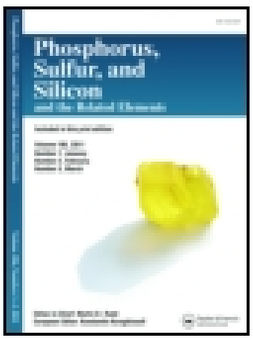

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CYANURIC CHLORIDE-CATALYZED THIOACETALIZATION FOR ORGANOCATALYTIC SYNTHESIS OF THIOACETALS

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Abstract The thioacetalization of aromatic aldehydes has been realized with broad diversity in the presence of various thiols and thiophenols using cyanuric chloride as an organocatalyst.

Key words: Thioacetalization, organocatalysis, cyanuric chloride

INTRODUCTION

Thioacetalization is a fundamental transformation in organic synthesis. It is one of the most useful strategies for the protection of carbonyl groups in linear synthesis owing to the stability of thioacetals and thioketals in both conventional acidic and basic atmosphere as well as their easy deprotection.[1] More notably, thioacetals are important precursors of carbon anions which have exhibited tremendous utilities in the construction of C-H and C-heteroatom bonds.[2-4] Therefore, catalytic methods towards efficient thioacetalization have been an issue of everlasting interest in organic synthesis. During the past decade, a variety of different catalytic conditions and/or agents have been developed for practical thioacetalization transformation. The typical examples such as hafnium triflate,[5] HCl,[6] $BF_3 \cdot Et_2O$,[7] $AlCl_3$,[8] $InCl_3$,[9] acidic ionic liquid,[10] trichloroisocyanuric acid,[11] silica supported sulfonic acid,[12] 1,3-dibromo-5,5-dimethylhydantoin (DBH),[13] SBA-15 functionalized sulfonic acid,[14] sulfonated polyanthracene,[15] graphene oxide[16] and glycerol,[17] to name but a few, have contributed significantly to the preparation of thioacetals. On the other hand, despite the benefits provided by these known protocols, one or more of the limits such as the dependence on metal catalyst, harsh reaction conditions or unsatisfactory substrate tolerance have been suffered. In this context, developing alternative catalytic approaches of improved sustainability with facile operation is still an issue of significance in the chemistry of thioacetals.

Cyanuric chloride, also named 2,4,6-trichloro-1,3,5-triazine (TCT), is a useful organocatalyst showing ability in catalyzing or promoting a vast array of important organic reactions.[18-22] Some

particular reactions involving the condensation of aldehydes such as acetalization,[23] transacetalization[24] and the deprotection of thioacetals have been also realized with TCT catalysis.[25] However, to the best of our knowledge, no report on TCT-catalyzed thioacetalization has been described. Herein, we present a mild, economical and highly efficient method of thioacetalization which tolerates the transformation of both thiols and thiophenols by using TCT as the catalyst.

RESULTS AND DISCUSSION

Originally, the model transformation on forming thioacetal **3a** via the condensation of benzaldehyde **1a** with ethanethiol **2a** was run in the presence of TCT. The tentative examination using 50 mol% TCT and heating at 80^{o}C under solvent free-condition gave a good yield of the target product (entry 1, Table 1). Subsequently, experiments on varying the loading of TCT indicated that 30 mol% TCT was the optimal loading (entries 2-3, Table 1). When the model reaction was run at different temperatures, in room temperature provided an equally good yield as elevated temperatures. Lower temperature showed a negative impact on the result (entries 4-6, Table 1). Finally, a further improved yield of product was obtained when dichloromethane was used as the reaction medium (entry 7, Table 1). In addition, a blank experiment performed at room temperature without using the catalyst gave a low yield of **3a** (entry 8, Table 1).

