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Improved protocols for the synthesis of Precursors of Thiazol-2-ylidene N-Heterocyclic Carbenes

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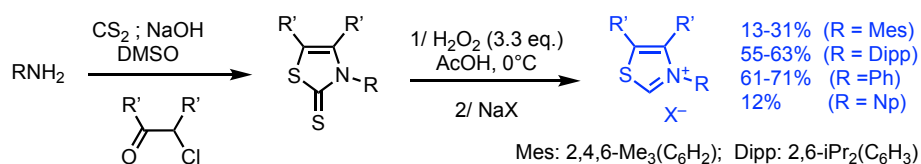
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Abstract We report improved protocols for the synthesis of thiazolium precatalysts from primary amines, carbon disulfide and α -halogenoketones. For N-alkyl substituted derivatives, yields for the corresponding thiazolethiones can be dramatically improved when isolating the intermediate dithiocarbamates. In most cases, meta-chloroperbenzoic acid can replace advantageously H₂O₂ in acetic acid for the oxidation of thiazolethiones into thiazoliums. This approach was applied to the synthesis of a thiazolium featuring a 2-adamantyl N-substituent, the corresponding persistent carbene and its dimer.

Thiazolium salts,¹ including thiamine, an important biological co-factor, are acidic forms of thiazol-2-ylidene N-heterocyclic carbenes (NHC). As such, they are precursors of efficient organic catalysts for a variety of reactions involving the *umpolung* of aldehydes and their derivatives.²⁻⁴ They can be obtained through two main synthetic routes.^{5,6} Small N-alkyl substituents can be introduced by quaternization of thiazoles. However, this requires harsh conditions and strong electrophilic alkylating agents, due to the low nucleophilicity of thiazoles.⁷ Alternatively, bulkier alkyl groups and aryl N-substituents are available through a variant of the Hantzsch synthesis⁸ of thiazoles. It consists in the condensation of α -halogeno ketones with *in situ* formed sodium dithiocarbamates, followed by oxidation of the resulting thiazoline-2-thione (Scheme 1). This is the classical approach for popular precatalysts with N-Aryl substituents, such as 2,6-bis(diisopropyl)phenyl (Dipp) or 2,4,6-trimethylphenyl. Reported overall yields are usually low to moderate.^{9,10}



Scheme 1: Reported overall yields for the two-step synthesis of typical thiazolium precatalysts: one-pot reaction of primary amines, α -halogenoketones and CS₂ to afford N-heterocyclic dithiocarbamates, followed by H₂O₂ oxidation and anion metathesis.

In turn, we faced the limitations of this synthetic route in the course of our study of redox intermediates in NHC-catalysis.¹¹ Among other targets, we were interested in derivatives stemming from a thiazolium featuring a neopentyl N-substituent (Np), which was recently introduced by the group of Ohmiya as a privileged organic precatalyst for the synthesis of dialkylketones from aliphatic aldehydes.^{12,13} This thiazolium was available from neopentylamine following the classical two-steps “Hantzsch” approach, but in only 12% overall yield.^{12a} Although sufficient for catalytic uses, such a low yield presented a challenge for further derivatization of this compound on the gram scale. Herein, we report an improved protocol. It includes the isolation of the intermediate dithiocarbamate salt and a modified oxidation step, which affords this compound in a rewarding overall yield of 56%. Furthermore, other thiazoliums are usually obtained in similar or better yields than previously reported in the literature. Our approach was also applied to the synthesis of a previously undisclosed thiazolium salt featuring a 2-adamantyl N-substituent, the corresponding persistent NHC and its dimer.

