MULTI-COMPONENT REACTION FACILITATES THE CONSTRUCTION OF MODULAR INDOLE ALKALOIDS.

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ABSTRACT

The indole alkaloids are a diverse class of natural chemicals with over 2000 members and a broad variety of therapeutic activities. Among the many indole alkaloids, the spirocyclic oxindole framework and enantiopure 3,3-disubstituted oxindole are recognised as valid heterocyclic motifs. Chiral 3,3-disubstituted- and spiro oxindole skeletons have drawn the interest of both synthetic and medicinal chemists since they are present in a wide range of bioactive naturally occurring chemicals and medications. The robust bioactivity profiles and structurally intriguing spiro architecture of these molecular skeletons motivated us to design new procedures for the enantiopure synthesis of spirooxindoles bearing natural products, drugs, and related analogues, as well as to create novel structural entities with promising biological activities. For many years, aziridine has been a powerful building block for the diversity-oriented synthesis of enantiopure amines and a number of N-heterocycles. Our group has achieved a notable breakthrough in the synthesis of chiral spiroaziridine oxindole, a new aziridine subgroup engaged at the C-3 position of oxindole. Since it already contains an oxindole unit, we believe that this spiroaziridine oxindole will be a powerful synthetic precursor for the synthesis of other spirooxindoles with azacycles and enantiopure oxindole amines. Therefore, ring-opening spiroaziridine oxindole at the C-3 stereocenter and ring-opening-cyclization with various nucleophiles would be a simple method to produce significant molecules for medicine as well as a large amount of oxindole and spiro-oxindole natural goods. This is an overview of our work on the reactivity of spiroaziridine oxindoles with respect to indole-based bioactive chemical production.

1 INTRODUCTION

Indole, also known as benzo pyrrole, is a heterocyclic aromatic molecule made up of a six-membered benzene ring fused to a five-membered pyrrole ring that contains nitrogen (Scheme 1.1). Indole is a crystalline solid with a planar structure and no colour. Indole has a melting point of 52 oC and is soluble in the majority of organic solvents. Adolf Baeyer made the discovery of indole. While researching the indigo plant's structure in 1866, Adolf Baeyer made the discovery of indole.1. Indigo 1 is a colouring agent that was isolated from the Indigofera species. Indigo, a deep blue dye, was first oxidised by Adolf Baeyer to produce isatin 2. Oxindole 3 was produced by reduction of isatin, while indole was produced by pyrolysis of oxindole (Scheme 1.1). The currently recognised indole formula and structure were proposed by Baeyer and Emmerling in 1869.

One of the most significant heterocyclic structures found in nature is the indole moiety. Coal tar is used to extract indole for commercial use. It is also undeniably successful to synthesise indole industrially from readily accessible starting ingredients like aniline, glycol,

ethylene, etc. The majority of indole derivatives that are marketed for sale are crystalline solids that are colourless and quite stable in air.

Production of indoles Chemists employ the Fischer indole synthesis extensively out of all the indole synthetic techniques. This technique was first devised by Hermann Emil Fischer, a German scientist.3. This method's basic idea is the acidic cyclization of aryl hydrazones 7 (Scheme 1.2). In this procedure, a variety of substituted indoles may be created at the expense of one ammonia molecule. A phenyl hydrazine 5 may be readily synthesised into the aryl hydrazones needed for this approach by condensation with either an aldehyde or a ketone. Ene-hydrazine, an isomer of aryl hydrazone, undergoes a sigmatropic rearrangement that is facilitated in this process by an acid catalyst. Additionally, the protonation of aryl hydrazone and the ene-hydrazine production process are aided by acid catalyst.4. 2-, 3-, and other variously substituted indoles in the benzene portion may be readily synthesised with the use of the Fischer indole synthesis procedure.

