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Tetrahedron Letters 45 (2004) 4449–4452
Tetrahedron Letters

Reeve's synthesis of 2-imino-4-thiazolidinone from alkyl (aryl) trichloromethylcarbinol revisited, a three-component process from aldehyde, chloroform and thiourea

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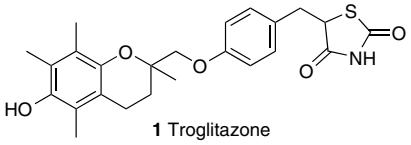
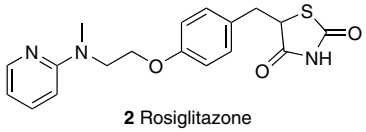
Received 25 March 2004; revised 9 April 2004; accepted 13 April 2004

Abstract—An efficient synthesis of 2-imino-4-thiazolidinones from readily accessible alkyl (aryl) trichloromethylcarbinols and thioureas under mild conditions is reported. A one-pot three-component synthesis of the title compounds from aldehyde, chloroform and thiourea is also developed for the first time

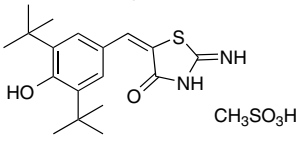
Thiazolinone or its tautomeric form, the hydroxy thiazole belongs to an important family of heterocyclic compounds and various synthetic approaches to these molecules have been documented.[1] These heterocycles display diverse biological activities such as tuberculostatic, anti-inflammatory, antidiabetic, antithyroidal, fungicidal, bactericidal and pesticidal. Among various subtypes, the 2,4-thiazolidinedione (TZD) class is particularly important as therapeutic agents and has been thoroughly investigated as PPAR-γ agonists that led to the development of several insulin-sensitizing drugs,[2] such as Troglitazone (**1**)[3] and Rosiglitazone[4] (**2**, Fig. 1) for the treatment of type 2 diabetes. In contrast, the isosteric 2-imino-4-thiazolidinone and its tautomeric 2-amino-4-thiazolinone have been less investigated in medicinal chemistry although potent anti-inflammatory (**3**)[5] and antiviral activities[6] have been found (Fig. 1). This is unfortunate since the presence of imino (amino) function introduced an additional diversity point allowing further structural tuning. The lack of efficient synthetic methods may be responsible for this observation.



1 Troglitazone



2 Rosiglitazone



3 Darbufelone

Figure 1. Medicinally relevant thiazolidinediones and imino thiazolidinone.

The synthesis of imino thiazolidinones (**4**) rely mainly on the condensations of thioureas (**5**) with α-haloalkanoic acid derivatives (**6**) in the presence of a base (Eq. 1, Scheme 1).[7] Alternatively, Robert and co-workers employed *gem*-dicyano epoxide (**7**) as a dicationic ketene equivalent for the synthesis of 2-imino-4-thiazolidinone derivatives (Eq. 2, Scheme 1).[8,9] In connection with our ongoing program aiming at the development of efficient accesses to medicinally relevant heterocycles,[10] we were interested in the construction of imino thiazolidinones **4** from aldehydes according to the reaction sequence outlined in Scheme 2. A one-pot three-component synthesis of **4** from aldehyde, chloroform and thiourea could also be envisaged if conditions for the preparation of **9** were compatible with its subsequent condensation process.

Keywords: 2-Imino-4-thiazolidinones; Multicomponent reaction; Thiourea; Trichloromethyl carbinol.
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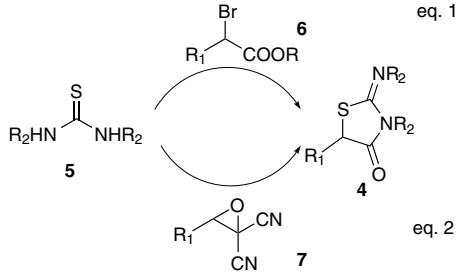
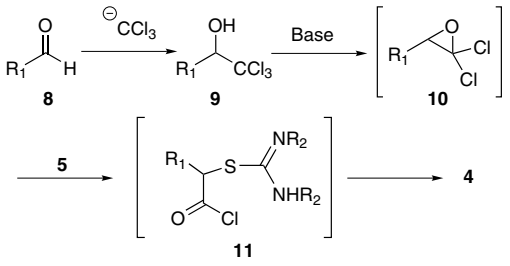
doi:10.1016/j.tetlet.2004.04.055



Scheme 1. Synthesis of 2-imino-4-thiazolidinone (**4**).

