

Letter

Preparation of Thioanisole Biscarbanion and C–H Lithiation/ Annulation Reactions for the Access of Five-Membered Heterocycles

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Supporting Information



ABSTRACT: The synthesis, isolation, and X-ray structure of a thioanisole-based trilithium complex are reported. On the basis of the double-lithiation strategy, two novel synthetic methodologies have been developed under mild reaction conditions (room temperature): (1) reactions of lithiated thioanisoles with nitriles give benzoisothiazoles via a [3 + 2]-type of approach with two new bond formations and (2) formation of benzothiophenes from thioanisoles and amides through a [4 + 1] pattern forming 4 new chemical bonds.

C arbanion as one of the most reactive species in organic chemistry has continuously been the core synthon in molecular design.¹ Two major strategies are commonly used for the generation of carbanions, including halogen-main group metal exchange² and hydrogen-metal exchange (deprotonation).³⁻⁶

The regioselective and stereoselective deprotonations are the main challenges in this field.^{7–9} Double lithiation of thioanisole 1 using nBuLi, followed by the reaction with diketone 2 provided a six-membered diol 3 in 59% yield (Scheme 1a).





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Scheme 2. Synthesis of Trilithium 4^{a}



 aReaction conditions: substrate 1 (0.25 mmol), nBuLi/TMEDA (1.0 mmol), in hexane (2.0 mL) at 65 $^\circ C$ for 3 h.

Our research interests on the studies of synthetically useful methodologies have previously focused on the regioselective C–H activation reactions, in particular, modular construction of heterocycles.¹⁰

Inspired by Xi's development of dilithium reagents and further applications in both organic chemistry and organometallic chemistry,¹¹ we focused on the studies of multilithiation processes. Herein, we report our recent discoveries on the preparation of bislithiated thioanisole complex 4 and two new synthetic methodologies for the synthesis of benzoisothiazoles 6 and benzothiophenes 8.^{12,13} Novel bond formation strategies and unprecedented cyclization approaches are disclosed (Scheme 1b).¹⁴

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Scheme 3. Synthesis of Benzaisothiazoles from Organolithium 4^a



"Reaction conditions: lithium 4 (0.2 mmol), R^1CN (1.0 mmol), in TBME (2.0 mL) at rt for 24 h.



^aReaction conditions: substrate 1 (0.20 mmol), nBuLi (1.0 mmol), TMEDA (0.60 mmol) in TBME (2.0 mL) at rt for 0.5 h, then RCN (1.0 mmol), at rt for 24 h.

We initiated our studies by investigating the formation of dianions on substituted arene at both the lateral and *ortho*-positions. Attempts on the lithiation of thioanisole 1¹⁵ with 2.0 equiv of organolithium reagent (nBuli, sBuli, or tBuLi) in ethereal solvent (Et₂O or THF) at low temperature (-78 °C) were not fruitful; no dianion was observed. Interestingly, when a solution of arene 1 was treated with 1.0 equiv of nBuLi with an equal molar amount of TMEDA in hexane at 65 °C, followed by trapping the reaction mixture with TMSCl as the eletrophile, a mixture of of silane 1-b and bissilane 1-c was detected, and the corresponding silanes 1-b and 1-c were isolated in 81% and 9% yields, respectively (Supporting Information, Scheme 1).

Scheme 5. Synthesis of Benzothiophenes from Trilithium 4^{a}



"Reaction conditions: substrate 4 (0.20 mmol), amide (2.0 mmol) in TBME (2.0 mL) at rt for 24 h

The ligand evaluation was also carried out; no lithiation was observed if no ligand was added. The use of (-)-sparteine¹⁶ generated a complicated reaction mixture; the disilylated product was only obtained in 8% yield. PMDTA¹⁷ was not an efficient ligand either, and no desired product was isolated.

To our surprise, the white powder isolated was not bislithium 4x, instead, the white solid was trilithiated product 4, as confirmed unambiguously by the X-ray crystallographic studies. Interestingly, complex 4 is insensitive and can be stored at room temperature for few days.¹⁸

Unlike previously known bidentate (κ^2) ligand,¹⁹ TMEDA was deprotonated during our processes.²⁰ Single crystals were obtained of the compound 4 isolated (Scheme 2). The distance of Li3–C12 is comparable to those of trimeric or tetrameric phenyllithium complexes reported previously in the literature.^{21,22}

With the optimal conditions for the synthesis of trilithiated thioanisole 4 available, we then investigated the possible cyclization reactions. Encouragingly, when benzonitrile was examined, benzoisothiazole 6a was isolated in 74% yield. We then tested the scope and limitation of this annulation reaction. As shown in Scheme 3, when lithium 4 was utilized, a range of substituted benzonitriles could be coupled to give the corresponding benzoisothiazoles 6a - m in useful to good yields.