With the optimized reaction conditions, we then examined the application scope of this mild thioacetalization protocol. A class of different aromatic aldehydes and thiols/thiophenols were

employed, respectively. As shown in Table 2, aldehydes containing various functional groups such as alkyl, halogen, nitro and cyano etc. were successfully converted to the corresponding thioacetals in the presence of either linear or branched alkyl thiols as reaction partners (**3a**-**3l**, Table 2). More notably, benzylthiol and thiophenols also took part in the thioacetalization transformation to give the corresponding product with good yield (**3m** and **3n**-**3p**, Table 2). Generally good to excellent yields of products were provided, and no evident impact of the reactant structure on the results was observed. Notably, the cyclic thioacetal **3q** was obtained with almost quantitative yield when ethane-1,2-dithiol was used (entry 17, Table 2). The results from this section clearly demonstrate a general applicability of this organocatalytic method for the preparation of thioacetals.

On the basis of the results on thioacetal synthesis in the presence of TCT, we propose a tentative reaction mechanism shown in Scheme 1. The electrophilic C–Cl bond of TCT could initially activate the formyl group by forming transition state **I**, which facilitates the subsequent nucleophilic attack of the thiol to give intermediate **4** and releasing HCl as an acid co-catalyst for the thioacetalization process. The nucleophilic substitution of another molecule of thiol to **4** then produces the thioacetal **3**, and 1,3,5-triazine-2,4,6-triol **5** is formed simultaneously as side product. Based on this mechanism, TCT is not only the source of HCl, but more importantly the scavenger of water formed during the thioacetalization. This assumption can also explain the excellent effect of TCT in promoting this thioacetalization process.

CONCLUSIONS

In conclusion, we have developed a facile new organocatalytic method for the thioacetalization transformation using TCT as organocatalyst. The present protocol consists of mild reaction conditions and economical reagents. Together with the satisfactory substrate tolerance, this method will reasonably be a useful complementary route of thioacetalization to known methods.

EXPERIMENTAL

General

All chemicals and reagents used in the experiments were obtained from commercial sources and used directly without further treatment. The NMR spectra were recorded in $CDCl_3$ solution at 600 MHz (^1H) and 150 MHz (^{13}C), respectively. Chemical shifts δ are reported in ppm (TMS as internal standard). The HRMS data for new compounds were obtained under ESI model.

General procedure for the TCT-catalyzed synthesis of thioacetals

The aldehyde (1.0 mmol), the thiol (2.0 mmol) and TCT (0.3 mmol) in CH_2Cl_2 (2 mL) were filled into a 25 mL round bottomed. The mixture was stirred at room temperature for 12 h (open air, TLC). Upon completion, water (5 mL) was added and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4. After filtration and removing the solvent under reduced pressure, and the resulting residue was subjected to silica gel column chromatography to provide the pure product by using mixed

petroleum ether and ethyl acetate (V_{PET} : V_{EA} = 200:1). The Supplemental Materials contains sample ^{1}H and ^{13}C spectra of the products 3a-3h (Figures S 1 – S 16)

(Phenylmethylene)bis(ethylsulfane) (**3a**).[5] Pale yellow liquid; ^{1}H NMR: δ 1.27 (t, 6 H, *J* = 6.0 Hz), 2.49-2.83 (m, 4 H), 4.97 (s, 1 H), 7.25 (t, 1 H, *J* = 6.0 Hz), 7.32 (t, 2 H, *J* = 6.0 Hz), 7.43 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.9, 28.9, 55.1, 130.3, 130.4, 131.1, 143.1.

[(4-Bromophenyl)methylene]bis(ethylsulfane) (**3b**).[5] Pale yellow liquid; ^{1}H NMR: δ 1.21 (t, 6 H, *J* = 6.0 Hz), 2.48-2.60 (m, 4 H), 4.86 (s, 1 H), 7.32 (d, 2 H, *J* = 6.0 Hz), 7.44 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.9, 28.9, 54.4, 124.2, 132.1, 134.3, 142.2.

[(4-Bromophenyl)methylene]bis(octylsulfane) (**3c**). Pale yellow liquid; ^{1}H NMR: δ 0.87 (t, 6 H, *J* = 6.0 Hz), 1.24-1.32 (m, 20 H), 1.51-1.53 (m, 4 H), 2.45-2.57 (m, 4 H), 4.81 (s, 1 H), 7.32 (d, 2 H, *J* = 6.0 Hz), 7.44 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.2,16.9, 23.8, 25.2, 28.9, 36.9, 54.8, 55.2, 55.5, 130.2, 131.8, 140.1, 140.2; ESI-HRMS Calcd. for $C_{23}H_{40}BrS_2$ $[M+H]^+$ 459.1749; found 459.1746.

