Tetrahedron 71 (2015) 4604–4607

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 3-substituted 2-bromoquinolines utilizing 2-bromo-3-lithioquinolines generated by the reaction of 2-(2,2-dibromoethenyl)phenyl isocyanides with butyllithium

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ARTICLE INFO

Article history:
Received 30 March 2015
Received in revised form 8 May 2015
Accepted 9 May 2015
Available online 14 May 2015

Keywords:
2-Bromoquinolines
2-Bromo-3-lithioquinolines
Isocyanides
Bromine/lithium exchange
Ring closure

ABSTRACT

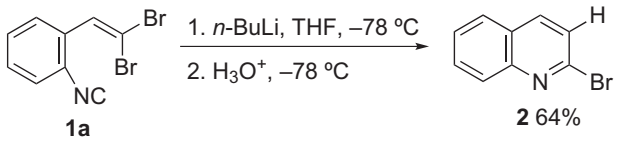
The first generation of 2-bromo-3-lithioquinolines can be achieved and they are utilized for the preparation of 3-substituted 2-bromoquinolines. Thus, 2-(2,2-dibromoethenyl)phenyl isocyanides are treated with butyllithium in THF at −78 °C to generate these novel lithium compounds, which are allowed to react with various electrophiles to afford the corresponding desired products in one-pot.

1. Introduction

2-Bromoquinolines have recently emerged as versatile precursors for the preparation of biologically important compounds[1] and light-emitting materials.[2] Although 2-bromoquinoline has been prepared by the reactions of quinolin-2(1*H*)-one[3] or quinoline 1-oxide[4] with brominating agents, no reports on the general preparation of substituted 2-bromoquinolines have appeared so far. Therefore, development of a convenient method for the preparation of such derivatives is of considerable merit. In this manuscript, we wish to report an efficient general synthesis of 3-functionalized 2-bromoquinolines. We have found that 2-(2,2-dibromoethenyl) phenyl isocyanides **1** are good precursors for the generation of 2-bromo-3-lithioquinolines. Thus, treatment of **1** with butyllithium generates these lithium compounds and their reaction with various electrophiles affords the desired compounds **6**. To the best of our knowledge, no previous procedures have been reported for the generation these lithium compounds.

2. Results and discussion

2-(2,2-Dibromoethenyl)phenyl isocyanides **1** can be easily prepared from the respective 2-(2,2-dibromoethenyl)benzenamines following literature procedures.[5] First, 2-(2,2-dibromoethenyl) phenyl isocyanide (**1a**) was treated with an equivalent of butyllithium in THF at −78 °C as shown in Scheme 1. After 5 min stirring, the mixture was worked up usually, and the crude product was purified by column chromatography on silica gel. The isolated material was shown by a direct comparison of its ^{1}H NMR spectra with that of a sample purchased from Tokyo Chemical Industry Co. Ltd. to be 2-bromoquinoline (**2**) with a 64% yield.



Scheme 1. Formation of 2-bromoquinoline (**2**).

A probable pathway leading to **2** from **1a** is illustrated in Scheme 2. The first step of the present transformation is the generation of the (*E*)-2-(2-bromo-2-lithioethenyl)phenyl isocyanide (**3**) by the bromine/lithium exchange between **1a** and butyllithium. The selective exchange can be reasoned by the coordination of the isocyano function to the lithium ion of butyllithium. Cyclization of this intermediate by the intramolecular insertion of the isocyano carbon into the C–Li bond affords 3-bromo-2-lithioquinoline (**4**),[6] which rearranges to 2-bromo-3-lithioquinoline (**5**). Protonation of

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http://dx.doi.org/10.1016/j.tet.2015.05.030
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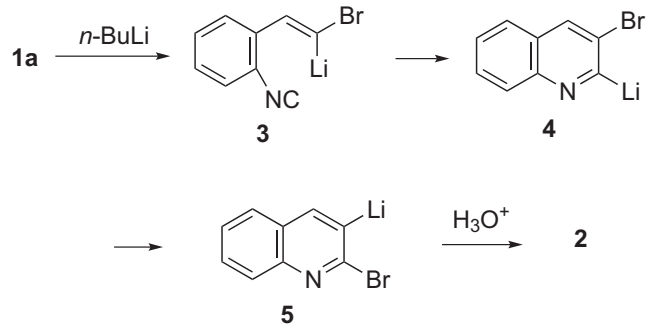
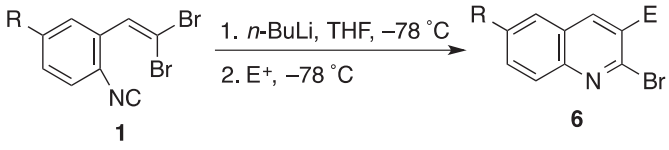
5 by aqueous workup provides **2**. 3-Bromoquinoline was not obtained at all. This indicates that the rearrangement of **4** to **5** occurs very rapidly, though its mechanism is not clear yet.



Scheme 2. Probable pathway to 2-bromoquinoline (**2**).