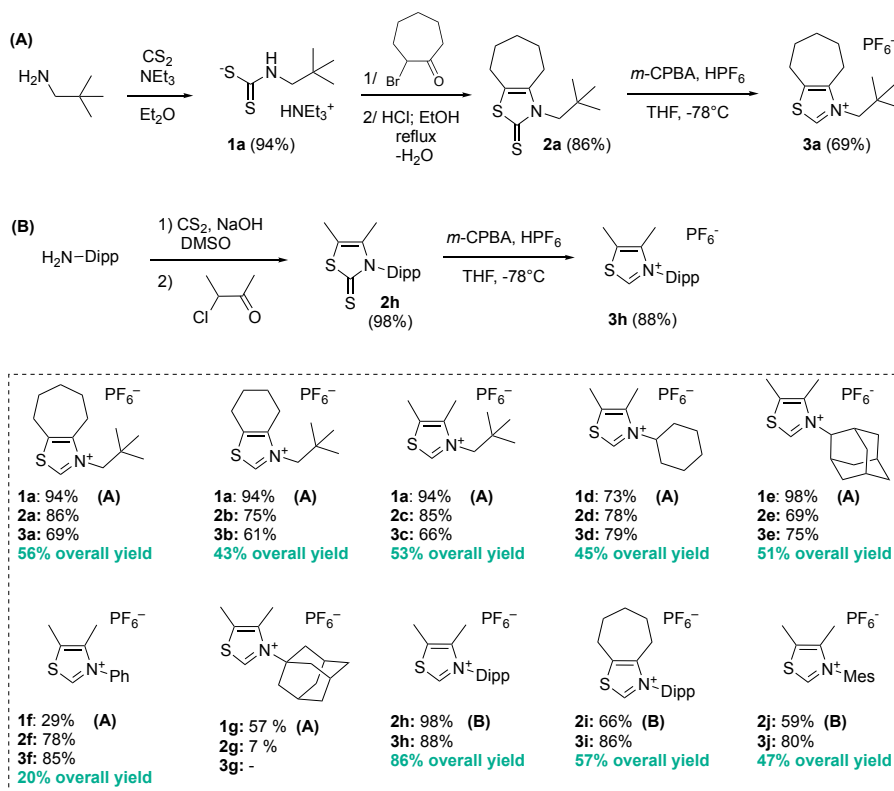
The reported one-pot procedure afforded thiazoline-2-thione **2a** in 20% yield from neopentylamine, CS₂ and 2-bromocycloheptanone^{9d} in presence of sodium hydroxide, via the transient formation of dithiocarbamate **1a**.

Oxidation of **2a** with H₂O₂ in acetic acid, followed by anion metathesis, yielded thiazolium **3a** in 61% yield. Thus, we tried to improve both steps, hoping of increasing the low 12% overall yield (Scheme 2).

First, we considered that the known instability of the *in-situ* formed dithiocarbamate salts **1a** in basic media¹⁴ could be the reason for the low yield of the one-pot synthesis of **2a**. Therefore, we prepared the triethylammonium salt of **1a**, which was isolated from the reaction of neopentylamine with CS₂ in the presence of Et₃N in diethyl ether in a nearly quantitative yield (Scheme 2).¹⁵ Treatment of this salt with 2-bromocycloheptanone in the presence of hydrochloric acid yielded the thiazoline-2-thione **2a** in 86% yield.

Second, we looked for an alternative to H₂O₂ in acetic acid for the oxidation of **2a** and considered to adapt a reported procedure for the oxidation of imidazole-based thiones with metachloroperbenzoic acid (*m*-CPBA).^{9a,16}

Whereas very poor yields were obtained in presence of perchloric or tetrafluoroboric acids, addition of *m*-CPBA to a solution of **2a** and hexafluorophosphoric acid in THF at -78°C led efficiently to the formation of the hexafluorophosphate salt of thiazolium **3a**, which was isolated in 69% yield. Although this procedure only allowed for a slight improvement of the yield in this case, it was found more convenient and safer, as it avoids the need to evaporate large amounts of acetic acid and the remaining slight excess of peracid could be easily monitored and quenched with sodium sulfite prior further work-up (see Supplementary Information). This three-step synthesis of **3a**•PF₆⁻ could be scaled up to 5 g with an overall yield of 56%.¹⁷

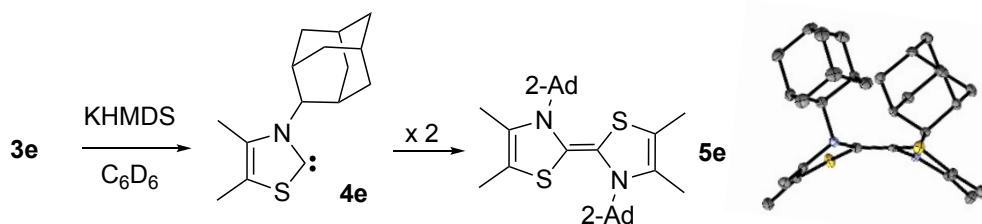


Scheme 2: Improved protocols for the synthesis of typical thiazolium precatalysts with *N*-alkyl (A) and bulky *N*-aryl substituents (B).

