Tetrahedron Letters 50 (2009) 7286–7287

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 4,5-disubstituted-3-trihalomethylisothiazoles

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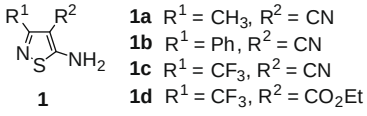
ARTICLE INFO

Article history:
Received 16 September 2009
Revised 5 October 2009
Accepted 8 October 2009
Available online 4 November 2009

ABSTRACT

Herein, we describe the synthesis of 4,5-disubstituted-3-trihalomethylisothiazoles from trihaloacetonitriles and 2-cyanothioacetamides or 2-ethoxycarbonylthioacetamides. The reactivity of the necessary trihaloacetonitriles has a significant impact on the observed reaction pathways. Reactions with CF_3CN require an oxidant to mediate cyclization, while CCl_3CN functions as both the reactant and oxidant.

Substituted isothiazoles such as **1** are important building blocks for the preparation of a wide range of compounds with industrial and pharmaceutical importance.[1] Towards our efforts to identify short acting calcium-sensing receptor (CaR) antagonists[2] we sought intermediate 3-trifluoromethylisothiazoles like **1c** or **1d** to synthesize CF_3-substituted isothiazolopyrimidinone CaR antagonists.[3] While several isothiazoles with a CF_3 group in the 3-position were known,[4] none contained the substitution at the 4- and 5-positions that we required. Isothiazoles **1a**[5] or **1b**[6] were readily available from the corresponding R^1-orthoester, however, attempts to prepare **1c** or **1d** by this route proved unsuccessful.



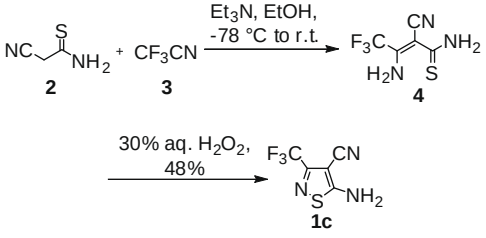
1

1a $R^1 = CH_3$, $R^2 = CN$
1b $R^1 = Ph$, $R^2 = CN$
1c $R^1 = CF_3$, $R^2 = CN$
1d $R^1 = CF_3$, $R^2 = CO_2Et$

Herein we wish to report a route to readily prepare CF_3-substituted isothiazoles **1c** and **1d**. We reasoned that 2-cyanothioacetamide (**2**) would react with electron-deficient CF_3CN (**3**) under basic conditions to directly form vinylogous thiourea intermediate **4** (Scheme 1). Subsequent oxidative cyclization would then give the desired isothiazole. In practice, triethylamine was added to a mixture of **2** and **3** in EtOH at −78 °C. After the mixture was warmed to room temperature, H_2O_2 was added to mediate oxidative cyclization to give isothiazole **1c** in 48% yield. A range of oxidants including *N*-bromosuccinimide, *N*-chlorosuccinimide, *N*-iodosuccinimide (NIS), Br_2, I_2 and SO_2Cl_2 effected the cyclization as judged by thin-layer chromatography (TLC).[7]

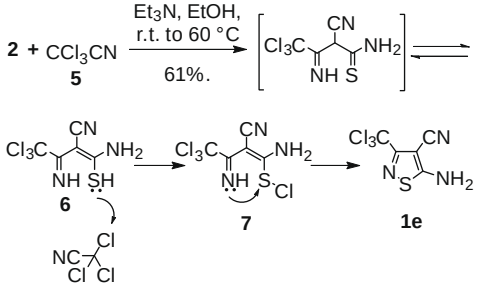
With a successful synthesis of **1c** in hand, we sought to further examine the scope of the transformation. Attempts to couple **2** with acetonitrile or benzonitrile to give **1a** and **1b**, respectively, proved unsuccessful, likely due to the relatively lower electrophilicity of the nitrile carbons. However, another electron-deficient nitrile, CCl_3CN (**5**), proved interesting. Nitrile **5** participates as both reactant and oxidant[8] (Scheme 2) during its reaction with **2**. The reaction occurred at or above room temperature to directly give the desired cyclized product **1e** without need for an added oxidant, such as H_2O_2.

We next examined the range of N-substituted isothiazoles that would react to form trihalomethylisothiazoles. We were pleased to find that *N*-alkyl thioamides could be employed to give moderate



2 **3** **4** **1c**

Scheme 1. Synthesis of isothiazole **1c**.



Scheme 2. Proposed mechanism for the formation of **1e**.

