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$Sc(OTf)_3$-Catalyzed Synthesis of Symmetrical Dithioacetals and Bisarylmethanes Using Nitromethane as a Methylene Source

Dattatraya H. Dethe,* Manmohan Shukla,† and Balu D. Dherange†

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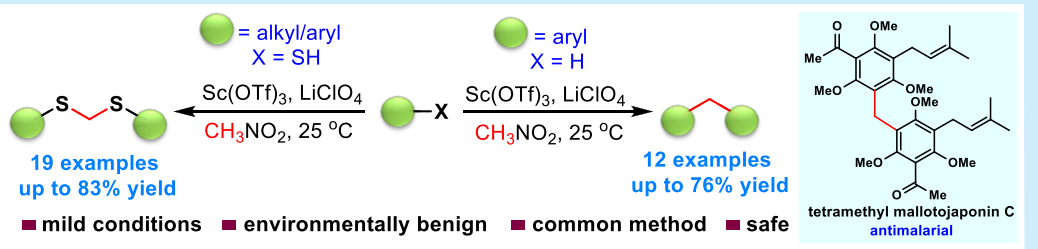

ABSTRACT: Use of nitromethane as an electrophilic methylene source for the synthesis of symmetrical dithioacetals and bisarylmethanes has been showcased using $Sc(OTf)_3$ as a catalyst. The procedure allows straightforward access to the densely functionalized dithioacetals and bisarylmethanes under mild conditions. Additionally, the method has been applied for the synthesis of antimalarial tetramethyl mellotojaponin C and anticancer dimeric phloroglucinol derivative.

Nitromethane is the simplest nitro compound, often used as a solvent, reagent, stabilizer, and fuel in motor sports and rockets.[1] In organic synthesis, owing to its strongly electron-withdrawing nature, nitromethane has served as pronucleophile to access a wide range of useful compounds such as nitroalkenes, β-nitroalcohols (Henry reaction), amines, and carbonyl compounds (Michael addition) (Scheme 1, B).[2] The reactivity of nitromethane as a nitrogen donor was recently explored by Jiao and co-workers in their Schmidt-type synthesis of amides and nitriles (Scheme 1, B).[3] In organic synthesis, nitromethane is employed as one carbon building block using a multistep reaction sequence.[4] In a classical Nef reaction, nitromethane on treatment with base forms nitronate salts, which on subsequent treatment with aqueous acid generate the corresponding ketone (Scheme 1, C).[5] We hypothesized that, analogous to the Nef process, nitromethane can be used as an electrophilic methylene source. The *aci* form of niromethane **I** on treatment with Lewis acid under mild conditions would act as source of electrophilic carbon **II**, which on nucleophilic attack of electron-rich substrates such as thiol or arenes would lead to the intermediate **III**. A second nucleophilic attack of thiol/arene on **III** along with the loss of HNO species and water could result in the formation of dithioacetal or bisarylmethanes (Scheme 1, C).

In the literature, numerous synthetic methods to access dithioacetals have been documented and can be categorized in two groups. The first one is homologation of disulfides using diazomethane,[6] sulfur ylide,[7] zinc carbenoid,[8] bromomethyllithium,[9] and acetone[10] as a methylene source (Scheme 1, A). The second method is condensation of aldehydes or halides with thiols.[11] Most recently, Xi and co-workers reported synthesis of dithioacetals by insertion of methylene into disulfide using reduction of CO_2 into methylene under the $NaBH_4/I_2$ system (Scheme 1, A).[12] Bisarylmethanes are another class of compounds, structurally related to dithioacetals. Bisarylmethane-based/derived architectures are commonly found in supramolecules such as calixarenes,[13] pillararene,[14] and many other synthetic receptors.[15] The importance of bisarylmethanes in pharmaceuticals and natural products has been well documented; for example, trimethophrim is used as antibacterial,[16] elvitegravir is used for HIV treatment,[17] PF-06827443 is used as an antitumor agent,[18] and papaverine isolated from *Papaver somniferum* is used for the treatment of visceral spasm and vasospasm.[19] In 2005, Yonezawa and co-workers reported Lewis acid catalyzed synthesis of symmetrical bisarylmethanes using α-methoxy acetic acid as a methylene source (Scheme 1, A).[20] In the subsequent year, Yin and co-workers utilized $InCl_3 \cdot 4H_2O$ to prepare bisarylmethanes using trioxane as a methylene source.[21a] In 2012, Endo et al. disclosed one-pot palladium-catalyzed Suzuki−Miyaura approach using diborylmethanes as a methylene source to prepare bisarylmethanes.[21b] Recently, Yan et al. reported $CuCl_2$ catalyzed synthesis of methylene-bridged bisindoles using *N*,*N*-dimethylaminoethanol as a

