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An Efficient Synthetic Approach for The Transition Metal-Free Preparation of 2-Bromo-3-(Bromomethyl)Naphthalene from Naphthalene

Musa Erdoğan*¹

Abstract

Herein, a new efficient method for the synthesis of 2-bromo-3-(bromomethyl)naphthalene is reported. The synthesis is based on (1) preparation of 1,4-dihydronaphthalene via Birch reduction with mild conditions from the reaction of naphthalene, and (2) the reaction between 1,4-dihydronaphthalene and dichlorocarbene formed *in situ* from chloroform and potassium *tert*-butoxide (*t*-BuOK), and (3) access to the key intermediate 1*H*-cyclopropa[*b*]naphthalene from the reaction of 1,1-dichloro-1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene with *t*-BuOK, followed by ring-opening of the cyclopropane via bromination with molecular bromine (Br₂). This synthetic sequence allows simple preparation of 2-bromo-3-(bromomethyl)naphthalene in higher yields compared to the two previously reported syntheses. The synthetic approach is modular, low cost, and rapid, and can be utilized to synthesize building blocks of naphthalene derivatives.

Keywords: Metal-free synthesis, Easy synthesis, Naphthalene, Naphthocyclopropane, 2-Bromo-3-(bromomethyl)naphthalene

1. INTRODUCTION

Naphthalene and its derivatives are some of the most functional polycyclic aromatic compounds (PAHs) made up of a large number of aromatic rings [1]. Due to its excellent physicochemical and spectroscopic properties, naphthalene scaffolds found application in various fields of scientific chemistry fields, such as synthetic, materials, medicinal, structural, macromolecular,

supramolecular, and fluorescence chemistry; and as backbones or functional devices [1-5]. They have found widespread use as sensors and a marker chromophore unit in biological systems. [6]. Additionally, these materials are an important chemical building block in materials science, as their load-bearing properties and stability make them unique in the fields of organic optoelectronics. [7]. It is also very important that halogenated naphthalene derivatives are synthesized by efficient means. The halogenated naphthalenes are important synthetic derivatives

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because the existence of a halogen affords an opportunity for further derivatization. They have established agents for a variety of bond-forming reactions and also serve as a key starting material for synthetic chemistry. The high utility of halogenated organic scaffold has led to the improvement of numerous transformations that place the carbon-halogen motif [8]. Naphthalene derivative **4** has significant synthetic potential, and has been used as a key building block or starting material for the synthesis of the important skeletons such as complex molecules [9], benzolactams with various Pd-catalyzed coupling reactions [10], functionalized chalcogen isochromene-fused chalcogenophene derivatives

[11], hydroacenes [12], pharmaceuticals and bioactive products [13], chiral polyaryl cyclophanes [14], and fluorescent π -expanded oxepins [15]. These are just a few examples of their reported synthetic application. In 1986, Smith and his research group reported for the first time the synthesis of 2-bromo-3-(bromomethyl)naphthalene (**4**) [16]. For this, 2-bromo-3-methylnaphthalene (**3**) was synthesized by bromination of the commercially available cyclopentadiene derivate **5** adduct of 2-methylnaphthalene (**6**) (Figure 1) [16]. In the next step, the synthesis of the product **4** was obtained via radical bromination with NBS of the product **3**.