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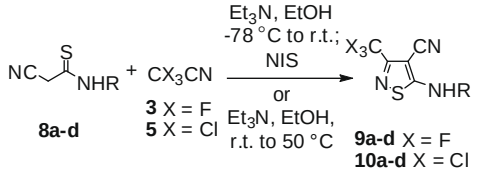
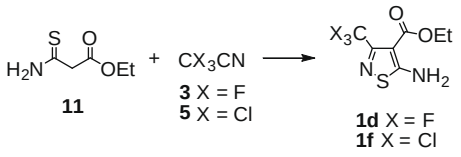
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.051

Table 1
Synthesis of isothiazoles **9a–d** and **10a–d**



R	Product	% Yield **9**	Product	% Yield **10**
CH_3	**9a**	44	**10a**	25
Benzyl	**9b**	36	**10b**	36
Cyclohexyl	**9c**	46	**10c**	49
Phenyl	**9d**	65	**10d**	56

Table 2
Synthesis of isothiazoles **1d** and **1f**



Entry	Nitrile	Conditions	Product	% Yield **1**
1	**3**	(1) Et_3N, −78 °C to room temperature; (2) H_2O_2	**1d**	0
2	**5**	Et_3N, −78 °C to room temperature	**1f**	14
3	**3**	(1) Et_3N, −78 °C, 1 h; (2) H_2O_2	**1d**	30

yields of the desired isothiazoles (Table 1). The highest yields were obtained using the *N*-phenyl thioamide.

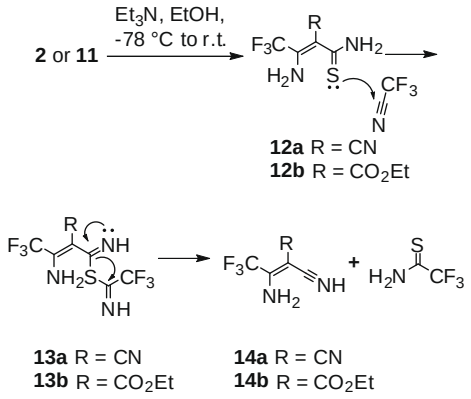
Towards the synthesis of isothiazole ester **1d**, we examined isothiazole formation with ester **11** in place of nitrile **2**. However, in the reaction of **11** with CF_3CN (**3**) using the conditions described above (Et_3N, −78 °C to room temperature; H_2O_2), none of the desired isothiazole (**1d**) was formed (Table 2, entry 1). In contrast, the reaction of **11** with CCl_3CN (**5**) provided isothiazole **1f** (Table 2, entry 2), albeit in modest yield (14%).

To better understand the different outcomes upon reaction of CF_3CN (**3**) with nitrile **2** and ester **11**, we sought to characterize the intermediates prior to oxidation. The reaction of nitrile **2** with CF_3CN (**3**) gave two products (Table 3, entry 4). The major product was the expected vinylogous thiourea **12a**, (35% isolated yield after purification), and the minor component was dinitrile **14a** which was likely formed by the mechanism shown in Table 3. When oxidant was added to purified **12a**, it proceeded to give the desired isothiazole **1c**.

In contrast, the reaction of ester **11** with CF_3CN (**3**) provided the desired intermediate **12b** as the minor product, while nitrile side-product **14b** was the predominant product (Table 3, entry 5). Furthermore, when the reaction was warmed or allowed to proceed for several hours, only **14b** was isolated. We therefore sought to generate intermediate **12b** and then oxidize it to **1d** before it could react with excess CF_3CN (**3**);[9] addition of H_2O_2 at −78 °C 1 h after the addition of Et_3N gave **1d** (Table 2, entry 3) in 30% yield.

In conclusion, we have developed a novel synthesis of 4,5-disubstituted-3-trihalomethylisothiazoles. This methodology is tolerant of N-substituted thioamides, but appears to require acetonitriles containing strongly electron-withdrawing groups. The reactivity of the necessary trihaloacetonitriles has a significant impact on the observed reaction pathways. Reactions with CF_3CN (**3**) require an oxidant to mediate cyclization, while CCl_3CN (**5**) functions as both the reactant and oxidant. CF_3CN (**3**) is more reactive with ester intermediate **12b** than with nitrile intermediate **12a**, thereby requiring oxidation at low temperature after a short time period to obtain ester **1d**.

Table 3
Proposed mechanism for the formation of **14a** and **14b**



Entry	Thioamide	% Yield **12**	% Yield **14**
4	**2**	35	4
5	**11**	6	68

Acknowledgements

We wish to thank Professor Andy Myers, Steven Wright and Daniel Kung for helpful suggestions with this chemistry.

Supplementary data

Supplementary data (experimental procedures and characterization of final products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.051.

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