An alternate method for creating the aryl hydrazone derivatives needed for the

Fischer indole synthesis process is the Japp-Klingemann coupling. Using this technique, the aryl hydrazone derivatives 7 are obtained by combining aryl diazonium salts 8 with β-ketoester or β-ketoacid 9 (Scheme 1.3).

Chemists have recently made various modifications to the conventional Fischer indole synthesis procedure. Using a titanium amine catalyst, they hydroaminated an alkyne with 1,1-disubstituted hydrazines to create the aryl hydrazone derivatives. Next, in the presence of a catalyst, aryl hydrazone derivatives are transformed into the corresponding indole (Scheme 1.4).

By using palladium catalyst to cross-couple aryl bromide and benzophenone hydrazine, Buchwald-Hartwig was able to synthesise N-arylbenzo phenol nehy drazones. The equivalent indole is produced via the hydrolysis of ketone in a single pot reaction with N-arylbenzo phenone hydrazones. This technique does not need the separation of the intermediate N-aryl benzophenone hydrazones (Scheme 1.5).

Sulphur substituted indole may be synthesised with the use of the Gassman indole synthesis process. Using tert-butyl hypochlorite, aniline is treated to create chloroamine 13a, which then combines with β-carbonyl sulphide derivative to make anilinosulfonium salt 13b. By forming ylide 13c, the addition of tert-ethyl amine activates the anilinosulfonium salt. Ultimately, the ylide undergoes [2,3]-sigmatropic rearrangement to form ketone 13d. This is then followed by ketone condensation, which yields the appropriate sulfur-substituted indoles (Scheme 1.6). For the synthesis of 7-substituted indoles, bartoli indole synthesis is crucial. This approach makes use of vinyl Grignard reagents and osubstituted nitrobenzenes (Scheme 1.7). The reaction fails when dealing with derivatives of nitrobenzene that are m- or p-substituted. To strengthen the [3,3]-sigmatropic shift and create the appropriate indole, bulky groups at o-position are required. For the synthesis of substituted indole on the pyrrole and benzene rings, Bartoli indole synthesis is very helpful.Scheme 1.7 Bartoli indole synthesis Reissert indole synthesis involves the use of a base catalyst to create an indole derivative from o-nitrotoluene and diethyl oxalate. O-nitrotoluene and diethyl oxalate react with KOEt to form potassium salt of o-nitrophenylpyruvate (Scheme 1.8). This potassium salt is then reductively

cyclized to produce an amino ketone, which is then transformed into indole-2-carboxylates. Different catalytic conditions may be utilised in this reductive cyclization process, including Pt/AcOH, 10 SnCl2-TiCl3 11, and Pd-C/EtOH.

Indoles that have been replaced with benzene may be synthesised using the Leimgruber-Batcho method. This technique yields o-nitro-β-pyrrolidino styrene by condensing o-nitrotoluene with N,N-dimethylformamide dimethyl acetate in pyrrolidine 21. Next, in the presence of Raney nickel, o-nitro-β-pyrrolidinostyrene provides the benzene substituted indole (Scheme 1.9). Only the benzene substituted indoles are produced using this approach. For the synthesis of 2,3-disubstituted indoles, the Larock indole synthesis is very efficient. 2,3-disubstituted indole is produced by treating the unsymmetrical alkyne with o-iodoaniline under Pdcatalytic conditions (Scheme 1.10).

2 LITREATURE SURVEY

Interesting biological activity are possessed by heterocyclic molecules containing a nitrogen atom. One of the most significant structural motifs found in many natural compounds, including aristotelone, brevianamide A, strobili anthoside A, and duocarmycin A, is indolin-3-one. It has a wide range of uses in the pharmaceutical industry. Furthermore, indolin-3-one has outstanding use as a building block for the synthesis of other heterocycles, alkaloids, and other physiologically active chemicals. Isatisine A 1, a 2,2-disubstituted indolin-3-one, is found in Isatisindigotica Fort's leaves and roots and is used to treat viral illnesses such hepatitis, mumps, pneumonia, and influenza. Thus, because of indolin-3-one's abundance in bioactive natural chemicals and remarkable biological features, research on the substance has gained significant attention.