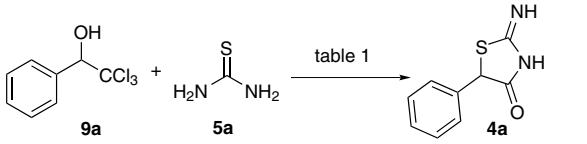


Scheme 2. From aldehyde to 2-imino-4-thiazolidinone.

Trichloromethylcarbinols **9** are useful intermediates for the synthesis of α-substituted carboxylic acid derivatives. The reactions are thought to involve formation of *gem*-dichlorooxirane (**10**) intermediate under basic conditions followed by ring opening by the nucleophiles.[11] More relevantly, the reaction of thiourea with phenyl (trichloromethyl)carbinol **9a** ($R_1 = Ph$) leading to heterocycle **4a** ($R_1 = Ph$, $R_2 = H$) has been studied by Reeve and Nees.[12] However, this potentially powerful transformation was not fully exploited in the intervening years probably due to the low applicability of the original Reeve's conditions.[13] In our hands, the reaction of cyclohexyl (trichloromethyl)carbinol **9b** ($R_1 =$ cyclohexyl) with thiourea **5a** ($R_2 = H$) under Reeve's conditions (MeOH, KOH, 50 °C) provided the expected imino thiazolidinone **4b** ($R_1 =$ cyclohexyl, $R_2 = H$) in only 30% yield. Indeed, several pitfalls exist under these conditions: (a) although thiourea is more nucleophilic, the intermediate **10** can be opened competitively by methanol, which is the solvent;[14] (b) imino thiazolidinones (**4**) can be hydrolyzed to α-mercaptophenylacetates under basic conditions upon heating.[13,14] These considerations prompted us to reinvestigate this transformation and we report herein our preliminary results.

Using **9a** as a model compound, the results of reaction optimization under different conditions varying the solvent, the temperature and the base are summarized in Table 1. As can be seen, the optimum conditions consist of using aqueous dimethoxyethane (DME) as solvent in the presence of sodium hydroxide as base (entry 11). In contrast to the earlier report, using MeOH as well as polar aprotic solvent DMF as solvent dramatically decreased the reaction rate and the conversion (entries 11 vs 12 and 13). Organic bases such as DBU and DABCO were inefficient for promoting the desired transformation, nor were the alkali metal carbonates (Li, K, Na, Cs). Using strong bases like NaH or *t*BuOK in THF led only to complex mixtures. On the other hand, using lithium hydroxide or potassium hydroxide under otherwise identical conditions provided the condensation product in comparable yields (entries 9, and 10 vs 11).

Table 1. Synthesis of **4a** using various conditions[a]



Entry	Base (equiv)	Solvent	Temp	Yield (%)[b]
1	DBU (1)	MeOH	rt	n.d.[c]
2	DBU (1)	MeOH	reflux	20
3	DABCO (4)	DME–H_2O[d]	rt	28
4	NaH (4)	THF	rt	n.d.
5	$NaHCO_3$(4)	DME–H_2O	rt	27
6	Bu^{t}OK	THF	rt	13
7	Li_2CO_3(4)	DME–H_2O	rt	16
8	Cs_2CO_3(4)	DME–H_2O	rt	18
9	LiOH(4)	DME–H_2O	rt	52
10	KOH(4)	DME–H_2O	rt	63
11	**NaOH (4)**	**DME–H_2O**	**rt**	**69**
12	NaOH (4)	DMF–H_2O	rt	<15
13	NaOH (4)	DME–MeOH	rt	<15

[a] Reaction time: 12 h, concentration: 0.1 M.
[b] Isolated yield.
[c] Not detected.
[d] DME/H_2O = 1/4.

