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SYNTHESIS OF *N*-ALKYLATED AZABENZIMIDAZOLES, THE BASE CATALYZED ISOMERIZATION OF *N*-PROPAGYL-ALLENYL AZABENZIMIDAZOLE AND THEIR CHARACTERIZATION[1]

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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*-allenyl substituted isomer. It is believed that the *N*-allenyl 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 pyrroles have also been thermally prepared from aminoallene (Pham and Houk, 2014; Reisser and Maas, 2004; Espenlaub *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 (δ_H 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

[1]Readers 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*. The residue was purified using column chromatography on silica gel; elution with ethyl acetate-hexane (2 : 1) to afford 1-*allyl*-5-*bromo*-7-*azabenzimidazole* **7a** as a brown oil (228.6 mg, 96%); δ_H/ppm (400 MHz; $CDCl_3$) 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-C=CH_{trans}), 5.20 (1H, d, *J* = 17.6 Hz, C-C=CH_{cis}) and 4.87 (2H, d, *J* = 5.7 Hz, CH_2); ä$_C$/ppm (100 MHz; $CDCl_3$) 145.6, 145.3, 145.1, 136.5, 131.8 (Ar-C), 130.5 (C-*C*H=C), 119.2 (Ar-C), 114.1 (C=*C*H_2) and 45.9 (CH_2); ESI HPLC-MS: *m/z* calcd for $C_9H_8BrN_3$ $(M)^+$ 236.9902, 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, 1.7 mmol) in 10 ml of NMP. The crude product was purified (column chromatography; elution with ethyl acetate – hexane 1:1) to yield 5-*bromo*-1-*pentyl*-7-*azabenzimidazole* **7b** as a colourless oil (354.0 mg, 88%); δ_H/ppm (300 MHz; $CDCl_3$) 8.42 (1H, d, *J* = 2.0 Hz, Ar-H), 8.18 (1H, d, *J* = 2.0 Hz, Ar-H), 8.02 (1H, s, Ar-H), 4.24 (2H, t, *J* = 7.2 Hz, N-CH_2), 1.97 – 1.84 (2H, m, N-C-CH_2), 1.40 – 1.24 (4H, m, N-C-C-CH_2-CH_2) and 0.87 (3H, t, *J* = 6.9 Hz, CH_3); δ_H/ppm (75 MHz; $CDCl_3$) 145.8, 145.2, 145.1, 136.7, 130.3, 113.9 (Ar-C) 44.1, 29.7, 28.90, 22.2 (CH_2) and 14.0 (CH_3); ESI HPLC-MS: *m/z* calcd for $C_{11}H_{15}BrN_3$ $(M+H)^+$ 268.0449, found 268.0238.

Synthesis of *5*-Bromo-*1*-(phenyl propan-1-one)-*7*-azabenzimidazole 7c.

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-chloropropiophenone (168.6 mg, 1 mmol) in NMP (15 ml). The crude product was purified (column chromatography; elution with ethyl acetate – hexane 2:1) to yield 5-*bromo*-1-*(propiophenone)*-7-*azabenzimidazole* **7c** as a white solid (155.2 mg, 47%); m.p. 104-106 °C; δ_H/ppm (400 MHz; $CDCl_3$) 8.40 (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_2), 3.62 and (2H, t, *J* = 6.0 Hz, $COCH_2$). δ_C/ppm (100 MHz; $CDCl_3$) 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_2), and 37.8 (CO-CH_2); ESI HPLC-MS: *m/z* calcd for $C_{15}H_{13}BrN_3O$ $(M+H)^+$ 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 (224.8 mg, 78%); m.p. 116-118 °C; δ_H/ppm (400 MHz; $CDCl_3$) 8.46 (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_2); δ_C/ppm (100 MHz; $CDCl_3$) 145.8, 145.4, 145.15, 136.5, 135.5, 130.5, 129.2, 128.6, 127.9, 114.2 (Ar-C) and 47.4 (CH_2); ESI HPLC-MS: *m/z* calcd for $C_{13}H_{11}BrN_3$ $(M+H)^+$ 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 3:1) to yield 6-*bromo*-1-*(4-nitrobenzyl)*- 7-*azabenzimidazole* **7e** as a brown solid (236.5 mg, 71%); m.p. 150-152 °C; δ_H/ppm (400 MHz; $CDCl_3$) 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, CH_2); δ_C/ppm (100 MHz; $CDCl_3$) 148.1, 146.1, 145.4, 144.8, 142.5, 135.8, 130.7, 128.6, 124.4, 114.9 (Ar-C) and 46.8 (CH_2); ESI HPLC-MS: *m/z* calcd for $C_{13}H_{10}BrN_4O_2$ $(M+H)^+$ 332.9987, found 333.0035.