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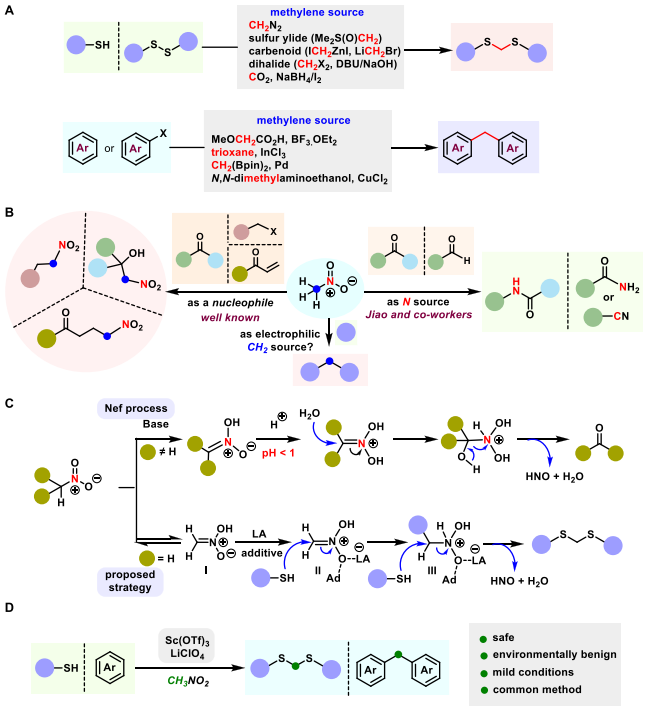
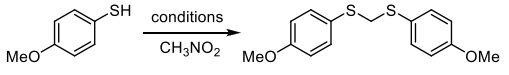
Scheme 1. (A) Various Approaches for the Synthesis of Dithioacetals and Bisarylmethanes. (B) Reactivity Patterns of Nitromethane. (C) Nef Process vs Proposed Strategy. (D) This Work



methylene source (Scheme 1, A).[22] In addition, numerous methods are reported for synthesis of unsymmetrical bisarylmethanes.[23] Herein, we report the $Sc(OTf)_3$-catalyzed efficient method for the synthesis of symmetrical dithioacetals and bisarylmethanes using abundant, inexpensive, and environmentally benign nitromethane as the methylene source.

To evaluate the feasibility of the hypothesis, we began our investigation with 4-methoxythiophenol (**1a**) as a test substrate. The effect of various Lewis acids, additives, and temperature were investigated, and the results are summarized in Table 1. When 4-methoxythiophenol was treated with $Cu(OTf)_2$, *p*-TsOH, or $Sc(OTf)_3$ at 25 °C or elevated temperatures (25 → 100 °C), it did not generate the desired dithioacetal **2a** (Table 1, entry 1−3). It was thought that use of only Lewis acid would not be enough to activate nitromethane and there is a need for some additive. $LiClO_4$ is well-known to accelerate the rate of Diels−Alder reaction by coordinating with dienophile.[24] Kobayashi and co-workers demonstrated that in Friedel−Crafts acylation, reactivity and turnover of metal triflates were dramatically increased when combined with $LiClO_4$.[25] Hence, it was decided to examine the effect of addition of perchlorates along with Lewis acid. To our delight, 4-methoxythiophenol on treatment with 20 mol % of $Cu(OTf)_2$ and 1 equiv of $LiClO_4$ yielded dithioacetal **2a** in 41% yield (entry 4). When the same reaction was performed in the absence of $Cu(OTf)_2$, no product formation was observed (entry 5), indicating that both Lewis acid and $LiClO_4$ are necessary in order to make NO_2 as a good leaving group. Among the other Lewis and Brønsted acids screened, namely, $In(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, AgOTf, $Fe(OTf)_3$, $Bi(OTf)_3$, trifluoromethanesulfonic acid, and camphorsulfonic acid (entries 6−13), best results were obtained with $Sc(OTf)_3$ (83% yield, entry 8). When the equivalents of $LiClO_4$ were reduced to 20 mol %, the yield of reaction was dropped to 23%, indicating the necessity of stoichiometric amount of $LiClO_4$ (entry 14). Use of other lithium or sodium salts instead of $LiClO_4$ were not found to be fruitful (entries 15−17).