Even reactions with very hindered aliphatic nitriles and curved aromatic nitriles are possible; the reactions provided the challenging benzoisothiazoles 6n-p in slightly lower yields. The low yields for the synthesis of these products was due to the poor solubility of the corresponding nitriles.

The direct synthesis of benzoisothiazoles under mild conditions (room temperature) was also examined; the preparation of benzoisothiazole **6a** was straightforward. The treatment of starting thioanisole **1** with organolithium reagent and TMEDA in TBME and then trapping of the lithiated species with benzonitrile as the electrophile gave the desired product **6a** in 72% yield. Reactions of other sulfides and nitriles were also successful; the desired products were obtained in good to useful yields. The reaction is more practical (instead of 65 °C lithiation), and the yields are similar compared to the procedures using separated lithium salt **4** (Scheme 4).

Lithium complex 4 was not only reacted with nitriles but also with amides via a [4 + 1]-type cyclization to give a benzothiopene skeleton. The treatment of trilithium salt 4 with DMF 7a and amide 7b resulted in benzothiophene 8a and 8b in 78% and 63% yields, respectively (Scheme 5).

Similar to the benzoisothiazole synthesis, the synthesis of benzothiophene from thioanisoles is also investigated. Pleasingly, the reaction of thioanisoles with a number of amides provided the corresponding benzothiophenes 8a-h in useful to





^aReaction conditions: thioether 1 (0.2 mmol), TMEDA (3.0 equiv), nBuLi (5.0 equiv), TBME (1 mL), rt, 3 h, then at 0 $^{\circ}$ C for 0.5 h, amide was added in one portion, rt, 24 h.

8h (20%)

good yields. Dimethylamine-substituted amides seem more reactive and provided higher yields than reactions using amides





Scheme 7. D-Labeled Experiments^a



^{*a*}Reaction conditions: thioether 1-D (0.2 mmol), TMEDA (3.0 equiv), nBuLi (5.0 equiv), TBME (2 mL), under standard conditions, then benzonitrile (5.0 equiv) at rt for 24 h.

Scheme 8. Proposed Mechanism



with bisisopropyl and piperidine ring protected amides (Table 1, entries 1-3). The four C–C bonds were formed within a single chemical step; the synthesis of these molecules via multilithiation bond formation provided a new pathway for molecular design.

To elucidate the reaction mechanism, we have attempted to isolate the possible reaction intermediate(s). Interestingly, as shown in Scheme 6, when lithium 4 was treated with 3.0 equiv of tBuCN, isothiazole **60** and ketone **9h** were isolated in 23% and 50% yields. Under similar conditions, and after being at room temperature for 24 h, the reaction mixture was then heated at 50 °C; isothiazole **60** was isolated in 40% yield instead. These two experiments implied that both carbanions may react with nitrile electrophile and the ^{sp3}C carbanion reacted first. Upon quenching with NH₄Cl(aq), the corresponding product **9i** was isolated. Further heating of the reaction mixture resulted in the formation of isothiazole **60** in a nearly doubled yield.

The D-labeled thioanisole **1-D** was treated with nBuLi/ TMEDA under our standard reaction conditions, then benzonitrile was introduced, and the desired benzoisothiazole **6a** was isolated in 65% yield with no D association. Interestingly, we have also isolated the corresponding side product **10** with 60% of D association (Scheme 7). These results indicate that the methyl group may have been deprotonated multiple times before being cleaved to form the benzoisothiazole ring system.

Density functional theory (DFT) calculations were also performed to explore the detailed reaction mechanism using the B3LYP-D3 method and the SMD solvation model. We chose the reactions of substrate 1 with phenylacetonitrile and DMF as representatives for the mechanistic investigation. Scheme 8 illustrates our proposed reaction pathways, which can be characterized by the following key steps, namely, deprotonations by the lithium reagent leading to the bislithium complex IN1, two successive electrophilic additions by the nitrile or DMF substrate, and an N–S or a C–C bond-forming reaction providing the final product **6a** or **8a**. The most favored reaction pathways for these reactions are presented (see the SI).

In summary, we have reported the synthesis and isolation of an interesting lithiated species (4). In addition, we have also reported (1) a new S–N bond-forming strategy for the modular synthesis of a range of benzoisothiazoles (2) multiple C–C bond formation approaches for the preparation of benzothiophenes via direct C–H lithiation/annulation reactions. The reaction mechanisms using DFT calculations have also been studied. These types of novel synthetic methods will provide new considerations for retrosynthetic analyses.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b00850.

General information, experimental procedures, spectral data, and energies and Cartesian coordinates (PDF)

Accession Codes

CCDC 1495213 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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