(*p*-Tolylmethylene)bis(octylsulfane) (**3d**). Pale yellow liquid; ^{1}H NMR: δ 0.88 (t, 6 H, *J* = 6.0 Hz), 1.25-1.33 (m, 20 H), 1.53-1.54 (m, 4 H), 2.33 (s, 1 H), 2.47-2.59 (m, 4 H), 4.85 (s, 1 H), 7.13 (d, 2 H, *J* = 6.0 Hz), 7.32 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.7, 23.7, 25.3, 31.5, 31.8, 34.4, 35.0, 55.6, 130.2, 131.8, 140.0, 140.3; ESI-HRMS Calcd. for $C_{24}H_{43}S_2$ $[M+H]^+$ 395.2801; found 395.2801.

[(4-Bromophenyl)methylene]bis(*sec*-butylsulfane) (**3e**). Pale yellow liquid; ^{1}H NMR: δ

0.89-0.95 (m, 6 H), 1.21-1.22 (m, 6 H), 1.46-1.50 (m, 2 H), 1.55-1.58 (m, 2 H), 2.64-2.81 (m, 2 H), 4.87 (s, 1 H), 7.35 (d, 2 H, *J* = 6.0 Hz), 7.44 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 13.8, 23.3, 32.2, 45.0, 52.7, 123.9, 132.1, 134.1, 143.0; ESI-HRMS Calcd. for $C_{15}H_{24}BrS_2$ $[M+H]^+$ 347.0497; found 347.0512.

(p-Tolylmethylene)bis(propylsulfane) (**3f**). Pale yellow liquid; ^{1}H NMR: δ 0.93-0.96 (m, 6 H), 1.54-1.59 (m, 4 H), 2.33 (s, 1 H), 2.45-2.57 (m, 2 H), 4.83 (s, 1 H), 7.12 (d, 2 H, *J* = 6.0 Hz), 7.32 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.2, 23.8, 25.2, 37.0, 55.5, 130.2, 131.8, 140.1, 140.3.0; ESI-HRMS Calcd. for $C_{14}H_{23}S_2$ $[M+H]^+$ 255.1236; found 255.1244.

[(2-Chlorophenyl)methylene]bis(ethylsulfane) (**3g**). Pale yellow liquid; ^{1}H NMR: δ 1.24 (t, 6 H, *J* = 6.0 Hz), 2.52-2.66 (m, 4 H), 5.49 (s, 1 H), 7.16-7.18 (m, 1 H), 7.26-7.28 (m, 1 H), 7.32-7.34 (m, 1 H), 7.74-7.75 (m, 1 H); ^{13}C NMR: δ 17.1, 29.1, 50.6, 129.9, 131.4, 132.0,132.3, 135.2, 140.9.0; ESI-HRMS Calcd. for $C_{11}H_{16}ClS_2$ $[M+H]^+$ 247.0376; found 247.0371.

[(2-bromophenyl)methylene]bis(ethylsulfane) (**3h**).[5] Pale yellow liquid; ^{1}H NMR: δ 1.25 (t, 6 H, *J* = 6.0 Hz), 2.51-2.66 (m, 4 H), 5.46 (s, 1 H), 7.09-7.12 (m, 1 H), 7.31-7.33 (m, 1 H), 7.51-7.52 (m, 1 H), 7.751-7.76 (m, 1 H) ; ^{13}C NMR: δ 17.1, 29.1, 53.4, 126.0, 130.6, 131.7,132.5, 135.3, 142.5.

4-[Bis(ethylthio)methyl]-*N,N*-dimethylbenzenamine (**3i**).[5] Pale yellow liquid; ^{1}H NMR: δ 1.21 (t, 6 H, *J* = 6.0 Hz), 2.49-2.60 (m, 4 H), 2.94 (s, 6 H),4.90 (s, 1 H), 6.68 (d, 2 H, *J* = 6.0 Hz), 7.32 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 17.0, 28.9, 43.2, 54.7, 114.9, 131.2, 152.7.