By applying the optimized conditions, the 2-imino-4-thiazolidinones with various substituents (**4a**–**n**) were synthesized from the ureas **5a**–**c** and the corresponding trichloromethylcarbinols (Fig. 2).[15] The primary thioureas **5b** and **5c** were prepared according to the procedure of Meckler by reaction of the aniline with potassium thiocyanate,[16] while the trichloromethylcarbinols were synthesized according to Corey (aldehyde, CCl_3COOH, CCl_3COONa in DMF),[17] except for **9e**, which was prepared by indium-mediated nucleophilic addition of allyl bromide onto chloral (Scheme 3).[18] As can be seen from Figure 2, various substituents including aliphatic and aromatic chains with different electronic and steric properties can be introduced to the C-5 position. In accord with previous observations, spectroscopic investigation indicated that the structure of these compounds corresponds to the 2-imino-4-thiazolidinone rather than the 2-amino-4-thiazolinone.[8,12,19]

We next turned our attention to a one-pot procedure that would allow us to develop a facile synthesis of the target heterocycles from readily available aldehydes.[20] The important solvent effects observed for the conversion of **9** to **4** nevertheless limited the choice of the reaction conditions. Thus, when Corey's synthesis of trichloromethylcarbinol (CCl_3COOH, CCl_3COONa, DMF) or Wyvratt's procedure (KOH in DMF)[21] were combined with our condensation conditions (NaOH, DME–H_2O), only low yield of the expected imino-

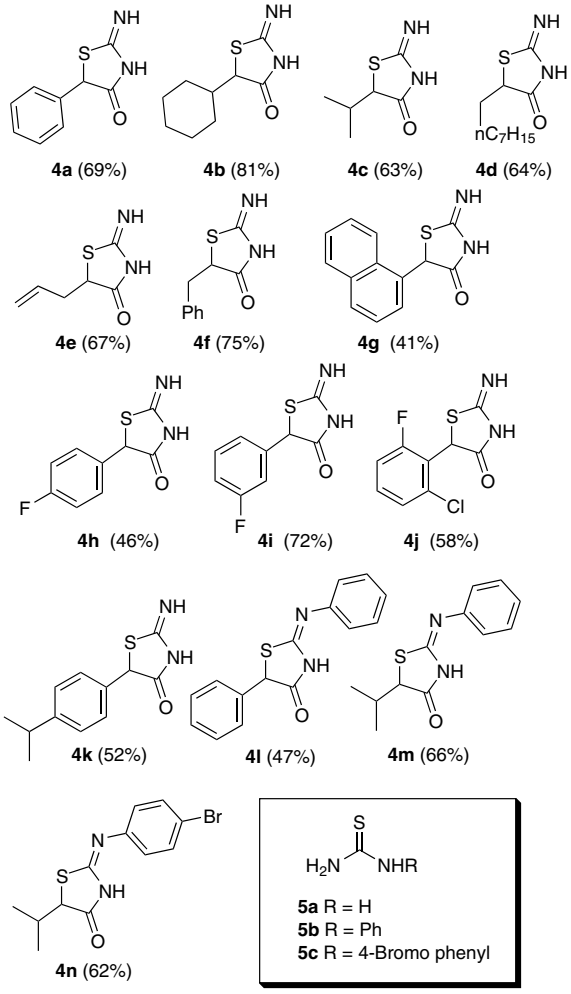
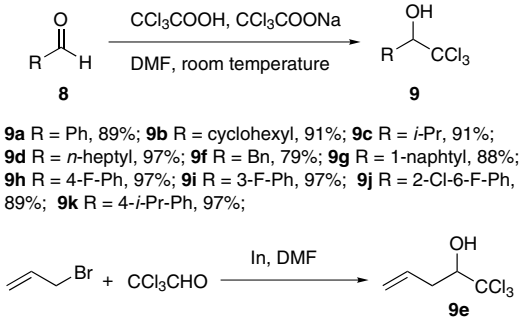
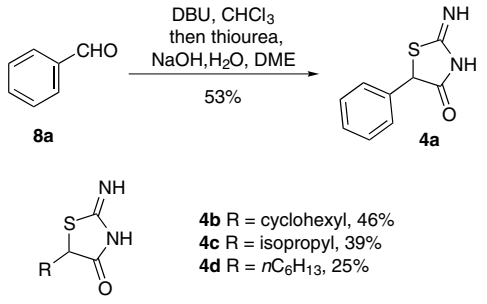


