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A Novel Anionic Domino Process for the Synthesis of *o*-Cyanoaryl-Methylthio/ Alkyl/Aryl/Heteroaryl Acetylenes‡

Sarvesh Kumar, Saravanan Peruncheralathan, Hiriyakkanavar Ila,* and Hiriyakkanavar Junjappa

Department of Chemistry, Indian Institute of Technology, Kanpur- 208016, India

hila@iitk.ac.in

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ABSTRACT

A novel unexpected anionic domino process involving *n*-BuLi-induced rearrangement of 3,3-bis(methylthio) or 3-methylthio-3-aryl/heteroaryl/ alkyl-*o*-bromoarylacrylonitriles to *o*-cyanoarylacetylenes in synthetically useful yields has been reported. The scope and generality of the reaction has been examined, and a possible mechanism has been proposed.

Functionalized alkyl and aryl acetylenes are important classes of molecules[1] that have found applications in diverse areas ranging from biologically active natural products[2] (such as laurencin[3] and neocarzinostatin chromophores[4]) to pharmaceuticals, molecular organic materials,[1c,5] and nanomaterials.[1d] Furthermore, their unsaturated high-energy structure makes alkynes an attractive functional group for further derivatization in many synthetic transformations[6] and natural product syntheses.[7] Metal-catalyzed cross-coupling reactions,[8] especially Sonogashira coupling,[9,10] are the most versatile and efficient methods for the synthesis of conjugated vinyl and arylacetylenes. Alkyne preparations by combination of two fragments involving formation of a triple bond via single or double elimination[11] in a one-pot integrated chemical process[12,13] are also of considerable interest in organic synthesis. However, development of such transformations has received

‡ Dedicated to Prof. George A. Olah on his 80th birthday.

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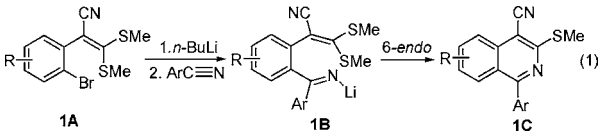
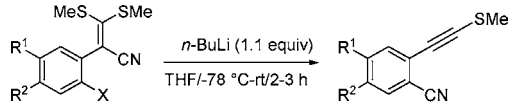
little attention. In the course of our ongoing program toward the development of new synthetic routes for biologically important heterocycles via polarized ketene dithioacetals,[14,15] we have uncovered a novel, unexpected anionic rearrangement of 3,3-bis(methylthio)-2-(2-haloaryl)acrylonitriles yielding *o*-cyanoarylacetylenes through a series of anionic domino processes. Herein, we report our findings on this rearrangement which constitutes a new method for the synthesis of aryl, heteroaryl, and alkyl-*o*-cyanoarylacetylenes.

We planned to develop a general synthesis of substituted isoquinolines **1C** by the treatment of ketene dithioacetals **1A** with *n*-BuLi followed by intermolecular trapping of the *o*-lithiated species with arylnitriles and subsequent 6-*endo* cyclization of the resulting lithiated imino adducts **1B** (eq 1). However, much to our surprise when **1a** was reacted with



n-BuLi (1.1 equiv, −78 °C) followed by the addition of benzonitrile, the product isolated was not the desired isoquinoline, but was characterized as (*o*-cyanoaryl)methylthioacetylene **3a** (50%) on the basis of its spectral, analytical, and X-ray diffraction data (Table 1, Figure 1

Table 1. Synthesis of *o*-Cyanoaryl Methylthioacetylenes **3** from Ketene Dithioacetals **1** and **2**