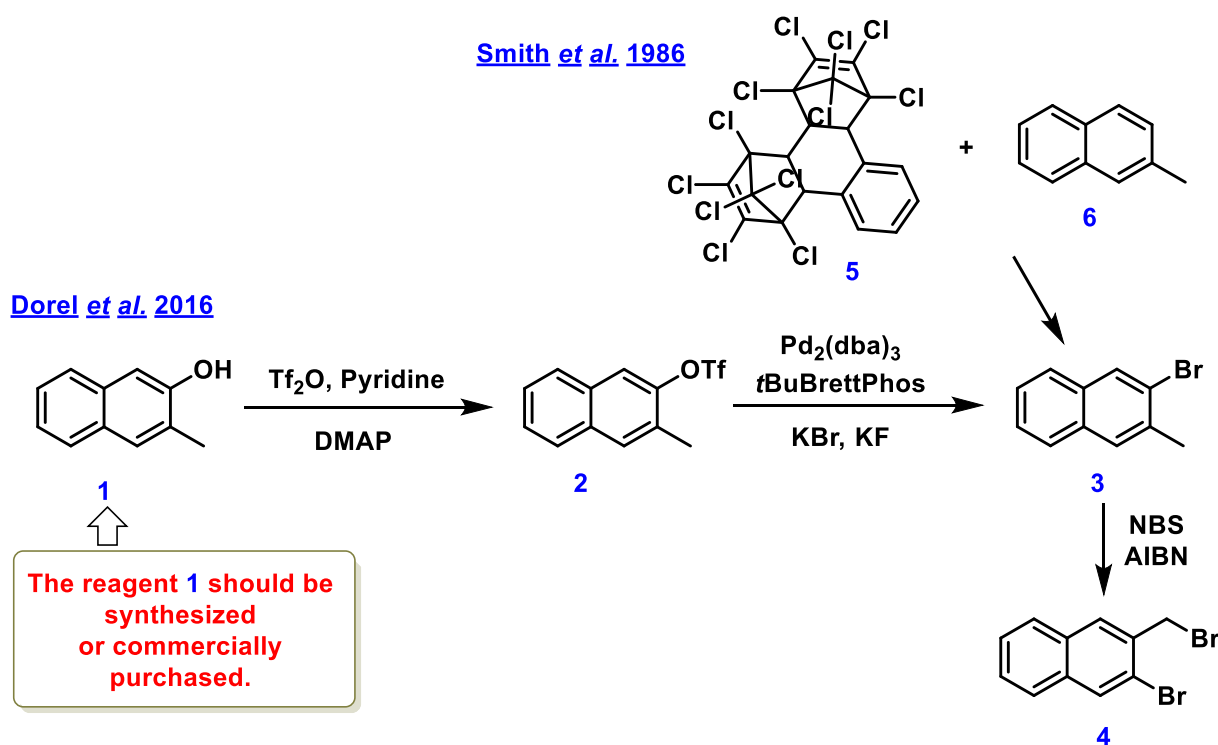


Figure 1 Reported synthesis methods of naphthalene derivative **4**

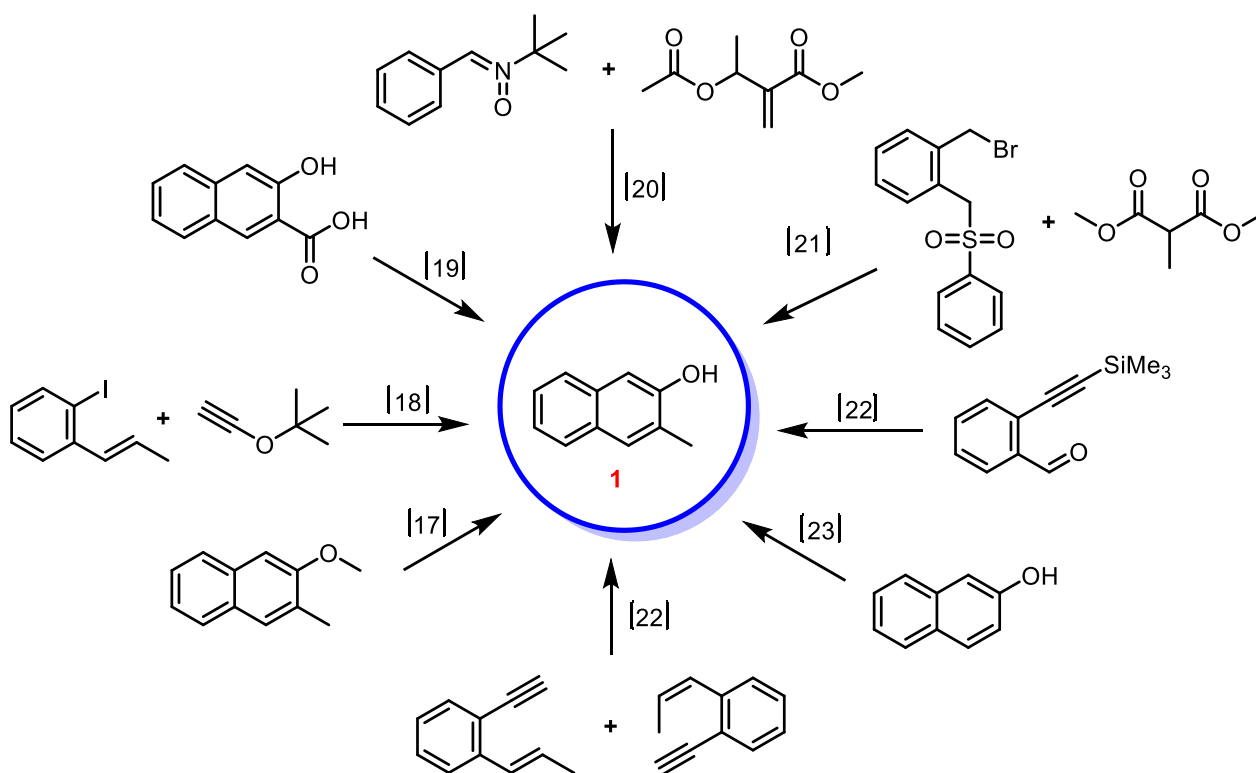


Figure 2 Some reported approaches for preparing 3-methylnaphthalen-2-ol (1)

In 2016, Dorel and co-workers reported the synthesis of 2-bromo-3-(bromomethyl)naphthalene (4) in three steps (Figure 1) [12]. According to Dorel's approach, starting material 3-methylnaphthalen-2-ol (1) should be purchased commercially or obtained by the synthetic methods given in Figure 2 [17-23]. The development of impressive synthetic approaches to obtaining substituted naphthalene and anthracene remains an attractive goal in organic chemistry. To the best of our knowledge, other than these two methods [12,16], no other synthesis method of naphthalene derivative 4 has been reported. These approaches several have certain handicaps including harsh reaction conditions, low reaction yield, and the necessity of using excess and expensive catalysts and ligands. Therefore, it is important to develop new method metal-free and an inexpensive methods. Herein, an useful transition metal-free and inexpensive method for the preparation of naphthalene derivative 4 starting from naphthalene (1) has been developed, and reported.

2. MATERIALS AND METHODS

2.1. Materials

