SYNTHESIS OF N-ALKYLATED AZABENZIMIDAZOLES, THE BASE CATALYZED ISOMERIZATION OF N-PROPAGYL-ALLENYL AZABENZIMIDAZOLE AND THEIR CHARACTERIZATION

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(Received: 20th March, 2020; Accepted: 21st May, 2020)

ABSTRACT

N-Allyl, N-pentyl, N-propiophenone, N-benzyl, N-p-nitrobenzyl, N-3,4-dichlorobenzyl and N-propargyl-substituted 7-azabenzimidazoles were prepared through a convenient method. Under basic condition, the N-propargyl substituted azabenzimidazole isomerized to its N-alleny1 substituted isomer. It is believed that the N-alleny1 isolated can serve as a vital precursor for the future preparation of medicinally bioactive cycloaddition derivatives of azabenzimidazole.

Key words: Azabenzimidazoles, N-Alkylation, Propargyl, Allene, Isomerization.

INTRODUCTION

Azabenzimidazoles are privilege scaffolds that have proven to be important cores in scores of reported novel chemotypes which are inhibitors of certain enzymes and active against infectious diseases (Stavenger et al., 2007; Hameed et al., 2014; Johannes et al., 2014; Ansell et al., 2014; Barsanti et al., 2015; Lapierre et al., 2016). Allene is an important precursors for the synthesis of numerous bioactive natural products. Alkoxyallene derived from propargylic ether had been demonstrated to possess a triple reactivity character because the α-hydrogen can be abstracted with ease by bases; the β-carbon atom of allene can undergo enol-ether reactivity while its γ-carbon site is activated towards attack by nucleophiles. Brasholz and co-workers have given accounts of numerous compounds prepared from lithiated alkoxyallene. Examples of such compounds synthesized from lithiated alkoxyallene are 2,6-deoxysugars, benannulated spiroketal, (-)-detoxinine and (-)-preussin (Brasholz et al., 2009). Under thermal condition, allenes undergo various pericyclic cycloaddition reactions and substituted pyroles have also been thermally prepared from aminoallene (Pham and Houk, 2014; Reisser and Maas, 2004; Esplenlaub et al., 2007).

This communication narrates how the N-alkylation of 7-aza-5-bromoazabenzimidazole with alkyl synthons such as allyl, pentyl, propiophenone, benzyl, p-nitrobenzyl, and the 3,4-dichlorobenzyl groups, respectively, resulted in successful isolation of azabenzimidazole derivatives (six examples) as the only products while on propargylation, an unexpected allene isomer was isolated along with the expected propargyl derivative – together, this forms the subject of discussion in this short communication.

EXPERIMENTAL

All chemicals were used as purchased from Sigma-Aldrich Chemical Co. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel plates (Ethyl acetate/Hexane as mobile phase). NMR spectra were recorded on Bruker 300 and 400 MHz NMR spectrometers, chemical shifts were calibrated relative to the residual proton signal in chloroform (δ̄H 7.26 ppm) and the NMR spectra were analysed using Mestrenova Software. Infrared spectroscopy experiments were run directly and the IR Spectra were recorded on a Perkin-Elmer ATR Sampling accessory Spectrum 100 FT-IR spectrometer with a diamond window and with wavenumber in the region of 650-4000 cm⁻¹. Melting points were determined using a hot-stage apparatus and are uncorrected. Molecular formulae were confirmed by HPLC-MS analysis using a Bruker Daltronics compact QTOF MS instrument with an

1Readers are advised to please contact the author for a supporting document to this paper.
electrospray ionization probe in the positive mode.