1, 2 3

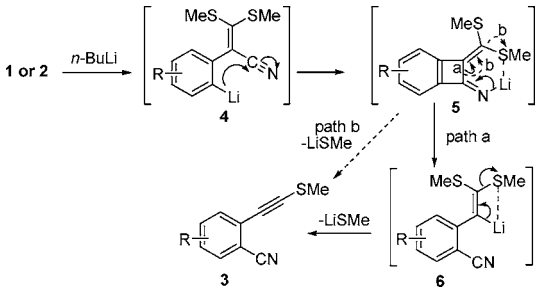
entry	**1, 2**	R^1	R^2	X	**3**	yield (%)[a]
1	**1a**	OMe	OMe	Br	**3a**	68[b]
2	**2a**	OMe	OMe	I	**3a**	73
3	**1b**	$-OCH_2O-$		Br	**3b**	65
4	**1c**	OMe	H	Br	**3c**	62
5	**1d**	H	Me	Br	**3d**	78
6	**1e**	H	H	Br	**3e**	59
7	**2b**	H	H	I	**3e**	92
8	**1f**	H	F	Br	−	*c*

[a] Yield of pure isolated product. [b] *n*-BuLi (1.1 equiv)/THF/−78 °C/PhCN then H_2O, yield 50%. [c] Complex mixture was obtained.

Supporting Information). The acetylene **3a** was obtained in improved yield (68%) when **1a** was treated with *n*-BuLi (1.1 equiv, −78 °C) in the absence of benzonitrile (Table 1). The generality of this transformation was demonstrated by subjecting other substituted (*o*-bromoaryl)cyano ketene dithioacetals **1b**−**e** to this rearrangement under identical conditions furnishing the respective *o*-cyanoaryl acetylenes **3b**−**e** in 59−78% yields (Table 1, entries 3−6). When similar reactions were performed with the corresponding *o*-iodo derivatives **2a** and **2b**, the *o*-cyanoarylacetylenes **3a** and **3e** were obtained in higher yields (Table 1, entry 1 vs 2 and entry 6 vs 7). On the other hand, attempted rearrangement of (2-bromo-4-fluorophenyl)cyano ketene dithioacetal **1f** under identical reaction conditions gave only complex product mixture (Table 1, entry 8).

The probable mechanism for the formation of alkynes **3** from ketene dithioacetals **1** is depicted in Scheme 1. The

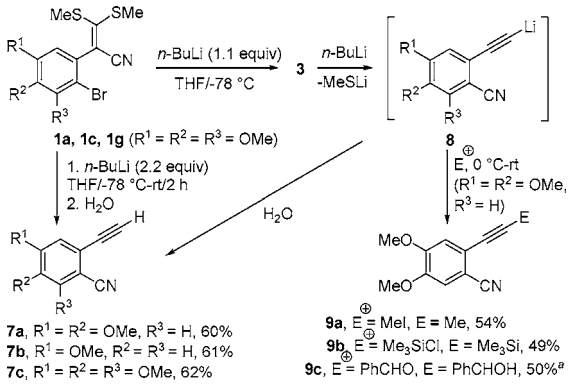
Scheme 1. Proposed Mechanism for the Formation of Acetylenes **3** from Ketene Dithioacetals **1** and **2**



initially formed *o*-lithioaryl species **4** by lithium−halogen exchange of **1** (or **2**) undergoes intramolecular nucleophilic attack on favorably located nitrile group of **1** (Figure 2, X-ray data of **1a**, see Supporting Information)[16] furnishing lithiated benzocyclobutanimine intermediate **5** which in turn fragments to 2-cyanoaryllithium species **6**. Subsequent elimination of methylthiolithium from **6** affords the (*o*-cyanoaryl)-methylthioacetylenes **3** in synthetically useful yields (path a, Scheme 1). Alternatively, the cleavage of the intermediate lithiobenzocyclobutanimine **5** to alkyne **3** may proceed by a concerted process with concomitant elimination of methylthiolithium (path b, Scheme 1) which is facilitated by favorable coordination of lithium ion with the lone pair of sulfur as shown in **5**.[17]

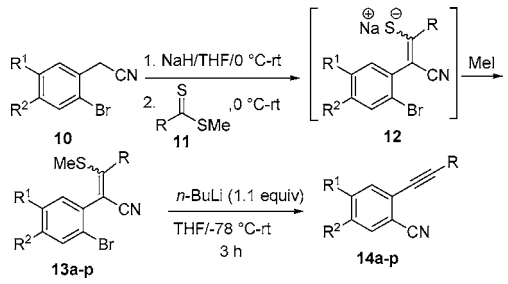
Interestingly, in one of the reactions, when ketene dithioacetal **1a** was exposed to 2.2 equiv of *n*-BuLi under similar reaction conditions, the product isolated was found to be dethiomethylated terminal (*o*-cyanoaryl)acetylene **7a** (60%) (Scheme 2). Similarly, the dethiomethylated acetylenes **7b**

Scheme 2. Synthesis and Mechanism of Formation of Terminal and Substituted Arylacetylenes **7** and **9** from **1**



[a] *t*-BuLi (2.2 equiv) was used.