The reactions were accomplished under N₂ gas atmosphere and followed by thin-layer chromatography (TLC). All reagents were used as purchased and used without further purification unless otherwise stated. Column chromatography was achieved with silica gel (60 mesh, Merck) or on neutral alumina. TLC was carried out on silica gel 60 HF254 aluminum plates (Fluka). The ¹H and ¹³C NMR spectra were recorded on a Varian-400 or a Bruker-400 spectrometer in CDCl₃ using TMS as the internal reference. All spectra were measured at 25 °C and coupling constants (*J* values) are given in Hz. Chemical shifts are given in parts per million (ppm).

2.2. Experimental procedure

2.2.1. Synthesis

Dihydronaphthalene **8** [31], the product **9** [29], and the product **10** [30] were synthesized according to a previously reported method. The spectral data are identical with those reported in the literature.

1,4-Dihydronaphthalene (8): ^1H NMR (400 MHz, CDCl_3) δ 7.33-6.96 (m, 4H), 5.92-5.87 (m, 2H), 3.39-3.35 (m, 4H).

1,1-Dichloro-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene (9): ^1H NMR (400 MHz, CDCl_3) δ 7.10 (s, 4H), 3.22 (ddd, $J = 17.0, 5.4, 2.7$ Hz, 2H), 2.80 (d, $J = 17.0$ Hz, 2H), 2.14-1.97 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 133.77, 128.50, 126.12, 66.27, 27.25, 24.77.