**Synthesis of 1- Allyl-5-bromo-7- azabenzimidazole 7a**

A mixture of 5-bromo-7-azabenzimidazole 6 (200 mg, 1 mmol) and caesium carbonate (651.6 mg, 2 mmol) in 10 ml of 1-methylpyrrolidinone (NMP) was stirred at room temperature for 15 minutes. To the solution was added allyl bromide (0.1 ml, 1 mmol). The resulting mixture was stirred vigorously at room temperature for 45 minutes while the progress of the reaction was monitored by thin layer chromatography. At the completion of the reaction, the organic crude product was extracted into ethyl acetate (2 × 70 ml). The combined organic phase was thoroughly washed with deionized water (4 × 140 ml), dried with anhydrous sodium sulphate and filtered. The solvent was removed in vacuo to afford a brown oil (228.6 mg, 96%); δ\textsubscript{NMR}/ppm (400 MHz; CDCl\textsubscript{3}) 8.42 (1H, d, J = 2.0 Hz, Ar-H), 8.19 (1H, d, J = 2.0 Hz, Ar-H), 8.04 (1H, s, Ar-H), 6.04 (1H, ddd, J = 16.6, 10.5, 5.7 Hz, C-CH=C), 5.30 (1H, d, J = 10.5 Hz, C-CH=C=CH\textsubscript{2}), 5.20 (1H, d, J = 17.6 Hz, C-C=CH\textsubscript{2}), and 4.87 (2H, d, J = 5.7 Hz, CH\textsubscript{2}); \textalpha\textsubscript{NMR}/ppm (100 MHz; CDCl\textsubscript{3}) 154.4, 145.5, 145.1, 136.5, 131.8 (Ar-C), 130.5 (C-CH=C), 119.2 (Ar-C), 114.1 (C=CH\textsubscript{2}) and 45.9 (CH\textsubscript{2}); ESI HPLC-MS: m/z calcd for C\textsubscript{13}H\textsubscript{13}BrN\textsubscript{3} (M+H\textsuperscript{+}) 237.0992, found 237.2171.

**Synthesis of 5-Bromo-1-pentyl-7- azabenzimidazole 7b**

The procedure described for the synthesis of 7a was used by stirring 5-bromo-7-azabenzimidazole 6 (300 mg, 1.5 mmol), caesium carbonate (488.7 mg, 1.5 mmol) and 1-bromopentane (0.2 ml, 1.5 mmol) in NMP (15 ml). The crude product was purified (column chromatography; elution with ethyl acetate – hexane 2:1) to yield 5-bromo-1-pentyl-7-azabenzimidazole 7b as a white solid (224.8 mg, 47%); m.p. 116-118 °C; δ\textsubscript{NMR}/ppm (400 MHz; CDCl\textsubscript{3}) 8.46 (1H, d, J = 1.7 Hz, Ar-H), 8.25 (1H, s, Ar-H), 8.14 (1H, d, J = 1.7 Hz, Ar-H), 7.88 (1H, d, J = 7.5 Hz, Ar-H), 7.53 (1H, t, J = 7.4 Hz, Ar-H), 7.41 (2H, t, J = 7.7 Hz, Ar-H), 4.72 (2H, t, J = 6.0 Hz, N-CH\textsubscript{2}), 3.62 and (2H, t, J = 6.0 Hz, COCH\textsubscript{2}); \textalpha\textsubscript{NMR}/ppm (100 MHz; CDCl\textsubscript{3}) 197.0 (C=O), 146.7, 145.6, 144.9, 136.7, 136.1, 133.8, 130.4, 128.8, 128.1, 114 (Ar-C), 38.8 (N-CH\textsubscript{2}), and 37.8 (CO-CH\textsubscript{2}); ESI HPLC-MS: m/z calcd for C\textsubscript{17}H\textsubscript{17}BrN\textsubscript{3}O (M+H\textsuperscript{+}) 330.0242, found 330.0089.

**Synthesis of 1-Benzyl-5-bromo-7- azabenzimidazole 7d**

The procedure described for the synthesis of 7a was used by stirring 5-bromo-7-azabenzimidazole 6 (200 mg, 1 mmol), caesium carbonate (488.7 mg, 1.5 mmol) and benzyl bromide (0.12 ml, 1 mmol) in NMP (15 ml). The crude product was purified (column chromatography; elution with ethyl acetate – hexane 2:1) to yield 1-benzyl-5-bromo-7-azabenzimidazole 7d as a white solid (228.6 mg, 47%); m.p. 116-118 °C; δ\textsubscript{NMR}/ppm (400 MHz; CDCl\textsubscript{3}) 8.44 (1H, d, J = 2.0 Hz, Ar-H), 8.21 (1H, d, J = 2.0 Hz, Ar-H), 8.02 (1H, s, Ar-H), 7.37 – 7.27 (5H, m, Ar-H) and 5.43 (2H, s, CH\textsubscript{2}); \textalpha\textsubscript{NMR}/ppm (100 MHz; CDCl\textsubscript{3}) 154.8, 145.4, 145.15, 136.5, 135.5, 130.5, 129.2, 128.6, 127.9, 114.2 (Ar-C) and 47.4 (CH\textsubscript{2}); ESI HPLC-MS: m/z calcd for C\textsubscript{18}H\textsubscript{18}BrN\textsubscript{3}O (M+H\textsuperscript{+}) 288.0058, found 287.9923.

