or chelation-induced driving force favoring this configuration, it can be stated that there is no free rotation (nor isomerisation) of the methylene bond during the conversion of intermediate **10** to thiazole **9**.

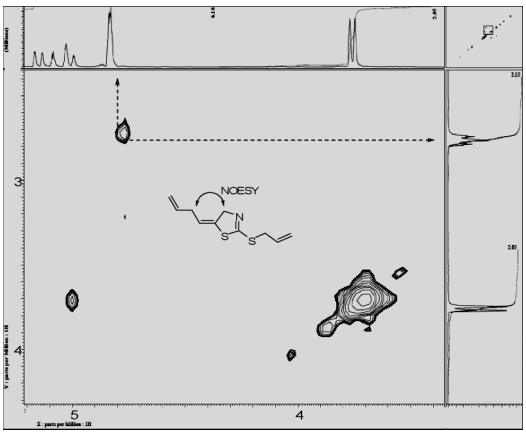
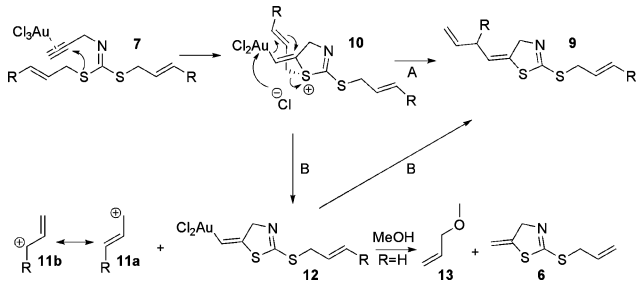


Fig. 3 NOESY experiment.



Scheme 2 Reaction mechanism.

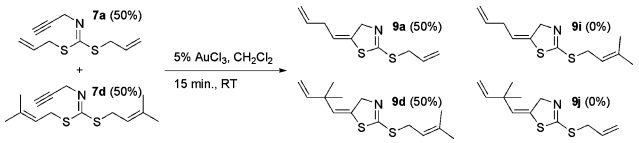
Keeping this information in mind, two reaction pathways can be proposed. Route A is a concerted mechanism through a thio-Claisen type rearrangement. Chloride-induced elimination of the gold catalyst induces an S_N' reaction of the liberated vinylic anion on to the activated allylic cation, delivering compound **9**.

Route B is a stepwise mechanism, passing through the initial elimination of free allylic cation **11a**, followed by recombination to **9**. The observed regioselectivity upon formation of compounds **9c**, **9d** and **9f** indicates an S_N'-type reaction (route A), but this evidence is not absolute since thermodynamic factors may cause cation **11** to react preferentially at the more substituted position (**11b**).

In order to disprove pathway B, the reaction was performed in methanol. In this solvent, the free allylic cation will be immediately quenched forming the corresponding methyl ether, leaving the residual anion available for protodeauration. Although the reaction proceeded somewhat sluggishly (50% conversion after 20 min) and the isolated product was not completely pure, none of the side products could be identified as **13** or **6** by NMR and LC-MS study, thus excluding pathway B.

Further exploration of the reaction mechanism confirms the conversion of **10** to **9** to occur intramolecularly. During a cross-over experiment, a 1 : 1 mixture of compounds **7a** and **7d** was treated with the gold catalyst (Scheme 3). Only products **9a** and **9d** were detected after reaction (in a 1 : 1 ratio) and no cross-over of alkyl groups, delivering **9i** or **9j**, had occurred.

On a final note of interest, it was not possible to isomerise the exocyclic double bond to an endocyclic one, delivering aromatic thiazoles. Treatment with sodium methoxide in methanol or deprotonation with sodium hydride delivered the starting material quantitatively. Treatment with tosic acid at room temperature



Scheme 3 Cross-over experiment.

caused severe product degradation after as little as 5 min, and no thiazole could be found. It was indeed shown that for a similar cyclisation of *N*-propargyl amides to oxazoles, stringent acidic conditions (110 °C, *p*-TsOH) were needed to achieve aromatization.[20]

Conclusions

A fast and high yielding gold catalysed synthesis of 5-alkylidene dihydrothiazoles was presented. The reaction proceeds through a concerted mechanism, comprising of a 5-*exo*-dig cyclisation followed by a thio-Claisen type rearrangement of the gold stabilized *E*-anion. The precursors to this methodology, *N*-propargylic dithiocarboimidates, were previously unknown and their syntheses has been elaborated from readily available and cheap starting materials.

Experimental part

General procedure 1: synthesis of dithiocarboimidates 7a–7f

In a dry 50 ml flask 0.600 g (10.9 mmol, 1 equiv.) propargylamine is dissolved in 30 ml of hexane. To this 11 g (109 mmol, 10 equiv.) Et_3N is added. The flask is placed under inert atmosphere and is cooled to 0 °C in order to buffer the exothermic reaction. Slowly 1.26 g (16.4 mmol, 1.5 equiv.) carbon disulfide is added, using a syringe. The cooling bath is removed, and the reaction is allowed to stir at room temperature for one hour. A white suspension is formed. Subsequently, 8 equivalents of an allylic bromide are added and the reaction is stirred at room temperature during an overnight period. The extraction is performed from aqueous saturated $NaHCO_3$ by means of dichloromethane (3×). The combined organic phases are dried using $MgSO_4$ and the volatiles are removed by rotary evaporation. Further purification is performed by means of column chromatography when the allylic bromide could not be evaporated.