1H-cyclopropa[b]naphthalene (10): ^1H NMR (400 MHz, CDCl_3) δ 7.93-7.86 (m, 2H), 7.53-7.41 (s, 2H), 7.46 (m, 2H), 3.53 (s, 2H).

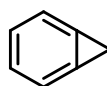
2.2.2. Synthesis of 2-bromo-3-(bromomethyl)naphthalene (**4**)

To a stirred solution of 1H-cyclopropa[b]naphthalene (**10**) (0.25 g, 1.78 mmol) in dry CCl_4 (15 mL) under N_2 atmosphere was added dropwise Br_2 (0.314 g, 0.10 mL, 1.96 mmol) in the CCl_4 (10 mL). The reaction mixture was refluxed for 1 h, and then cooled to rt. After evaporation of the solvent, the solid product was recrystallized from CH_2Cl_2 to give the 2-bromo-3-(bromomethyl)naphthalene (**4**) as white crystals. Yield 0.52 g (97%). The spectroscopic data were consistent with those previously reported [12].

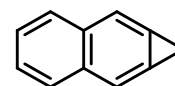
2-Bromo-3-(bromomethyl)naphthalene (4): ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.95 (s, 1H), 7.84-7.77 (m, 1H), 7.776-7.67 (m, 1H), 7.59-7.42 (m, 2H), 4.78 (s, 2H).

3. RESULTS AND DISCUSSION

The chemistry of benzocyclopropenes dates back to ancient times [24]. Nowadays, the science of chemistry owes its development and finding different applications to these ancient synthetic approaches. However, synthetic chemistry has begun to give way to applied chemistry, and interest in compounds with high synthetic potential has decreased. Naphthocyclopropenes's chemistry is interesting chemistry for synthetic applications and may be useful in the synthesis of crucial skeletons to applied chemistry [25,26]. There are a limited number of studies on benzo- or naphthocyclopropenes and its derivatives in the literature [25-27].



Benzocyclopropene



Naphthocyclopropene

Figure 3 The chemical structure of benzocyclopropenes and naphthocyclopropene

The easy cleavage of the three-member benzocyclopropene ring by electrophiles such as bromine, iodine, HCl , and AgNO_3 in the presence of ethanol and aniline previously reported, is of interest both in mechanism and synthesis [26].

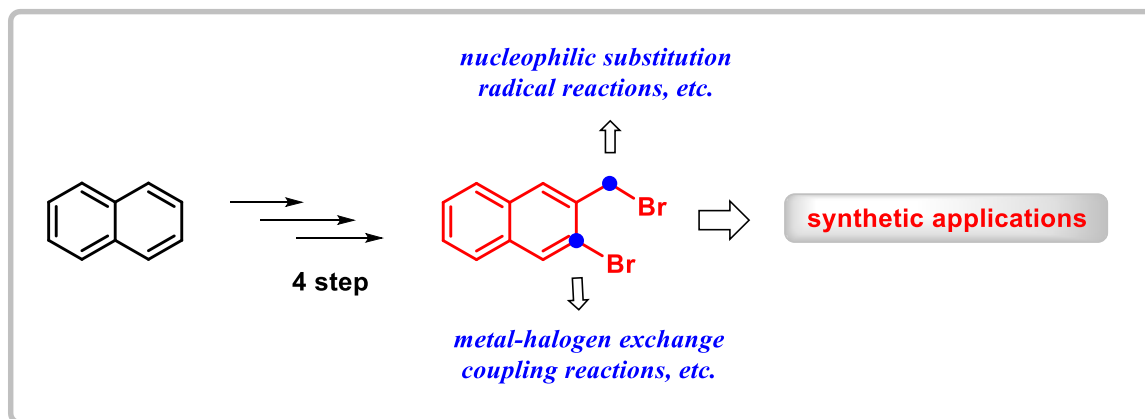


Figure 4 General reactivity of 2-bromo-3-(bromomethyl)naphthalene (**4**)