Table 1. Optimization of Reaction Conditions for the Synthesis of Symmetrical Dithioacetals[a]



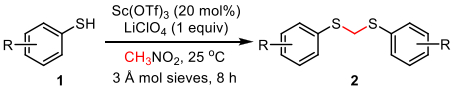
1a 2a

entry	catalyst	additive	yield[b] (%)
1	$Cu(OTf)_2$		0[c]
2	*p*-TsOH		0[c]
3	$Sc(OTf)_3$		0[c]
4	$Cu(OTf)_2$	$LiClO_4$	41
5		$LiClO_4$	0
6	$In(OTf)_3$	$LiClO_4$	48
7	$Yb(OTf)_3$	$LiClO_4$	26
8	$Sc(OTf)_3$	$LiClO_4$	83
9	AgOTf	$LiClO_4$	58
10	$Fe(OTf)_3$	$LiClO_4$	61
11	$Bi(OTf)_3$	$LiClO_4$	42
12	CF_3SO_3H	$LiClO_4$	65
13	CSA	$LiClO_4$	19
14	$Sc(OTf)_3$	$LiClO_4$	23[d]
15	$Sc(OTf)_3$	$NaClO_4$	26
16	$Sc(OTf)_3$	NaOAc	trace
17	$Sc(OTf)_3$	LiCl	trace

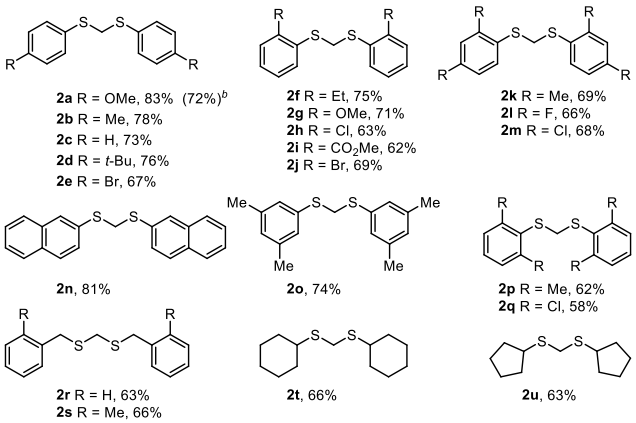
[a]Reaction conditions: **1a** (0.5 mmol), $Sc(OTf)_3$ (20 mol %), $LiOCl_4$ (0.5 mmol), nitromethane (1.0 mL), and 3 Å molecular sieves at 25 °C for 8 h, if otherwise stated. [b]Isolated yields. [c]No additives were used. [d]20 mol % of additive was used. CSA: (1*S*)-(+)-10-camphorsulfonic acid.

Once the optimal reaction conditions had been established, reactions of a variety of thiols under identical conditions were performed, and the results are summarized in Table 2. Higher reactivity and yields were observed for aryl thiols containing

Table 2. Synthesis of Symmetrical Dithioacetals[a]



1 2



[a]Reaction conditions: **1** (0.5 mmol), $Sc(OTf)_3$ (20 mol %), $LiClO_4$ (0.5 mmol), and nitromethane (1.0 mL) at 25 °C. [b]Reaction was performed on 6 mmol scale.

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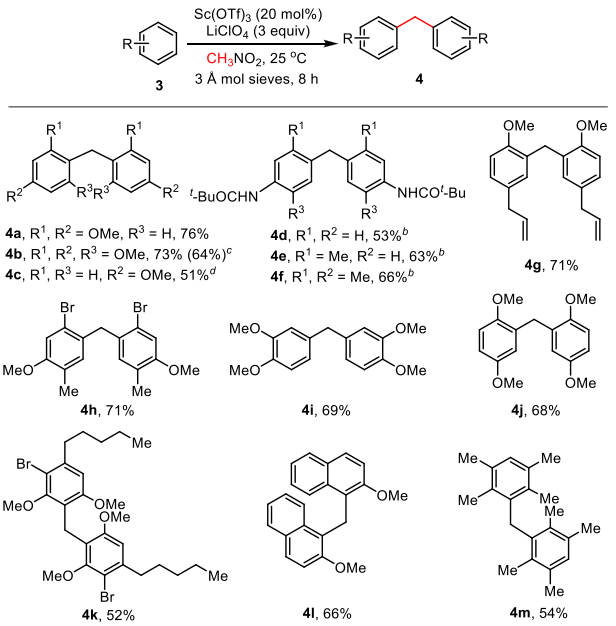
electron-donating groups (OMe, Me, Et, *t*-Bu) at the *ortho* or *para* positions, giving dithioacetals with excellent yields (Table 2, entries **2a**,**b**, **2d**, **2f**,**g**, **2k**, **2n**), while thiols bearing electron-withdrawing substituents (F, Cl, Br, CO_2Me) were found to be comparatively less reactive and furnished the corresponding dithioacetals in moderate to good yields (Table 2, entries **2e**, **2h**−**j**, **2l**−**m**). It is worth mentioning that sterically demanding dithioacetals were also synthesized in moderate yield from the corresponding aryl thiols bearing substituents at both *ortho* positions (Table 2, entries **2p**−**q**). The method was also tested for less reactive aliphatic thiols, generating corresponding dithioacetals in moderate yield (**2r**−**u**). To demonstrate the applicability of the present method for scale-up, the reaction of **1a** was performed on 6 mmol scale under the identical conditions, resulting in formation of **2a** in 72% yield.

