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Solvent-Free Multigram Synthesis Using Camphor Derivatives as Versatile Building Blocks in Drug Discovery

Síntese multi-grama sem solvente utilizando derivados de cânfora como blocos de construção versáteis na descoberta de fármacos

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ABSTRACT

This paper describes a multigram-scale synthesis for the preparation of the new building blocks, *N*-allyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-imine and (*E*)-1,7,7-trimethyl-N-(prop-2-yn-1-yl)bicyclo[2.2.1] heptan-2-imine, by using a solvent-free methodology utilizing Camphor nitroimine derivative as starting material. These new building blocks were evaluated against leishmaniasis disease *in vitro* in the preliminary tests. These new building blocks can also be a critical intermediate useful to prepare various substances with biological interest in drug discovery through chemical transformations, given that Camphor has a privileged structure with applications in medicinal chemistry.

Keywords: Camphor, Multigram Synthesis, Building Block, Drug Discovery.

RESUMO

Este artigo descreve a síntese de novos blocos de construção em escala multigramas, N-alil-1,7,7-trimetilbiciclo[2.2.1]heptan-2-imina e (E)-1,7,7-trimetil-N-(prop-2-in-1-il)biciclo[2.2.1]heptan-2-imina, utilizando-se de uma metodologia sem solvente e com nitroiminas derivadas da Cânfora como material de partida. Estes novos blocos de construção tiveram sua atividade contra a doença de leishmania testada *in vitro* em testes preliminares. Estes novos blocos de construção também podem ser intermediários úteis para a preparação de diveras substâncias com atividade biológica de interesse na descoberta de novos fármacos através de transformações químicas, uma vez que a Cânfora possui uma estrutura provilegiada com diversas aplicações em química medicinal.

Palavras-chave: Cânfora; Síntese Multigrama; Blocos de construção; Descoberta de Fármacos.

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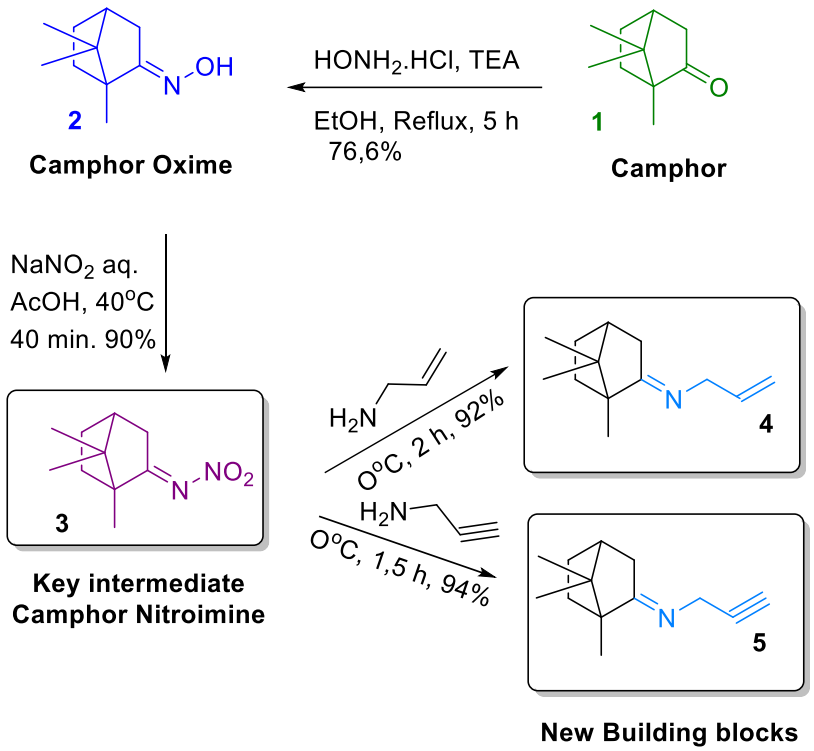
INTRODUCTION

The concept of building blocks is widely applied in various areas, including organic chemistry (Ripenko, 2021), biocatalysis (Dolan, 2023), pharmaceutical industry (Demchuk, 2023), and in special medicinal chemistry (Grygorenko, 2021). It is described in the literature as a synthetic molecular fragment employed for obtaining congeners with simple or complex architectures (Shokova, 2016).

