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A Convenient Synthesis towards 2-Bromo-2-(methoxy(phenyl)methyl)malononitrile and 2-Iodo-2-(methoxy(phenyl)methyl)malononitrile

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Abstract: This short note elaborates a concise protocol for the synthesis of two novel vicinal haloethers bearing a malonontrile group, 2-bromo-2-(methoxy(phenyl)methyl)malononitrile (1) and 2-iodo-2-(methoxy(phenyl)methyl)malononitrile (2). The structures of the synthesized compounds were confirmed by 1H, 13C-NMR spectroscopy. The final products indicate that methanol not only acts as solvent but also participates in and dominates the reaction result.

Keywords: β; β-dicyanostyrene; difunctionalization; vicinal haloether

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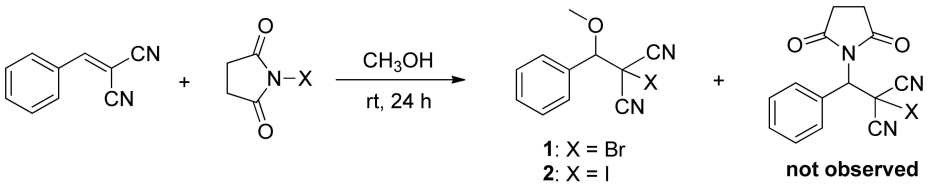
1. Introduction

The difunctionalization of olefins has become an attractive strategy for rapidly increasing molecular complexity from abundant and cheap feedstock [1–4]. Up to now, much work on difunctionlization has been reported, such as the representative aminohalogenation reaction, which provides an effective platform to convert simple olefins [5–7], α, β-unsaturated ketones [8–10], and β-nitrostyrene derivatives [11–13] into vicinal haloamine compounds. β, β-Dicyanostyrene derivatives are a kind of reaction raw material containing a multifunctional group which can be converted into the skeleton structures in drugs and natural products, via difunctionalization, such as enamine [14], β-hydroxy sulfide [15], dicyanocyclobutane [16], and so on. Recently, an unexpected vicinal bromoether product was obtained when we performed an aminobromination reaction of β, β-dicyanostyrene. On this basis, we developed a synthetic protocol for vicinal haloethers, including 2-bromo-2-(methoxy(phenyl)methyl)malononitrile (**1**) and 2-iodo-2-(methoxy(phenyl)methyl)malononitrile (**2**), which are verified to be novel compounds and to possess the potential to be building blocks in organic synthesis by easy conversion into amounts of useful functional derivatives via intermolecular or intramolecular nucleophilic substitution of halogens.

2. Results

Many synthetic methods are available for the aminobromination reaction of β, β-dicyanostyrene; most of them require catalysts such as Na_2CO_3 [14], K_3PO_4 [17], and $NaHCO_3$ [18]. In 2012, Chen reported a NaOAc-catalyzed aminobromination of β, β-dicyanostyrene, with NBS as nitrogen/bromine source, to yield *N*-[2-Bromo-2,2-dicyano-1-phenylethyl]pyrrolidine-2,5-dione [19]. Recently, we slightly modified this reaction by replacing CH_3CN with methanol as the solvent and abandoning the catalyst. Surprisingly, the expected product was not observed in the reaction. Alternatively, β, β-dicyanostyrene was converted into 2-bromo-2-(methoxy(phenyl)methyl)malononitrile (**1**) in moderate yield (Scheme 1). Subsequently, we also tried ethanol, isopropyl alcohol, and tert-butanol as solvents, but none of the reactions formed 2-bromo-2-(methoxy (phenyl)methyl)malononitrile

or N-[2-bromo-2,2-dicyano-1-phenylethyl]pyrrolidine-2,5-dione. Most of the starting material, β, β-dicyanostyrene, was recovered, and some was converted to benzaldehyde. The relative mechanism is still under further study.



Scheme 1. Synthesis of compound **1** and **2**.