After preparation of symmetrical dithioacetals, the method was extended to synthesis of bisarylmethanes under identical conditions. To our delight, when 2,4-dimethoxybenezene (**3a**) was reacted under identical conditions, the desired bisarylmethane (**4a**) was furnished in 76% yield. Likewise, reactions of various arenes were performed, and the results are summarized in Table 3. Higher reactivity and yields were

Table 3. Synthesis of Symmetrical Bisarylmethanes[a]



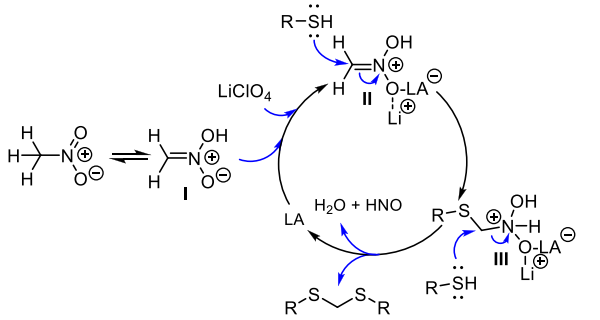
[a]Reaction conditions: **3** (0.5 mmol), $Sc(OTf)_3$ (20 mol %), $LiClO_4$ (0.5 mmol), nitromethane (1.0 mL), and 3 Å molecular sieves at 25 °C for 8 h. [b]Reactions were performed at 70 °C. [c]Reaction was performed on 6 mmol scale. [d]16% of *ortho*−*para* regioisomer was formed.

observed for arenes bearing more electron-donating groups, furnishing bisarylmethanes with good yields (Table 3, entries **4a**, **4g**−**j**). Reactions of arenes containing an amide group were very slow at 25 °C, but elevation of temperature from 25 to 70 °C accelerated the reaction and resulted in increased yields (entries **4d**−**f**). Sterically demanding bisarylmethanes were also synthesized in moderate to good yields from corresponding arenes bearing substituents at both *ortho* positions (entry **4b**, **4k**−**m**). Reaction of 4-methoxybenzene (**3c**) led to the formation of desired bisarylmethane **4c** in 51% yield along with 16% of the *ortho*−*para* regioisomer.

Unfortunately, arenes containing substituents with no electron-donating effect (benzene or bromobenzene) did not produce a detectable amount of corresponding bisarylmethanes. In addition, the reaction of mixed thiols or arenes to yield unsymmetrical dithioacetals or bisarylmethanes resulted in poor yields of the desired products owing to formation of competing symmetrical products.

Plausible reaction mechanism for the synthesis of dithioacetals is shown in Scheme 2. The mechanism is

Scheme 2. Plausible Reaction Mechanism for Synthesis of Dithioacetals



analogous to the classical Nef reaction.[5] To begin with, $Sc(OTf)_3$ and Li from $LiClO_4$ coordinates with the *aci* form of nitromethane **I** to form intermediate **II**. Nucleophilic attack of thiol on methylene carbon accounts for C−S bond formation generating intermediate **III**. Nucleophilic attack of the second thiol on **III** in S_N2 fashion results in the formation of dithioacetal along with the elimination of water and HNO. The mechanism for the synthesis of bisarylmethanes would be analogous to that of dithioacetal (not shown in Scheme 2).