These procedures worked as well for the synthesis of thiazoliums **3b-c** from other typical α -halogeno ketones, and thiazoliums **3d-e** featuring secondary alkyl *N*-substituents, which cannot be accessed through quaternization of the corresponding thiazole. Of note, the condensation of dithiocarbamate **1e** with 1-chlorobutan-2-one to afford **2e** (with a 2-adamantyl *N*-substituent) required refluxing the compound in the presence of *para*-toluenesulfonic acid in toluene and azeotropic distillation of water with a Dean Stark apparatus. Unfortunately, even the latter procedure failed to afford thiazoline-2-thione **2g** with a bulkier 1-adamantyl *N*-alkyl group in a decent yield. In addition, thiazolium **3f** (with a *N*-phenyl substituent) was obtained only in 20% overall yield. Similarly, we failed to properly isolate dithiocarbamates **1h-j**, stemming from bulkier anilines with Dipp and Mes groups, which are ubiquitous substituents in thiazolium-based organocatalysis. Thus, thiazoline-2-thiones **2h-j** were synthesized in good yields from the classical reported one-pot procedure.^{9d} However, in these cases,

subsequent oxidation with *m*-CPBA proceeded in far better yields than the previously reported H₂O₂/AcOH approach and thiazoliums **3h-j** were isolated in good to excellent yields.

Most thiazol-2-ylidenes NHCs readily dimerize. In 1997, Arduengo reported the first observation of the carbene, which was generated by deprotonation of the Dipp *N*-substituted thiazolium **3h**.^{2a,18} This persistent NHC could be isolated and even crystallized, but it ultimately dimerized in solution within two days. The dimerization of the NHC with slightly smaller Mes group was considerably faster and its observation was only possible at 0 °C. Thus, the synthesis of thiazolium **3e** with a bulky 2-adamantyl *N*-substituent provided us with a rare opportunity to study a novel persistent thiazol-2-ylidene. We reacted a suspension of **3e** in C₆D₆ with an equivalent of potassium hexamethyldisilazide (Scheme 3). The NMR spectra were consistent with the formation of the corresponding NHC **4e**. In particular, ¹³C NMR revealed a very high field singlet at 246.2 ppm, which is expected for a carbenic carbon of thiazol-2-ylidenes. Carbene **4e** decayed within few hours. Its dimer **5e** was isolated and suitable single crystals were obtained from a saturated solution of toluene at -20 °C. Electron-rich olefins stemming from the dimerization of thiazolylidenes often feature a variety of geometrical distortions around the C=C double bond.^{2a,11b,19} Dimer **5e** provided another example of unusual topology. Indeed, X-ray diffraction study revealed the non-planar structure of the *E*-isomer with *syn* out-of-plane bending and pronounced pyramidalization at the nitrogen atoms. An electrochemical study showed that **5e** is a rather weak reductant, which undergoes a reversible two-electrons oxidation at E = -0.3 V vs SCE (see Supporting Information). This was interpreted as the result of the easy hybridization of nitrogens in **5e** and the ensuing destabilisation of radical **5e^{••}**. In marked contrast the dimer **5h** stemming from **3h**, features *N*-Dipp substituents, which force the nitrogen atoms into a planar geometry and result in a remarkably stable radical **5h^{••}**.^{11b}



Scheme 3: Generation of persistent NHC **4e**, formation and representation of the X-ray structure of its dimer **5e**

In conclusion, the isolation of the intermediate dithiocarbamates can dramatically improve the yield of the synthesis of thiazolethiones from carbon disulfide and α -halogenoketones in the case of alkyl primary amines.