After optimization of the experimental conditions (details of the condition optimization are shown in Table S1), the reaction was performed in methanol at room temperature by using β, β-dicyanostyrene/NBS (1:1 ratio) as the starting materials. Compound **1** was obtained in 76.8% yield and confirmed by NMR. Firstly, the ^{1}H-NMR spectrum (Supplementary Materials) exhibits the typical signals for the methoxy and methyne group as a single peak at 3.47 and 4.67 ppm, respectively. The chemical shifts of the five hydrogen atoms on the substituted benzene ring are concentrated in the range of 7.45 to 7.55 ppm. The ^{13}C-NMR spectrum exhibits nine peaks which fully agree with the proposed structure for **1** (Supplementary Materials).

As an expansion of the reaction, N-iodosuccinimide (NIS) was selected as the iodine source, and we obtained 2-iodo-2-(methoxy(phenyl)methyl)malononitrile (**2**) in 70.5% yield under the same reaction conditions. The molecular structure of compound **2** was also unambiguously confirmed by ^{1}H-NMR and ^{13}C-NMR, with the peak at 1.02 ppm in the ^{13}C-NMR spectrum representing the typical chemical shift of C–I bond.

3. Discussion

All reagents were purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd. (Shanghai, China) and used without further purification. The starting β, β-dicyanostyrene was synthesized according to the literature [17]. NMR spectra were recorded on a Bruker Avance AV400 (400/100 MHz ^{1}H/^{13}C) spectrometer (Bruker, Billerica, MA, USA), and chemical shifts (δ, ppm) were down field from TMS.

2-Bromo-2-(methoxy(phenyl)methyl)malononitrile (**1**): in a 100 mL three-neck flask, N-bromosuccinimide (0.35 g, 2 mmol) was added to the solution of β, β-dicyanostyrene (0.31 g; 2 mmol) in absolute methanol (10 mL). The reaction mixture was stirred at room temperature for 24 h, and then the excess methanol was removed by rotary evaporation. The residue was purified by column chromatography over silica gel (EtOAc/petroleum = 1/10) to yield a yellow oil (0.34 g, 76.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.52–7.45 (m, 3H), 4.64 (s, 1H), 3.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.38 (s), 130.94 (s), 128.96 (s), 128.60 (s), 111.11 (s), 110.81 (s), 86.05 (s), 58.74 (s), 30.54 (s).

2-Iodo-2-(methoxy(phenyl)methyl)malononitrile (**2**): in a 100 mL three-neck flask, N-iodosuccinimide (0.45 g, 2 mmol) was added to the solution of β, β-dicyanostyrene (0.31 g; 2 mmol) in absolute methanol (10 mL). The reaction mixture was stirred at room temperature for 24 h, and then the excess methanol was removed by rotary evaporation. The residue was purified by column chromatography over silica gel (EtOAc/petroleum = 1/10) to yield a brown oil (0.44 g, 70.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2H), 7.53–7.48 (m, 3H), 4.45 (s, 1H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 131.83 (s), 130.80 (s), 129.00 (s), 128.38 (s), 112.87 (s), 112.66 (s), 86.21 (s), 58.61 (s).

4. Conclusions

Two novel vicinal haloether compounds, 2-bromo-2-(methoxy(phenyl)methyl) malononitrile (**1**) and 2-iodo-2-(methoxy(phenyl)methyl)malononitrile (**2**), were handily synthesized from β, β-dicyanostyrene and characterized by NMR. Future work will

emphasize exploring the scope of β, β-dicyanostyrene derivatives and illustrating the reaction mechanism.

Supplementary Materials: The following supporting information can be downloaded online, ^{1}H-NMR and ^{13}C-NMR spectra of compounds **1**, **2**. Reference [17] is cited in Supplementary Materials. Table S1. condition optimization. Figure S1. H-NMR and 13C-NMR spectra of compound **1**. Figure S2. 1H NMR and 13C NMR spectra of compound **2**.

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Data Availability Statement: The data from this study are available in this paper and in its Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest.

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