Camphor (**1**), an abundant natural product, and its derivatives have interesting biological properties such as antiseptic, analgesic, repellent, and antimicrobial properties (da Silva, 2022). However, the ketone group in the camphor structure is considered to be less reactive. To solve this problem, a strategy to obtain new camphor derivative compounds is to introduce the nitroimine function into the camphor molecule as a leaving group (da Silva, 2020).

The camphor nitroimine, *N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene) nitramide **3** was produced in large scale by our research group as described in the **Scheme 1** in two steps, and it was used to make several camphor derivatives. Based on our previous studies we, in this work, used this intermediate to produce, on a large scale, two new building blocks that will be used for the synthesis of several new camphor derivatives that will be employed in our drug discovery program for Leishmaniosis. In past studies our group developed derivatives from camphor with activities against Leishmaniasis (da Silva, 2019). The new building blocks 4 and 5 were also evaluated against Leishmaniasis with IC_{50} preliminary activities of 100 µM and 94.95 µM, respectively.

Scheme 1: Multigram-scale synthesis of new building blocks



In this work, we developed new building blocks with alkene and alkyne from the key intermediate camphor nitroimine. The functionalization will subsequently allow access to a variety of products of biological interest after suitable chemical transformations.

RESULTS AND DISCUSSION

Initially, we carried out the large-scale synthesis of camphor nitroimine in 2 steps according to the methodology developed by our group (**Scheme 1**) (Da Silva, 2022) describe the first synthesis of two new building blocks (**Scheme 1**), using the key intermediate camphor nitroimine as the starting material. Its functionalization was carried out through nucleophilic attacks using allylamine and propargylamine as nucleophiles, using the nitro group as the leaving group. Aiming for a green chemistry approach, which adheres to a principle that aims to decrease the reliance on solvents and by-products, the applied methodology was conducted solvent-free, making it suitable for industrial-scale applications involving large-scale production. Compound **4** was obtained easily from camphor nitroimine in 92% yield upon treatment with 3 equiv. of allylamine after 2 hours of reaction. The structure of the compound was confirmed through ^{1}H and ^{13}C NMR, with a double triplet of doublets observed in the δ 5.97 ppm region, confirming the formation of the double bond and the carbon of imine in δ 183.55 ppm region. Compound **5** was obtained in 94% yield using 2 equiv. of propargylamine after 1,5 hours of reaction and was confirmed by ^{1}H and ^{13}C NMR. We observed a singlet with an integration of 2 hydrogens in the region of δ 3.99 ppm, confirming the presence of the terminal alkyne function in the molecule.

EXPERIMENTAL SECTION

Materials and Methods

NMR spectra were determined using 400 or 500 MHz Bruker AC spectrometers using tetramethylsylane as standard internal. Splitting patterns are as follows: s, singlet; d, duplet; t, triplet; quin, quintet; m, multiplet; Brl, broad signal. Infrared spectra were obtained using a Thermo Nicolet 6700 spectrometer. Mass spectra were recorded on Agilent 122 5532 GC/MS column by electron impact and high-resolution spectra on Bruker compact-Tof. The progress of the reactions was monitored by thin-layer chromatography (TLC) on 2.0cm X 6.0 cm aluminum sheets (silica gel 60, HF-254, Merck) with a thickness of 0.25 mm, and ultraviolet light irradiation was used for visualization.