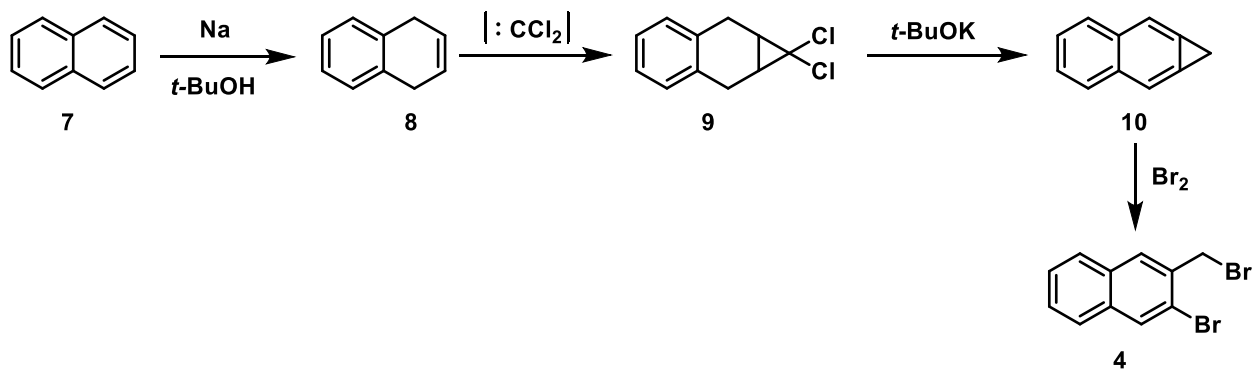


Figure 5 Four-step efficient synthesis of 2-bromo-3-(bromomethyl)naphthalene (4)

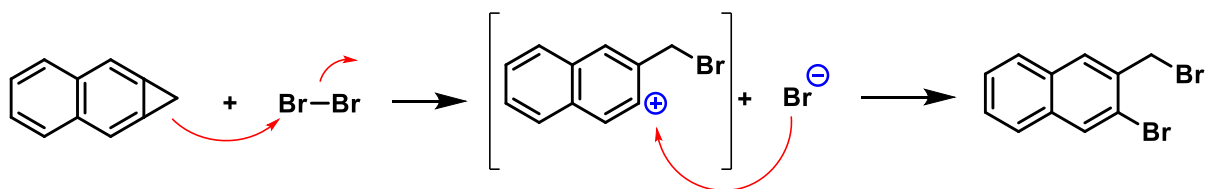
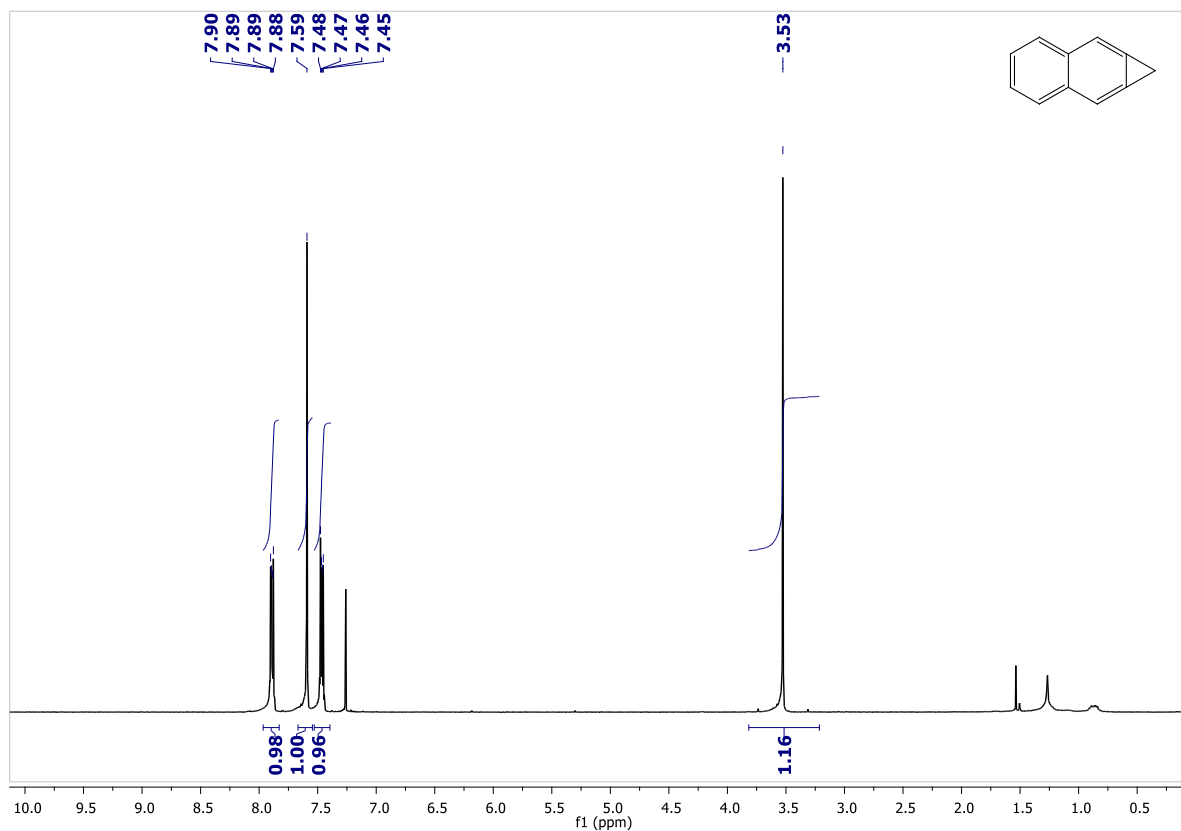