However, tertiary alkyl groups remain out of reach of this methodology and aryl groups are better introduced using the former one-pot procedure. Furthermore, in the final oxidative step, *meta*-chloroperbenzoic acid performs better than H₂O₂ in acetic acid, including with bulky aryl *N*-groups. Overall, these updated protocols improve the previously reported approaches, as they allow for the synthesis of key organic pre-catalysts in good to excellent yields on multigram scales.

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Conflict of Interest

The authors declare no conflict of interest.

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17. To a solution of neopentylamine (3.5 mL, 30 mmol) and triethylamine (4.5 mL, 32 mmol) in 50 mL of Et₂O, carbon disulfide (9 mL, 150 mmol) was added at 0 °C. The reaction mixture was stirred 2 h at room temperature. The white precipitate **1a** was filtered off, washed with Et₂O, dried under vacuum and used without further purification (7.09 g, 28 mmol, yield: 94%). ¹H NMR (DMSO-*d*₆): δ 9.51 (br s, 1H), 7.88 (t, *J* =

6.0 Hz, 1H), 3.32 (d, $J = 6.1$ Hz, 2H), 3.12 (q, $J = 7.3$ Hz, 6H), 1.20 (t, $J = 7.3$ Hz, 9H), 0.86 (s, 9H) ppm. $^{13}\text{C NMR}$ ($\text{DMSO-}d_6$): δ 214.7, 57.8, 45.5, 32.0, 27.6, 8.6 ppm.

The dithiocarbamate salt **1a** (28 mmol) was dissolved in 50 mL of MeCN and the α -halogenated ketone MeCOCHClMe (2.8 mL, 28 mmol) was added dropwise and stirred at room temperature overnight. The solvent was removed under vacuum, EtOH (28 mL) and conc. HCl (1.4 mL) was added and heated to reflux for 1 h. The solvent was removed under vacuum, the resulting oil was dissolved in water (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with NaHCO_3 (20 mL), water (3 x 20 mL) and brine (20 mL), dried over MgSO_4 and evaporated to afford **2a** as a yellow powder (6.08 g, 23.8 mmol, yield: 86%). $^1\text{H NMR}$ (CDCl_3): δ = 4.98 (br s, 1H), 3.42 (br s, 1H), 2.69 (br s, 2H), 2.56-2.53 (m, 2H), 1.83-1.82 (m, 2H), 1.68-1.64 (m, 4H), 1.03 (s, 9H) ppm. $^{13}\text{C NMR}$ (CDCl_3): δ = 187.2, 142.8, 124.0, 56.3, 35.6, 31.8, 30.5, 29.4, 27.6, 26.8, 26.4 ppm.

To a solution of thiazolin-2-thione **2a** (20 mmol) in THF was added hexafluorophosphoric acid, 60 wt. % in H_2O (8.8 mL, 60 mmol) and then cooled to -78°C . 3-Chloroperbenzoic acid, 70-75 wt. % in H_2O (14.8 g, 60 mmol) was added portion wise. The resulting was stirred for 2 h at room temperature. Water (60 mL) and conc. aq. Na_2SO_3 (40 mL) were added. Dichloromethane (40 mL) was added and then the organic phase was washed with H_2O (2x50 mL). The organic phase was transferred in an Erlenmeyer flask and a solution of conc. aq. NaHCO_3 (60 mL) was added under vigorous stirring until pH = 7-8. The organic phase was extracted and washed with brine (30 mL), dried over MgSO_4 and evaporated. The residue was washed with Et_2O and filtered off to afford **3a** as a white powder (5.12 g, 14 mmol, yield: 69%). $^1\text{H NMR}$ (CDCl_3): δ = 9.21 (s, 1H), 4.27 (s, 2H), 3.00-2.96 (m, 4H), 1.94-1.91 (m, 2H), 1.80-1.73 (m, 4H), 0.99 (s, 9H) ppm. $^{13}\text{C NMR}$ (CDCl_3): δ = 153.2, 149.2, 139.5, 63.7, 33.7, 31.0, 28.1, 27.8, 27.2, 26.4, 25.1 ppm. $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3): δ = -72.1 (d, $J = 713$ Hz) ppm. **m. p.**: 108°C . **HRMS (ESI)**: m/z calcd for $\text{C}_{13}\text{H}_{22}\text{NS}$: 224.1468 [M-PF_6] $^+$; found: 224.1463.

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