Scheme 3. Synthesis of *o*-Cyanoaryl Acetylenes **14a**−**p** from Adducts **13a**−**p**

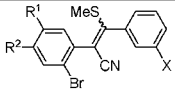
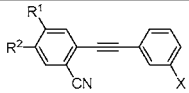
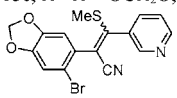
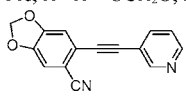
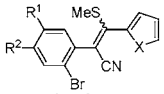
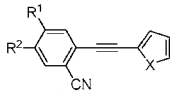
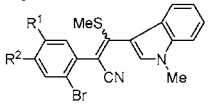
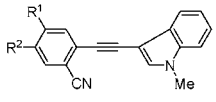
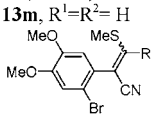
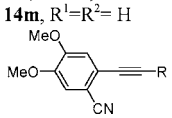


and **7c** were obtained in good yields from the respective ketene dithioacetals **1c** and **1g** upon treatment with 2.2 equiv of *n*-BuLi (Scheme 2). Formation of **7a**−**c** in the presence of excess *n*-BuLi can be rationalized by the cleavage of the C−S bond by nucleophilic attack of *n*-BuLi on the sulfur atom of acetylene **3** to give lithiated acetylene **8** which on quenching with water yields **7** (Scheme 2).[11,18] In separate experiments, attempts were made to trap the *o*-cyanoarylacetylene anion **8a** with reactive electrophiles (MeI, Me_3SiCl, PhCHO), yielding the substituted acetylenes **9a**−**c** in moderate yields (Scheme 2).

To further explore the scope and generality of this novel acetylene synthesis, we next investigated the analogous rearrangement of the corresponding 3-(methylthio)-3-(aryl/heteroaryl/alkyl)-2-(2-bromoaryl) acrylonitriles **13** prepared by the base-induced condensation of nitriles **10** with appropriate aryl/heteroaryl/alkyl dithioesters **11** followed by in situ *S*-methylation of the resulting enethiolate salts **12** with methyl iodide (Scheme 3, Table 2). Rearrangement of **13** with 1.1 equiv of *n*-BuLi under previously described reaction conditions was found to be very facile, yielding various disubstituted acetylenes in good yields (Scheme 3). These results are depicted in Table 2. As shown, a number of (*o*-cyanoaryl)acetylenes substituted at the other terminal with aryl (**14a**−**c**, entries 1−3), 3-pyridyl (**14d**, entry 4), and five-membered heteroaryl groups (**14e**−**m**, entries 5−13) could be obtained in reasonably good yields following the simple procedure. The methodology could also be extended successfully for the synthesis of alkylarylacetylenes (**14n**−**p**, entries 14−16) in good yields from the appropriate 3-methylthio-3-alkylacrylonitrile precursors **13n**−**p**.