Figure 6 A plausible mechanism for the synthesis of naphthalene derivative 4



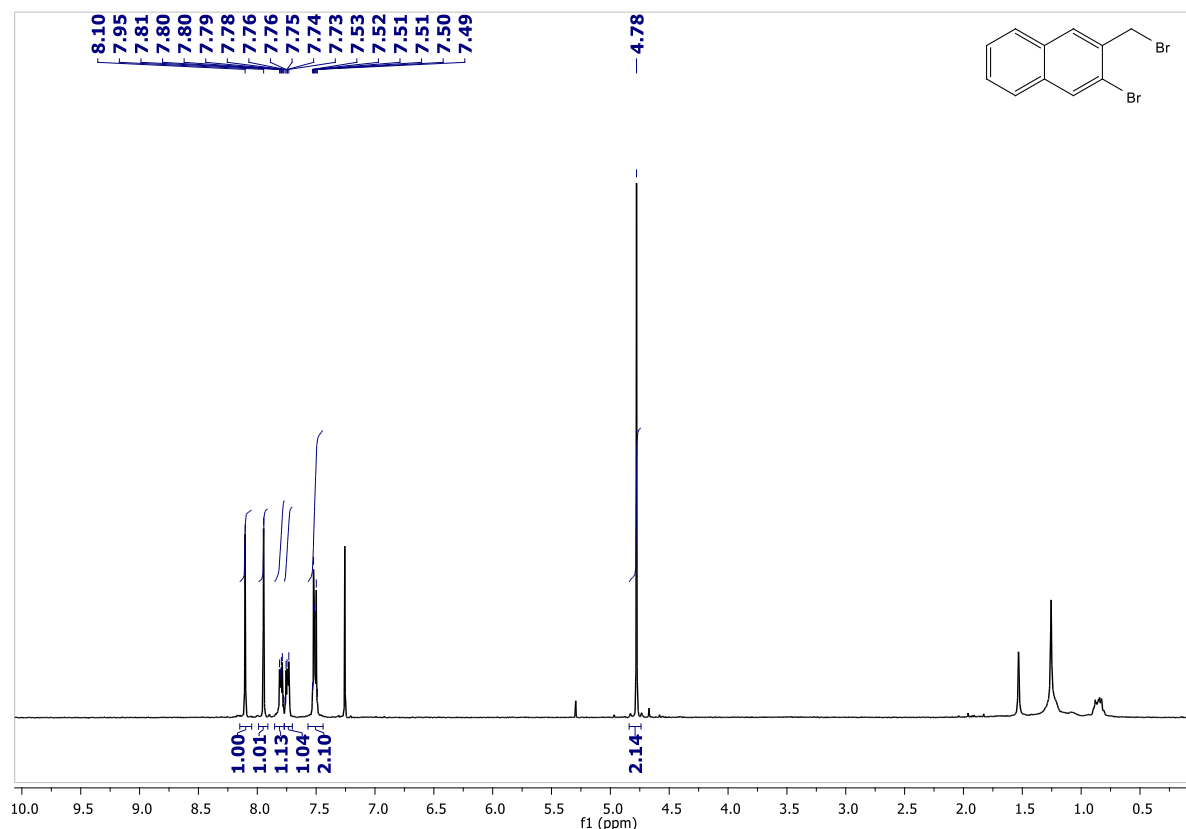


Figure 7 $^1\text{H-NMR}$ (400 MHz, CDCl_3) spectrum of **4**

However, presumable and selective activation and derivatization of naphthalene derivative **4** can be achieved under different conditions. This fact gives naphthalene derivative **4**, which contains the carbon-halogen bond (C-X), important tasks in synthetic organic chemistry. The naphthalene scaffold **4** has particularly significant potential for coupling and substitution reactions (Figure 4).

In the current study an easy, economical, four-step protocol for synthesis of the product **4** is announced (Figure 5). Firstly, 1,4-dihydronaphthalene (**8**) was obtained via Birch reduction with mild conditions starting from naphthalene which is selectively reduced from the 1,4 positions, according to a method previously reported in the literature [28]. In the next step, the reaction between 1,4-dihydronaphthalene (**8**) and dichlorocarbene which generated *in situ* from CHCl_3 and *t*-BuOK gave the previously reported the dichlorocyclopropane derivate **9** [29]. Then, treatment of the dichlorocyclopropane derivate **9** with *t*-BuOK gave the naphthocyclopropene **10** [29]. The naphthocyclopropene **10** became the starting material that allowed us to prepare 2-

bromo-3-(bromomethyl)naphthalene (**4**) with ring-opening of the three-membered cyclopropane by bromination. The product **4** was obtained by treatment with Br_2 under refluxing dry CCl_4 for 1 h in excellent yield (97%) (Figure 5). Figure 6 shows the possible reaction mechanism for synthesis of the product **4**.