[(4-Nitrophenyl)methylene]bis(ethylsulfane) (**3j**).[5] Pale yellow liquid; ^{1}H NMR: δ 1.23 (t, 6 H, *J* = 6.0 Hz), 2.55-2.67 (m, 4 H), 5.76 (s, 1 H), 7.39 (t, 1 H, *J* = 6.0 Hz), 7.60 (t, 1 H, *J* = 6.0 Hz), 7.82 (d, 1 H, *J* = 6.0 Hz), 7.98 (d, 1 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.9, 29.5, 48.8, 126.9, 131.0,133.2, 135.8, 138.6,150.5.

4-[Bis(ethylthio)methyl]benzonitrile (**3k**).[5] Pale yellow liquid; ^{1}H NMR: δ 1.21 (t, 6 H, *J* = 6.0 Hz), 2.47-2.62 (m, 4 H), 4.90 (s, 1 H), 7.55 (d, 2 H, *J* = 6.0 Hz), 7.61 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.9, 29.0, 54.7, 114.2, 131.1, 131.2, 135.0, 148.8.

[(4-Chlorophenyl)methylene]bis(ethylsulfane) (**3l**).[5] Colorless liquid; ^{1}H NMR: δ 1.21 (t, 6 H, *J* = 6.0 Hz), 2.47-2.61 (m, 4 H), 4.88 (s, 1 H), 7.28 (d, 2 H, *J* = 6.0 Hz), 7.38 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 16.9, 28.9, 54.4, 131.3, 131.7, 136.0, 141.8; ESI-HRMS Calcd. for $C_{11}H_{16}ClS_2$ $[M+H]^+$ 247.0382; found 247.0329.

(Phenylmethylene)bis(benzylsulfane) (**3m**).[26] Pale yellow liquid; ^{1}H NMR: δ 3.60 (d, 2 H, *J* = 12.0 Hz), 3.82 (d, 2 H, *J* = 12.0 Hz), 4.53 (s, 1 H), 7.20 (d, 4 H, *J* = 6.0 Hz), 7.28-7.30 (m, 7 H), 7.34-7.39 (m, 4 H); ^{13}C NMR: δ 39.1, 53.7, 129.7, 130.7, 131.2, 131.3, 140.4, 142.3.

(Phenylmethylene)bis[(4-isopropylphenyl)sulfane] (**3n**). Colorless liquid; ^{1}H NMR: δ 1.24 (d, 12 H, *J* = 12.0 Hz), 2.86-2.90 (m, 2 H), 5.37 (s, 1 H), 7.12 (d, 4 H, *J* = 12.0 Hz), 7.27-7.30 (m, 7 H), 7.38 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR: δ 26.6, 36.5, 63.9, 129.6, 129.7, 130.5, 130.6, 131.1, 134.1, 135.5, 142.8, 151.4; ESI-HRMS Calcd. for $C_{25}H_{29}S_2$ $[M+H]^+$ 393.1705; found 393.1730.

(Phenylmethylene)bis(phenylsulfane) (**3o**).[5] Colorless liquid; ^{1}H NMR: δ 7.37-7.35 (m, 6 H),

7.28-7.24 (m, 9 H), 5.44 (s, 1 H); ^{13}C NMR: δ 139.8, 134.6, 132.6, 128.9, 128.6, 128.1, 128.0, 127.9.

(Phenylmethylene)bis[(4-fluorophenyl)sulfane] (**3p**).[27] Colorless liquid; ^{1}H NMR: δ 7.32-7.30 (m, 4 H), 7.25-7.22 (m, 5 H), 6.95-6.92 (m, 4 H), 5.23 (s, 1 H); ^{13}C NMR: δ 166.2, 164.5, 141.9, 138.3, 131.7, 131.1, 130.8, 130.3, 118.7, 118.5, 64.6.