The preparation of 3-substituted 2-bromoquinolines **6** from 2-(2,2-dibromoethenyl)phenyl isocyanides **1** was carried out as follows (Scheme 3). After treatment of **1** with butyllithium as described above, a variety of electrophiles were added at the same temperature prior to aqueous workup. Purification of the crude products with column chromatography on silica gel afforded the desired products **6**. The results obtained are summarized in Table 1. For example, the reaction of 2-bromo-3-lithioquinoline, generated from 2-(2,2-dibromoethenyl)phenyl isocyanide (**1a**), with benzaldehyde afforded (2-bromoquinolin-3-yl)phenylmethanol (**6a**) in 52% yield (Entry 1). Acetone, aroyl chlorides, di-*tert*-butyl dicarbonate, diethyl oxalate, and diphenyl disulfide are usable and the yields of the corresponding desired products are also generally moderate. The moderateness of the yields is probably due to production of by-products arising from reactions of lithium (2-isocyanophenyl)acetylides, formed by the rearrangement of carbenoids (e.g., **3**) via the corresponding carbenes.[7] The desired products **6** were easily separated from these by-products.



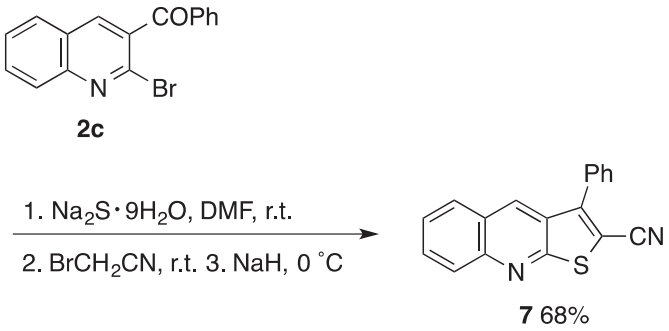
Scheme 3. Preparation of 3-substituted 2-bromoquinolines **6**.

Table 1
Preparation of 3-substituted 2-bromoquinolines **6**

Entry	R in **1**	E^+	E	**6**	Yield/%[a]
1	H	PhCHO	PhCH(OH)	**6a**	52
2	H	Me_2CO	Me_2COH	**6b**	48
3	H	BzCl	Bz	**6c**	54
4	H	2-ClC_6H_4COCl	2-ClC_6H_4CO	**6d**	39
5	H	$(Boc)_2O$	Boc	**6e**	52
6	H	$(MeOCO)_2$	MeOCOCO	**6f**	50
7	H	$(PhS)_2$	PhS	**6g**	55
8	Cl	PhCHO	PhCH(OH)	**6h**	48
9	Cl	BzCl	Bz	**6i**	47
10	OMe	Me_2CO	Me_2COH	**6j**	50
11	OMe	2-ClC_6H_4COCl	2-ClC_6H_4CO	**6k**	40

[a] Yields of isolated products.

Subsequently, a brief exploration of the utility of the products thus obtained was carried out. As shown in Scheme 4, (2-bromoquinolin-3-yl)phenylmethanone (**6c**) was treated with sodium sulfide nonahydrate in DMF at room temperature, and to the resulting reaction mixture were added successively 2-bromoacetonitrile and sodium hydride.[8] 3-Phenylthieno[2,3-*b*]quinoline-2-carbonitrile (**7**) was isolated in a satisfactory yield. Some compounds with the thieno[2,3-*b*]quinoline structure have been reported to exhibit biological activities.[9]



Scheme 4. Preparation of a thieno[2,3-*b*]quinoline derivative.

As mentioned above, the treatment of 2-(2,2-dibromoethenyl) phenyl isocyanides with butyllithium allows generation of 2-bromo-3-lithioquinolines, of, which reaction with various electrophiles afford novel 3-functionalized 2-bromoquinolines in one-pot. Although the yields of the products are not so high, the present method has advantages in the ready availability of the starting materials and the simplicity of the operations, and may find its value in possibilities of the construction of polycyclic heterocycle systems.

3. Experimental

3.1. General

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive Spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

3.2. Starting materials

n-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

*3.2.1. 1-(2,2-Dibromoethenyl)-2-isocyanobenzenes (**1**).* These compounds were prepared from the respective 2-(2,2-dibromoethenyl)-4-methoxybenzenamines via *N*-[2-(2,2-dibromoethenyl)phenyl] formamides according to the procedure reported previously.[5] The physical, spectral, and analytical data for new compounds are as follows.

3.2.1.1. N-[2-(2,2-dibromoethenyl)-4-methoxyphenyl]formamide. Yield: 87%; a colorless needles; mp 100–102 °C (hexane/CH_2Cl_2); IR (KBr) 3227, 1651, 1603 cm^{-1}; ^1H NMR δ 3.81 and 3.83 (2s, combined 3H), 6.91–8.40 (m, 6H). Anal. calcd for $C_{10}H_9Br_2NO_2$: C, 35.85; H, 2.71; N, 4.18. Found: C, 35.83; H, 2.82; N, 4.04.