This synthetic approach allows simple preparation of the product **4** in higher yields compared to the two previously reported syntheses [12,16]. Consequently, the preparation of 2-bromo-3-(bromomethyl)naphthalene (**4**) by the method described herein is experimentally easy and effective. The simplicity, rapidity, and low cost of this procedure make it useful for the synthetic organic chemistry community. The chemical structures of synthesized compounds in this study were determined only by NMR analysis since there are previously reported compounds. (Figure 7). The spectroscopic data were consistent with those previously reported (see experimental section).

4. CONCLUSION

As a result of an economical and practical point of view, an efficient and easy-to-handle metal-free procedure was developed using inexpensive starting material such as naphthalene. The aimed product was synthesized in four steps with high yields. A synthetic sequence to the 2-bromo-3-(bromomethyl)naphthalene core has been developed, which could be approved for the synthesis of variously substituted naphthalene derivatives with this skeleton. The synthesis represents a new approach to the 2-bromo-3-(bromomethyl)naphthalene nucleus and particularly presented an approach for the easy preparation of differently substituted naphthalene derivatives.

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The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the author.

Authors' Contribution

ME: This paper is a single-author study. Everything was done by the author. The Declaration of Ethics Committee Approval

The author declares that this document does not require an ethics committee approval or any special permission.

The Declaration of Research and Publication Ethics

The author of the paper declares that they comply with the scientific, ethical and quotation rules of SAUJS in all processes of the paper and that they do not make any falsification on the data collected. In addition, they declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

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