2-Phenyl-1,3-dithiolane (**3q**).[5] Colorless liquid; ^{1}H NMR: δ 7.52 (d, 2 H, *J* = 6.0 Hz), 7.31 (t, 2 H, *J* = 6.0 Hz), 7.25 (d, 1 H, *J* = 6.0 Hz), 5.64 (s, 1 H), 3.52-3.47 (m, 2 H), 3.38-3.32 (m, 2 H); ^{13}C NMR: δ 142.9, 134.1, 130.7, 130.6, 58.9, 42.8.

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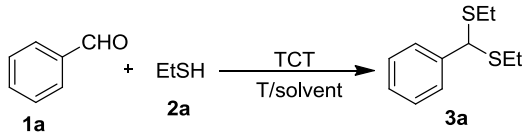
Table 1 Condition optimization on TCT-catalyzed thioacetalization[a]

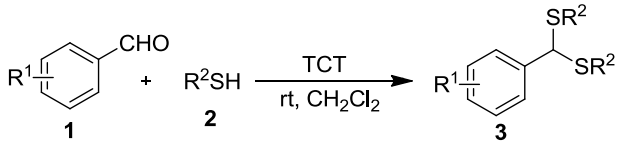


Entry	TCT loading (%)	T (^{o}C)	Yield (%)[b]
1	50	80	83
2	30	80	84
3	10	80	64
4	30	60	82
5	30	rt	84
6	30	10	55
7[c]	30	rt	88
8	0	rt	37

[a]General conditions: benzaldehyde **1a** (1.0 mmol) and EtSH (2 mmol) with TCT, stirred for 12 h.

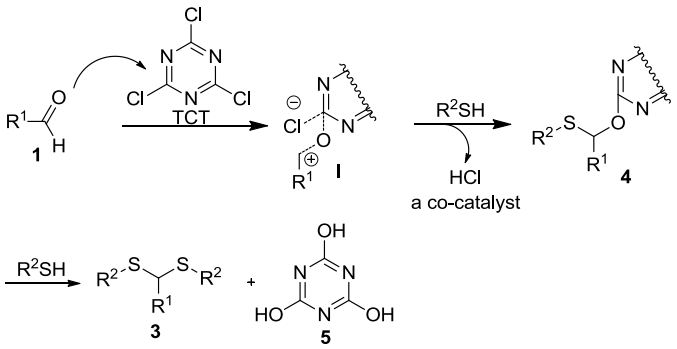
[b]Yield of isolated product. [c]2 mL CH_2Cl_2 was used.

Table 2 Scope of TCT-catalyzed thioacetalization[a]

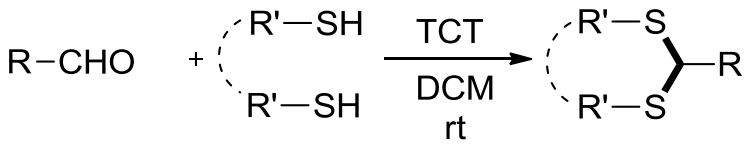


Entry	R^1	R^2	Product	Yield (%)[b]
1	H	Et	**3a**	88
2	4-Br	Et	**3b**	84
3	4-Br	*n*-Oct	**3c**	76
4	4-Me	*n*-Oct	**3d**	81
5	4-Br	*sec*-Bu	**3e**	76
6	4-Me	*n*-Pr	**3f**	86
7	2-Cl	Et	**3g**	88
8	2-Br	Et	**3h**	84
9	4-NMe_2	Et	**3i**	81
10	4-NO_2	Et	**3j**	73
11	4-CN	Et	**3k**	71
12	4-Cl	Et	**3l**	76
13	H	$PhCH_2$	**3m**	74
14	H	4-*i*-PrC_6H_4	**3n**	79
15	H	Ph	**3o**	91
16	H	4-FC_6H_4	**3p**	93
17	H	CH_2CH_2SH	**3q**	99

[a] General conditions: Aldehyde **1** (1.0 mmol), TCT (0.3 mmol) and thiol **2** (2.0 mmol) in CH_2Cl_2 (2 mL), stirred at room temperature for 12 h. [b]Yield of isolated product.



Scheme 1 The proposed reaction mechanism



mild organocatalysis, R' = Aryl, alkyl