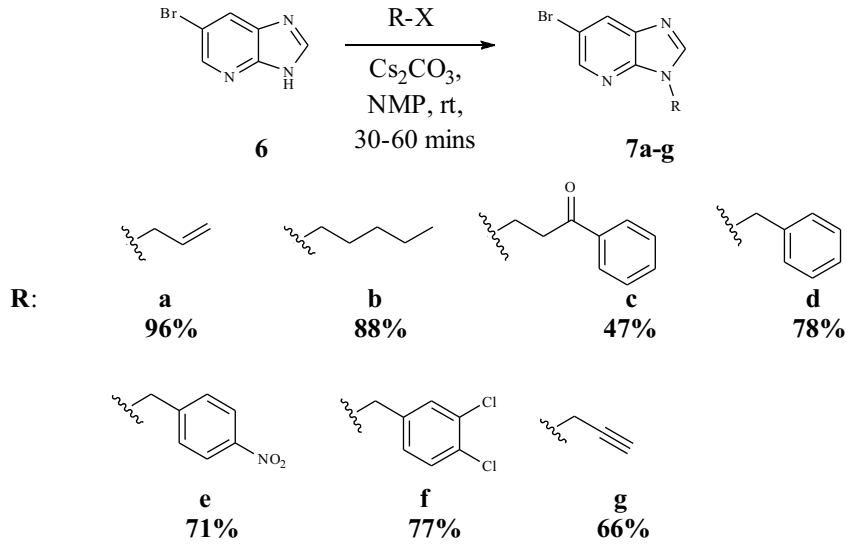
Synthesis of *5*-bromo-*1*-(*3,4*-dichlorobenzyl)-*7*-azabenzimidazole 7f.
The procedure described for the synthesis of **7a** was used by stirring *5*-bromo-*7*-azabenzimidazole **6** (200 mg, 1 mmol), caesium carbonate (488.7 mg, 1.5 mmol) and 3,4-dichlorobenzylchloride (0.14 ml, 1 mmol) in NMP (20 ml). The crude product was purified (column chromatography; elution with ethylacetate – 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; δ_H/ppm (400 MHz; $CDCl_3$) 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, CH_2); δ_C/ppm (100 MHz; $CDCl_3$) 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 (CH_2); ESI HPLC-MS: *m/z* calcd for $C_{13}H_9BrCl_2N_3$ $(M+2)^+$ 356.9279, found 356.9106.

Synthesis of *5*-bromo-*1*-propagyl-*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; δ_H/ppm (300 MHz; $CDCl_3$) 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, CH_2) and 2.53 (1H, t, *J* = 2.6 Hz, C≡*CH*); δ_C/ppm (75 MHz; $CDCl_3$) 145.4, 144.34, 144.33, 136.5, 130.6 and 114.3 (Ar-C), 78.8 (N-*C*H_2), 75.2 and 75.1 (*C*≡CH and C≡*C*H); ESI HPLC-MS: m/z calcd for $C_9H_7BrN_3$ $(M+2)^+$ 236.9745. Found 236.9598

Synthesis of *1*-allenyl-*5*-bromo-*7*-azabenzimidazole 8
5-bromo-*1*-propargyl-*7*-azabenzimidazole **7g** (23.6 mg, 0.1 mmol) was dissolved in dry dichloromethane (5 ml), anhydrous caesium carbonate or anhydrous potassium carbonate or aqueous sodium hydroxide (1.5 equivalent) was added and the mixture was stirred for 1 hour. Upon completion of the reaction as confirmed by TLC, the crude product was extracted three time into ethyl acetate. The combined organic extract was dried in anhydrous Na_2SO_4, concentrated and purified (column chromatography; elution with ethyl acetate – hexane 2:1) to afford *1*-allenyl-*5*-bromo-*7*-azabenzimidazole **8** as a white solid (17.9 mg, 76%); m.p. 112-114 °C; δ_H/ppm (400 MHz, $CDCl_3$) 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≡C*H*), 5.71 (2H, d, *J* = 6.6 Hz, CH_2); δ_C/ppm (100 MHz, $CDCl_3$) 202.8, 145.71, 143, 136.1, 130.8, 114.48 (ArC), 92.90 (C=*C*H_2), 88.98 (N-*C*H_2), 77.36 (*C*=CH_2); ESI HPLC-MS: *m/z* calcd for $C_9H_7BrN_3$ $(M+2)^+$ 236.9745, found 236.9601.

RESULTS AND DISCUSSION

Chemistry
A series of *N*-alkylated 5-bromo-7-azabenzimidaole 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



Scheme 1. Synthesis of *N*-alkylated *5*-bromo-*7*-azabenzimidazoles **7a-g**.