Diallylprop-2-ynyl dithiocarboimidate 7a

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.26 (1H, t, J = 2.8 Hz, $C_q{\equiv}CH$); 3.67 (2H, d, J = 7.2 Hz, SCH_2); 3.72 (2H, d, J = 6.6 Hz, SCH_2); 4.23 (2H, d, J = 2.8 Hz, NCH_2); 5.08 (1H, d, J = 9.9 Hz, $CH{=}C\underline{H}_EH_Z$); 5.15 (1H, d, J = 9.9 Hz, $CH{=}C\underline{H}_EH_Z$); 5.23 (1H, d, J = 16.5 Hz, $CH{=}CH_E\underline{H}_Z$); 5.28 (1H, d, J = 15.7 Hz, $CH{=}CH_E\underline{H}_Z$); 5.79–5.94 (2H, m, 2x $C\underline{H}{=}CH_2$). ^{13}C-NMR (75 M Hz, $CDCl_3$): δ 34.5 (SCH_2); 35.5 (SCH_2); 42.3 ($C_q\underline{C}H_2$); 71.1 ($C_q{\equiv}\underline{C}H$); 81.6 ($\underline{C}_q{\equiv}CH$); 118.3 ($CH{=}\underline{C}H_2$); 119.0 ($CH{=}\underline{C}H_2$); 132.7 ($\underline{C}H{=}CH_2$); 133.0 ($\underline{C}H{=}CH_2$); 159.7 ($NC_qS_2$). MS (ESI): m/z (%): 212 (M + H$^+$, 100). HRMS (ESI): m/z calcd for $C_{10}H_{13}NS_2$+H$^+$ 212.0568, found 212.0571. IR (cm^{-1}) vmax: 1567 ($N{=}CS_2$); 1636 ($CH{=}CH_2$); 3296 ($C{\equiv}CH$). Chromatography: PE/EtOAc 95/5 R_f 0.20. Y: 78%.

General procedure 2: synthesis of dihydrothiazoles 9a–9f

In a dry 25 ml flask under inert atmosphere, dithiocarboimidate **7** is dissolved in dry dichloromethane. Subsequently 0.05 equivalents of $AuCl_3$ is added and the reaction is stirred at room temperature for 15 min. The reaction mixture is filtered over a small plug of silica gel and after evaporation of the volatiles, dihydrothiazoles **9** are obtained.

(*E*)-2-(Thioallyl)-5-(but-3-enylidene)-4,5-dihydrothiazole 9a

^{1}H-NMR (300 M Hz, $CDCl_3$): δ 2.76 (2H, dd, J = 7.7 Hz, J = 6.1 Hz, HCC$\underline{H}_2$CH); 3.76 (2H, d, J = 6.6 Hz, SCH_2); 4.83 (2H, ~d, J = 3.0 Hz, NCH_2); 5.01 (1H, ~dd, J = 9.9 Hz, J = 1.1 Hz, $CHCH_2CH{=}C\underline{H}_EH_Z$); 5.06 (1H, ~dd, J = 17.1 Hz, J = 1.1 Hz, $CHCH_2CH{=}CH_E\underline{H}_Z$); 5.15 (1H, dd, J = 9.9 Hz, J = 1.1 Hz, $SCH_2CH{=}C\underline{H}_EH_Z$); 5.28 (1H, dd, J = 17.1, J = 1.1 Hz, $SCH_2CH{=}CH_E\underline{H}_Z$); 5.50 (1H, tt, J = 7.7 Hz, J = 3.0 Hz, $C_q{=}CH$); 5.76 (1H, ddt, J = 17.1 Hz, J = 9.9 Hz, J = 6.1 Hz, $C_qCHCH_2C\underline{H}$); 5.93 (1H, ddt, J = 17.1 Hz, J = 9.9 Hz, J = 6.6 Hz, $SCH_2C\underline{H}$). ^{13}C-NMR (75 M Hz, $CDCl_3$): δ 34.3 (HC$\underline{C}H_2$CH); 34.7 (SCH_2); 67.1 (NCH_2); 115.6 (CH=$\underline{C}H_2$); 116.1 ($C_q{=}\underline{C}H$); 118.7 ($SCH_2CH{=}\underline{C}H_2$); 132.7 ($SCH_2\underline{C}H$); 135.0 ($HCCH_2\underline{C}H{=}CH_2$); 139.8 ($S\underline{C}_qCH_2$); 163.1 ($NC_qS_2$). MS (ESI): m/z (%): 212 (M + H^+, 100). HRMS (ESI): m/z calcd for $C_{10}H_{13}NS_2{+}H^+$ 212.0567, found 212.0564. IR (cm^{-1}) ν_{max}: 1573 ($N{=}CS_2$); 1637 ($HC{=}CH_2$). Y: 92%.

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