**Synthesis of 5-Bromo-1-(4-nitrobenzyl)-7- azabenzimidazole 7e**
The procedure described for the synthesis of 7a was used by stirring 5-bromo-7-azabenzimidazole 6 (200 mg, 1 mmol), caesium carbonate (488.7 mg, 1.5 mmol) and 4-nitrobenzyl bromide (216.0 mg, 1 mmol) in NMP (20 ml). The crude product was purified (column chromatography; elution with ethyl acetate – hexane 2:1) to yield 5-bromo-1-(4-nitrobenzyl)-7-azabenzimidazole 7e as a brown solid (236.5 mg, 71%); m.p. 150-152 °C; δH/ppm (400 MHz; CDCl3) 8.47 (1H, d, J = 1.9 Hz, Ar-H), 8.26 (1H, s, Ar-H), 8.25 (1H, d, J = 1.8 Hz, Ar-H), 8.19 (2H, d, J = 8.6 Hz, Ar-H), 7.46 (2H, d, J = 8.6 Hz, Ar-H) and 5.58 (2H, s, CH2); δC/ppm (100 MHz; CDCl3) 145.7, 145.6, 144.8, 136.5, 130.7, 128.6, 124.4, 114.9 (Ar-C) and 46.8 (CH2); ESI HPLC-MS: m/z calc for C13H13BrN3O2 (M+H)+ 356.9106, found 356.9103.

Synthesis of 5-bromo-1-(5,4-dichlorobenzyl)-7-azabenzimidazole 7f. The procedure described for the synthesis of 7a was used by stirring 5-bromo-7-azabenzimidazole 6 (200 mg, 1 mmol), caesium carbonate (488.7 mg, 1.5 mmol) and 3,4-dichlorobenzylchloride (0.14 ml, 1 mmol) in NMP (20 ml). The crude product was purified (column chromatography; elution with ethyl acetate – hexane 2:1) to yield 5-bromo-1-(3,4-dichlorobenzyl)-7-azabenzimidazole 7f as a white solid (274.9 mg, 77%); m.p. 128-130 °C; δH/ppm (400 MHz; CDCl3) 8.46 (1H, d, J = 1.2 Hz, Ar-H), 8.23 (1H, d, J = 1.2 Hz, Ar-H), 8.05 (1H, s, Ar-H), 7.40 (2H, d, J = 8.6 Hz, Ar-H), 7.12 (1H, dd, J = 8.2, 1.5 Hz, Ar-H) and 5.39 (2H, s, CH2); δC/ppm (100 MHz; CDCl3) 145.7), 145.6, 144.8, 136.5, 135.7, 133.4, 132., 131.2, 130.8, 129.8, 127.1, 114.5 (Ar-C) and 46.3 (CH2); ESI HPLC-MS: m/z calc for C14H12BrClN3 (M+H)+ 332.9987, found 332.9985.

Synthesis of 5-bromo-1-(1-alkenyl)-7-azabenzimidazole 8. The procedure described for the synthesis of 7a was used by stirring 5-bromo-7-azabenzimidazole 6 (257.4 mg, 1.3 mmol), caesium carbonate (488.7 mg, 1.5 mmol) and propargyl bromide (0.1 ml, 1.3 mmol) in NMP (20 ml). The crude product was purified (column chromatography; elution with ethyl acetate – hexane 2:1) to yield 5-bromo-1-(1-alkenyl)-7-azabenzimidazole 8 as a white solid (236.9 mg, 77%); m.p. 112-114 °C; δH/ppm (400 MHz; CDCl3) 8.47 (1H, d, J = 1.9 Hz, Ar-H), 8.22 (1H, d, J = 1.9 Hz, Ar-H), 8.20 (1H, s, Ar-H), 7.42 (1H, t, J = 6.6 Hz, C=CH2), 5.71 (2H, d, J = 6.6 Hz, CH2); δC/ppm (100 MHz; CDCl3) 145.7, 145.6, 144.8, 136.5, 135.7, 133.4, 132., 131.2, 130.8, 129.8, 127.1, 114.5 (Ar-C) and 46.3 (CH2); ESI HPLC-MS: m/z calc for C14H12BrC3N3 (M+2)+ 333.9987, found 333.9993.

Synthesis of 5-bromo-1-propargyl-7-azabenzimidazole 7g. The procedure described for the synthesis of 7a was used by stirring 5-bromo-7-azabenzimidazole 6 (257.4 mg, 1.3 mmol), caesium carbonate (488.7 mg, 1.5 mmol) and propargyl bromide (0.1 ml, 1.3 mmol) in NMP (20 ml). The crude product was purified (column chromatography; elution with ethyl acetate – hexane 2:1) to yield 5-bromo-1-propargyl-7-azabenzimidazole 7g as a white solid (202.5 mg, 66%); m.p. 102-104 °C; δH/ppm (300 MHz; CDCl3) 8.47 (1H, d, J = 2.0 Hz, Ar-H), 8.26 (1H, s, Ar-H), 8.22 (1H, d, J = 2.0 Hz, Ar-H), 5.05 (2H, d, J = 2.6 Hz, CH2) and 2.53 (1H, t, J = 2.6 Hz, C=CH); δC/ppm (75 MHz; CDCl3) 154.5, 144.34, 144.33, 136.5, 130.6 and 114.3 (Ar-C), 78.8 (N=CH2), 75.2 and 75.1 (C=CH and C=CH); ESI HPLC-MS: m/z calc for C16H15BrN3 (M+2)+ 326.9745, found 326.9598.