Interestingly, when the cyclic ketene dithioacetals **1h** and **1i** from the *o*-bromoarylacetonitriles were subjected to rearrangement in the presence of *n*-BuLi, workup and analysis of the reaction mixture revealed formation of exclusive products which were characterized as 2-(*n*-butylthio)-3-

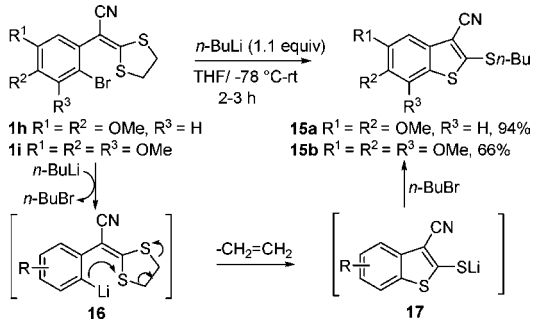
Table 2. Synthesis of (*o*-Cyanoaryl)aryl/heteroaryl/alkylacetylenes **14a**−**p** from Adducts **13a**−**p**

entry	13	yield (%)[a]	14	yield (%)[a]
				
1	**13a**, R^1=R^2= OMe; X= H	79	**14a**, R^1=R^2= OMe; X= H	75
2	**13b**, R^1=R^2=X= OMe	85	**14b**, R^1=R^2=X= OMe	61
3	**13c**, R^1=R^2= OCH_2O; X= H	99	**14c**, R^1=R^2= OCH_2O; X= H	71
				
4	**13d**	88	**14d**	48
				
5	**13e**, R^1=R^2= OMe; X= S	99	**14e**, R^1=R^2= OMe; X= S	63
6	**13f**, R^1=R^2= OCH_2O; X= S	95	**14f**, R^1=R^2= OCH_2O; X= S	69
7	**13g**, R^1=R^2= OMe; X= NMe	85	**14g**, R^1=R^2= OMe; X= NMe	65
8	**13h**, R^1=R^2= OCH_2O; X= O	90	**14h**, R^1=R^2= OCH_2O; X= O	53
9	**13i**, R^1= OMe; R^2=H; X= O	87	**14i**, R^1= OMe; R^2=H; X= O	56
10	**13j**, R^1=R^2= H; X= O	63	**14j**, R^1=R^2= H; X= O	100
				
11	**13k**, R^1=R^2= OCH_2O	96	**14k**, R^1=R^2= OCH_2O	66
12	**13l**, R^1= H; R^2= Me	86	**14l**, R^1= H; R^2= Me	86
13	**13m**, R^1=R^2= H	92	**14m**, R^1=R^2= H	91
				
14	**13n**, R= Et	95	**14n**, R= Et	65
15	**13o**, R= *i*-Pr	53	**14o**, R= *i*-Pr	62
16	**13p**, R= *n*-Bu	81	**14p**, R= *n*-Bu	64

[a] Yield of pure isolated product

cyanobenzothiophenes **15a** and **15b**, respectively. The probable mechanism for the formation of benzothiophenes **15a** and **15b** is shown in the Scheme 4. The *o*-lithioaryl anion

Scheme 4. Mechanism for the Formation of Benzothiophenes **15a**,**b** from Cyclic Ketene Dithioacetals **1h**,**i**



16 appears to undergo nucleophilic attack on suitably located sulfur atom of the cyclic ketene dithioacetal with concomitant cleavage of the 1,3-dithiolan ring along with the elimination of ethylene to furnish 3-cyanobenzothiophene-2-thiolate salt **17** which upon alkylation with in situ generated *n*-BuBr yields the corresponding **15a** and **15b** in high yields (Scheme 4).

In summary, we have reported a novel anionic domino rearrangement of 3,3-(bis-methylthio) or 3-(methylthio)-3-aryl/heteroaryl/alkyl-2-(*o*-bromoaryl) acrylonitriles leading to *o*-cyanoarylacetylenes in synthetically useful yields. The proposed mechanism for this rearrangement sequence involves a series of cascade processes consisting of lithium−halogen exchange, intramolecular nitrile group transfer through fragmentation of the lithiobenzocyclobutanimine intermediate, and elimination of thiomethyllithium to give (*o*-cyanoaryl)acetylenes. Studies addressing the scope of this novel rearrangement and attempts to exploit this reactivity mode for the synthesis of other ortho-functionalized acetylenes are currently underway.

Acknowledgment. S.K. and S.P. thank CSIR, New Delhi, for SRF and RA, respectively.

Supporting Information Available: Experimental details and spectroscopic/analytical data for all new compounds; ORTEP diagrams of **1a** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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