Figure 2. Structure and isolated yield of iminothiazolidinone.



Scheme 3. Synthesis of alkyl (aryl) trichloromethyl carbinol.

thiazolidinone was obtained. Attempts to perform the decarboxylative trichloromethylation of aldehydes in DME also met with failure. Finally, application of the Aggarwal solventless procedure,[22] followed by addition of aqueous solution of thiourea and NaOH provided thiazolidinone **4a** in a 53% yield (Scheme 4). Compounds **4b–d** were similarly prepared. Although yields remained moderate, the procedure is easy to perform and represents the first examples in which 2-imino-4-thiazolidinones were prepared in a one-pot fashion from aldehydes.



Scheme 4. One-pot synthesis of 2-imino-4-thiaoxazolidinone.

In conclusion, we report a convenient and reliable synthesis of 2-imino-4-thiazolidinones starting from thioureas and alkyl (aryl) trichloromethylcarbinols. Furthermore a one-pot three-component synthesis from aldehydes is developed. The chemistry described herein complements the previous routes. Efforts towards improvement of the one-pot three-component procedure and further applications of this reaction to the synthesis of other heterocycles are undergoing.

Acknowledgements

Financial support from CNRS and ICSN is gratefully acknowledged.

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15. Typical experimental procedure: To a vigorously stirred solution of carbinol **9b** (232 mg, 1.0 mmol) and thiourea (152 mg, 2 equiv) in 2 mL of DME is added at 0 °C a solution of 8 mL of 0.5 M aqueous NaOH (4 equiv) over 20 min. The cloudy monophasic solution is well stirred for 12 h at room temperature and the reaction is neutralized with dilute hydrochloric acid. The aqueous layer is extracted with ethyl acetate. The organic layers are combined, washed with water and brine, dried over Na_2SO_4 and evaporated to furnish a slightly coloured solid. Pure thiazolone **4b** was precipitated from EtOAc/heptane as a white solid (160 mg, 81% yield).
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19. In DMSO-d_6, the ^{1}HNMR spectra of **4g** displayed 2N*H* signals around 9.27, 9.01 ppm, respectively, corresponding to the zwitterionic form of the imino thiazolidinone. 2-Imino-5-naphthalen-2-yl-thiazolidin-4-one **4g**: R_f: 0.3 (EtOAc); FTIR (KBr): 3048, 1633, 1505, 1359, 1269, 1235, 1168, 1123, 1082 cm^{-1}; ^{1}H NMR (300 MHz, [$(CD_3)_2SO$)] δ 9.27 (s, 1H), 9.01 (s, 1H), 7.89 (m, 4H), 7.53 (m, 2H), 7.29 (d, 1H, $J = 7.1$ Hz), 5.61 (s, 1H); ^{13}C NMR (62.5 MHz, $(CD_3)_2SO$) δ 187.9, 181.5, 135.0, 132.8, 132.4, 128.6, 127.7, 127.6, 126.6, 126.4, 125.6 (2C), 59.4; HRMS (EI) calcd for $C_{13}H_{10}N_2OSNa$ 265.0412, found 265.0429; mp (EtOAc/heptane) 165 °C.
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