Procedure

N-allyl-1,7,7-trimethylbicyclo [2.2.1] heptan-2-imine (4). In an ice bath a 125 mL round-bottom flask was charged with 50 g (0.255 mol) of nitroimine (**3**). After a few minutes stirring 33 mL of allylamine was added dropwise over 18 minutes using a 125 mL pressure-equalizing addition funnel under vigorous stirring. After 2 hours, TLC indicated the total consumption of the starting material. It was then concentrated on reduced pressure to remove the volatiles. Water (30 mL) was added and extracted with ethyl acetate (3 X 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, the solvent was removed under reduced pressure leaving the pure product as an oil with a yield of 92 %. RMN ^{1}H ($CDCl_3$, ppm): δ 5.97 (dtd, J = 15.8, 10.6, 5.5 Hz, 1H, $CH=CH_2$), 5.17 – 5.02 (m, 2H $CH=CH_2$), 3.89 (qd, J = 15.1, 5.4 Hz, 2H $C=N-CH_2$), 2.39 – 2.29 (m, 1H $CHCH_aCH_bC=N$), 1.94 (t, J = 4.4 Hz, 1H CH), 1.90 – 1.76 (m, 2H), 1.71 – 1.63 (m, 1H $CH2-CH_aCH_b$), 1.42 – 1.33 (m, 1H $CH_2CH_aCH_b$), 1.27 – 1.14 (m, 1H $CHCH_aCH_bCH_2$), 0.99 (s, 3H CH_3), 0.93 (s, 3H CH_3), 0.75 (s, 3H CH_3).

RMN ^{13}C ($CDCl_3$, ppm): C=N 183.55, 136.01, 114.74, 54.69, 53.79, 47.11, 43.84, 35.40, 32.20, 27.45, 19.57, 19.00, 11.43

(E)-1,7,7-trimethyl-N-(prop-2-yn-1-yl)bicyclo[2.2.1]heptan-2-imine (**5**). In an ice bath a 100 mL round-bottom flask was charged with 10,001 g (0.050 mol) of nitroimine (**3**). After a few minutes stirring 4,9 mL of propargylamine was added dropwise over 10 minutes using a 25 mL pressure-equalizing addition funnel under vigorous stirring. After 1 hour, TLC indicated the total consumption of the starting material. It was then concentrated on reduced pressure to remove the volatiles. Water (20 mL) was added and extracted with ethyl acetate (3 X 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered, the solvent was removed under reduced pressure leaving the pure product as an oil with a yield of 94%. RMN ^{1}H ($CDCl_3$, ppm): δ 3.99 (s, 2H), 2.47 – 2.39 (m, 1H $CHCH_aCH_bC=N$), 2.20 (t, J = 2.6 Hz, 1H), 1.97 (t, J = 4.5 Hz, 1H, CH), 1.93 – 1.81 (m, 2H), 1.68 (td, J = 12.4, 4.1 Hz, 1H $CH_2-CH_aCH_b$), 1.43 – 1.33 (m, 1H $CH_2CH_aCH_b$), 1.26 – 1.18 (m, 1H $CHCH_aCH_bCH_2$), 1.00 (s, 3H CH_3), 0.93 (s, 3H CH_3), 0.76 (s, 3H CH_3).

RMN ^{13}C ($CDCl_3$, ppm): C=N δ 186.74, 81.31, 70.55, 54.09, 47.54, 43.85, 40.78, 35.56, 31.80, 27.38, 19.49, 18.99, 11.24.

CONCLUSION

The new building blocks *N*-allyl-1,7,7-trimethylbicyclo [2.2.1] heptan-2-imine (**4**) and (*E*)-1,7,7-trimethyl-*N*-(prop-2-yn-1-yl)bicyclo[2.2.1]heptan-2-imine (**5**) were efficiently obtained in a solvent-free reaction on a multigram scale with respective yields of 92% and 94%. The main highlights in this methodology are its simplicity, safety, not using solvents, and that the reagents are commercially available with perspectives to be optimized for industrial scale. The building blocks will be used in our drug discovery program for Leishmaniasis, and additionally, compounds **4** and **5** were also evaluated against Leishmaniasis, showing IC_{50} preliminary activities of 100 µM and 94.95 µM, respectively. From these intermediates, it will be possible to obtain various compounds with biological interest through chemical transformations, given that camphor has a privileged structure with applications in medicinal chemistry.

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