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 triger propargyl-allenyl isomerization (Zhao *et al*., 2013; Lim *et al*, 2014; Navarro-Vazqez, 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, potassium carbonate and aquous sodium hydroxide successively, compound **8** was isolated in each case with excellent yield.

The two isolated products were characterization 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).

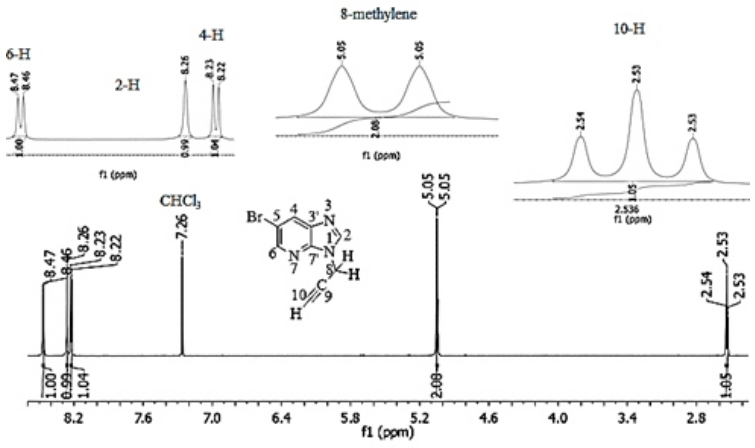


Figure 1. 400 MHz ^{1}H NMR spectrum of **7g** in Chloroform-*d*.

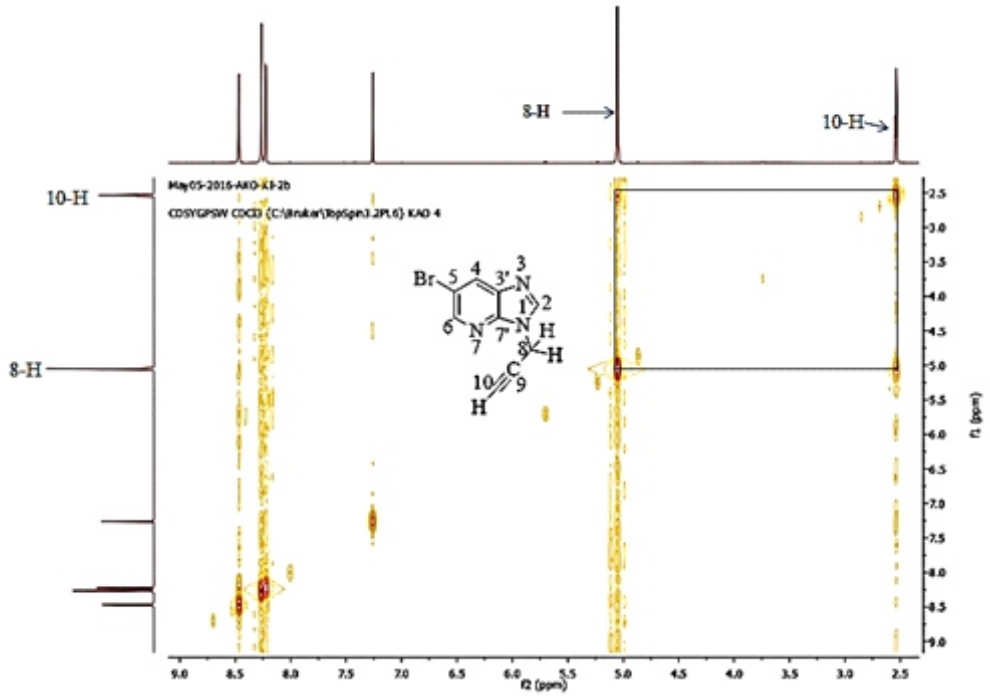


Figure 2. 400 MHz ^{1}H-^{1}H COSY NMR spectrum of **7g** in $CDCl_3$.

The proton NMR spectrum of **8** ($C_9H_6BrN_3$) 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.