RESULTS AND DISCUSSION

Chemistry

A series of N-alkylated 5-bromo-7-azabenzimidazole derivatives 7a-f were prepared as highlighted in Scheme 1 - a nucleophilic substitution reaction which required the use of caesium carbonate to abstract the NH proton from azabenzimidazole 6 in order to generate a nucleophilic centre followed by the introduction of the electrophile. The reaction proceeded to completion at room temperature within 30-60 minutes and the desired derivatives 7a-f were isolated in good yields. NMR experiments were
The propargylation of 5-bromo-7-azabenzimidazole for 60 minutes led to the isolation of an unexpected by-product 8 (28%) in addition to the expected propargyl substituted azabenzimidazole 7g (66%). Repeated reaction with a reduced reaction time (40 minutes) yielded 15% of 8 and 52% of 7g. On allowing the reaction mixture to stir for 90 minutes, 44% and 54% of 8 and 7g were isolated respectively.

It is known that bases have the ability to trigger propargyl-allenyl isomerization (Zhao et al., 2013; Lim et al., 2014; Navarro-Vazquez, 2015), this therefore suggested that the unexpected isolate 8 was the 1-substituted allenyl 5-bromo-7-azabenzimidazole 8. In order to affirm this, little amount of the isolated compound 7g was treated with 1.5 equivalent of caesium carbonate and aqueous sodium hydroxide successively, compound 8 was isolated in each case with excellent yield.

The two isolated products were characterized by NMR experiments and spectra analysis indicated that the second eluent was the expected 1-substituted propargyl azabenzimidazole 7g. As seen in Figure 1, the propargyl methine proton 10-H is represented by a triplet signal at 2.53 ppm (upfield as expected due to its diamagnetic anisotropy) while the 8-methylene protons are represented by the signal at 5.05 ppm (more deshielded when compared to 10-H). These two protons couple to one another as clearly seen in the COSY spectrum with a coupling constant of 2.6 Hz (Figures 1 and 2).

\[ \text{Scheme 1. Synthesis of } N\text{-alkylated 5-bromo-7-azabenzimidazoles 7a-g.} \]

\[ \text{Figure 1. } 400 \text{ MHz } ^1\text{H NMR spectrum of 7g in Chloroform-}d. \]
The proton NMR spectrum of 8 (C₆H₆BrN₃) shows a triplet signal at 7.42 ppm which couples to a doublet signal at 5.71 ppm (J = 6.6 Hz) [Figures 3 and 4] – this is unexpected because the methine protons of acetylenes are more shielded than methylene protons.

Figure 2. 400 MHz ¹H-¹H COSY NMR spectrum of 7g in CDCl₃.

Figure 3. 400 MHz ¹H NMR spectrum of 8 in Chloroform-d.
The methine protons in the two envisage isomers of 7g (compounds 9 and 10) in Figure 6 will also experience more shielding effect compared to the methylene group. Therefore, the triplet signal at 7.42 ppm is not an acetylenic proton signal. The NMR spectra data also cancelled out the possibility of having compounds 11 to 13 (Figure 5).

Figure 4. 400 MHz $^1\text{H}-^1\text{H}$ COSY NMR spectrum of 8 in Chloroform-$d$.

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CONCLUSION
In conclusion, an attempt to synthesis 1-alkylated 5-bromo-7-azabenzimidazoles have led the discovery of caesium carbonate, potassium carbonate and aqueous sodium hydroxide as bases that can catalyse the rearrangement of 1-substituted propargyl 5-bromo-7-azabenzimidazole 7g to its allenyl isomer 8 at room temperature. The allenyl analogue may be a useful precursor in future study to access various bioactive azabenzimidazole pericyclic adducts.

ACKNOWLEDGEMENT
The author is indebted to Dr. Rosalyn Klein and Prof. P. T. Kaye (Department of Chemistry, Rhodes University); the Tertiary Education Trust fund (TETFund) for a bursary; Adekunle Ajasin University, Akungba-Akoko, Nigeria for study leave and Rhodes University, Grahamstown South Africa.

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