Furthermore, to demonstrate the applicability of the method, it was decided to expand the scope by synthesizing the related biologically active molecules. In 2013, Kingston and co-workers isolated mallotojaponins B (**5**) and C (**6**).[26] Compounds **5**−**7** showed potent antimalarial activity against chloroquine-resistant *Plasmodium falciparum*, with IC_{50} values of 0.75, 0.14, and 2.2 μM, respectively.[26] In 2016, the same group reported the synthesis of mallotojaponin C (**6**),[27] while the synthesis of mallotojaponins B (**5**) and C (**6**) was reported by Cariou and co-workers.[28] In 2012, Singh and co-workers reported synthesis of structurally related phloroglucinol derivative **8** with potent anticancer and antidepressant activity.[29] Encouraged by the potent biological activity of these molecules, we became interested in the synthesis of tetramethyl mallotojaponin C (**7**) and phloroglucinol derivative **8** (Figure 1).

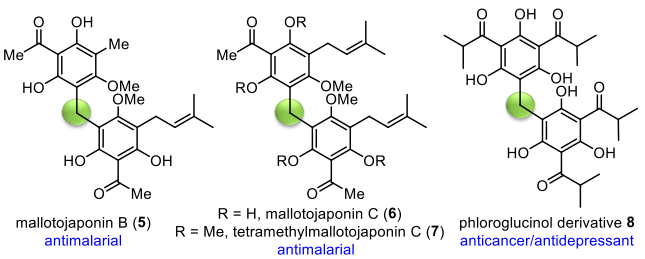


Figure 1. Structures of mallotojaponins **5**−**7** and pholoriglucinol derivative **8**.

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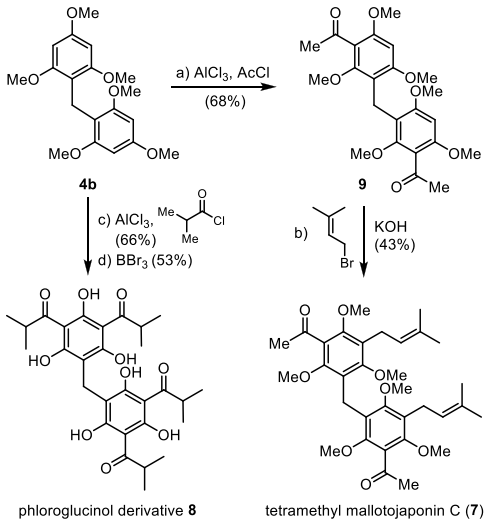
To begin, compound **4b** upon controlled acylation generated acetophenone derivative **9**, which on subsequent alkylation with 1-bromo-3-methylbut-2-ene under basic conditions furnished tetramethyl mallotojaponins C (**7**) (Scheme 3).[26] On the other hand, bisarylmethane **4b** on

Scheme 3. Synthesis of Tetramethyl Mallotojaponin C (7) and Dimeric Phloroglucinol Derivative 8[a]



[a]Reagents and conditions (a) $AlCl_3$ (3.0 equiv), AcCl (5.0 equiv), CH_2Cl_2, 25 °C, 12 h, 68%; (b) 1-bromo-3-methylbut-2-ene (2.4 equiv), KOH (3.0 equiv), MeOH, 0 °C, 24 h, 43%; (c) $AlCl_3$ (8.0 equiv), AcCl (7.0 equiv), CH_2Cl_2, 25 °C, 24 h, 66%; (d) BBr_3 (7.0 equiv), CH_2Cl_2, 0 °C, 4 h, 53%.

exhaustive acylation using $AlCl_3$ and isobutyryl chloride generated the corresponding tetra-acylated derivative which on deprotection using BBr_3 furnished the desired dimeric phloroglucinol derivative **8** (Scheme 3).[29]

In summary, we have demonstrated the use of nitromethane as an electrophilic methylene source for the synthesis of bisarylmethanes and dithioacetals. Activation of nitromethane was achieved using the $Sc(OTf)_3$–$LiClO_4$ combination. Synthesis of sterically demanding *ortho*-disubstituted bisarylmethanes and dithioacetals was achieved from the corresponding arenes and thiols, which are otherwise difficult to synthesize. Furthermore, the method was applied for the synthesis of antimalarial tetramethyl mallotojaponin C and antidepressant, anticancer dimeric phloroglucinol derivative **8**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01831.

Details of the experimental procedure and characterization data for all new compound (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Dattatraya H. Dethe − *Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India;* orcid.org/0000-0003-2734-210X; Email: ddethe@iitk.ac.in

Authors

Manmohan Shukla − *Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India*

Balu D. Dherange − *Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India;* orcid.org/0000-0002-4123-5012

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01831

Author Contributions

†M.S. and B.D.D. contributed equally.

Notes

The authors declare no competing financial interest.

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