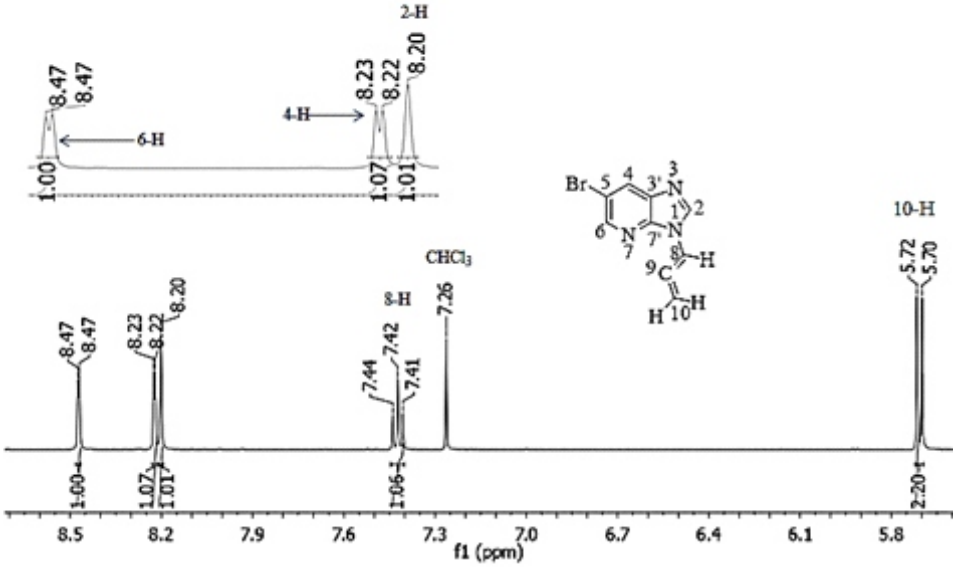


Figure 3. 400 MHz ^{1}H NMR spectrum of **8** in Chloroform-*d*.

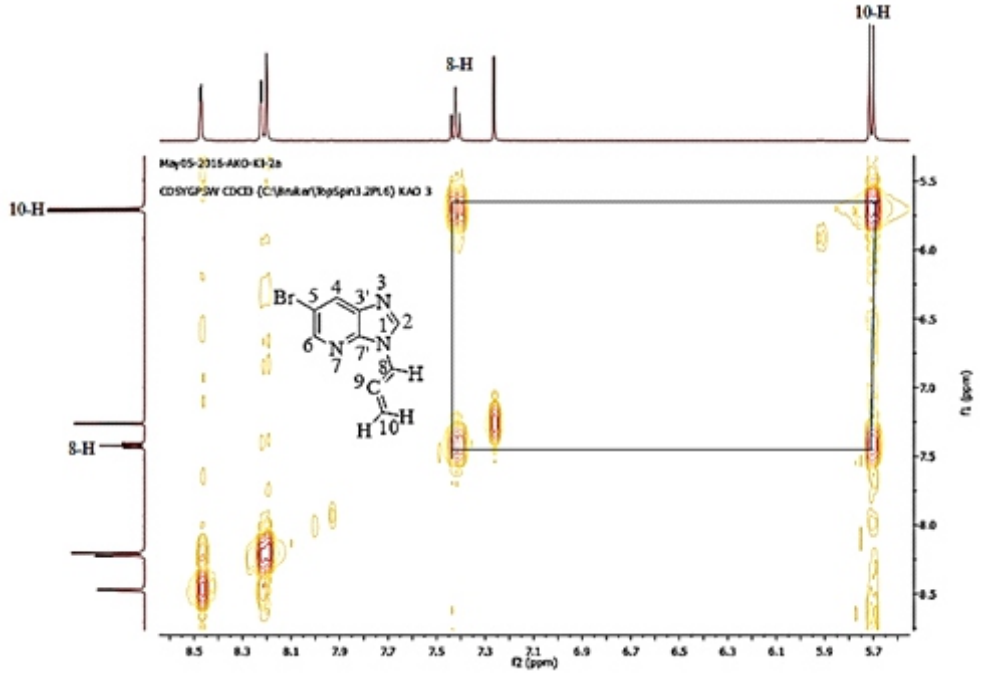


Figure 4. 400 MHz ^{1}H-^{1}H COSY NMR spectrum of **8** in Chloroform-*d*.

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).

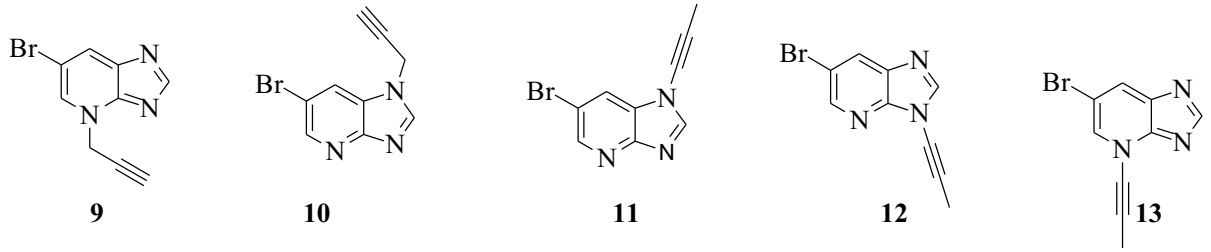


Figure 5. Other possible isomers of **7g**.

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.

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