One of the key instruments for the synthesis of different organic compounds is the dehydromatization process. Dearomatization of stable aromatic molecules yields a large number of organic compounds with a broad range of uses in synthetic, medical, and pharmaceutical chemistry, among other fields. The technique of dearomatization is a potent and affordable way to build complex compounds. Dearomatization of stable aromatic compounds is a major area of interest for chemists since it produces

very reactive intermediates that are then used to build carbon-carbon and carbon-heteroatom bonds. Dearomatization of indoles, pyrroles155, phenols, pyridines, etc., has been extensively explored in the last several decades in order to get a variety of bioactive natural chemicals and alkaloids. Among them, the creation of the quaternary carbon centre in indoles by dearomatization was the subject of the greatest research, using a variety of regio-, chemo-, and enantioselective techniques. A few techniques to dearomatize indole rings to indolin-3- ones have recently been revealed by researchers. Li and colleagues documented the oxidative dearomatization/spirocyclization of indole-2-carboxamides 3 with tert-butyl hydroperoxide acting as an oxidant and Cu acting as a catalyst. At 60 oC in DCE, they produced C2-spiro-pseudoindoxyls 4 with a moderate to excellent yield (Scheme 2.1).

Another example of deraromatization of indole 5 for the synthesis of trisindolones 6 in the presence of visible-light photocatalysis was shown by the Lee group (Scheme 2.2). This response is an example of a benign response to the environment. No additional catalyst is required for the photoreaction of indole when it is facilitated by water. Compact fluorescent lights from the home may also be used as a visible light source for the response.

Using TBHP and a Pd catalyst, Guchhait et al. created a cascade electrophilic indolylation process. Peroxygenation and a Kornblum- DeLaMare- type reaction are involved in this process, which results in a reactive 3H-indol-3-one motif 6 (Scheme 2.3). They use a chemo- and regioselective technique that works with a variety of substrates.

Some significant disadvantages of these techniques, meanwhile, include the need for metal catalysts, lengthy reaction times, heated conditions, and potentially dangerous solvents. Moreover, laccase catalyst was used, but it produced a comparatively poor yield and required more time under pressure.159 As a result, organic chemists find that dearomatization of indole under moderate conditions is crucial and in high demand. Iodine's use in organic synthesis has garnered a lot of interest because of its accessibility, affordability, low toxicity, easy handling, and moderate reactivity. As such, a plethora of innovative synthetic techniques for forming carbon-carbon and carbon-

heteroatom bonds have been created via the use of iodine as a catalyst. 160 Conversely, the creation of C-C bonds is among the most essential reactions in organic synthesis; in recent years, there has been a significant advancement in the development of cross dehydrogenative coupling (CDC) reactions, which are potent C-C bond generating methods.

Here, we report the room-temperature synthesis of 2,2-disubstituted indolin-3-ones without the use of metals or solvents. The novel catalytic system, iodine-TBHP-cyclohexanone, uses TBHP as the oxygen source (Scheme 2.4).

Optimising reaction conditions to synthesise indolin3-ones: We began by analysing the reaction of 1H-indole (5a) with stoichiometric TBHP (1.0 equiv.) as an oxidant and catalytic I2 (10 mol%) in standard solvents. Nevertheless, regardless of whether the reactions were conducted at room temperature or under heating, the reaction did not react in any of the instances. We intended to employ cyclopentanone as the reaction's solvent after carefully reading the article by Klussman et al., which covered the synergistic impact of ketone and

hydroperoxide in the presence of Brønsted acid. As anticipated, the reaction produced a 77% yield of the trimeric product 6a at room temperature, and we were able to acquire excellent results. A superior result with 80% of 6a was obtained when cyclohexanone was used as the solvent. The yield of 6a was unaffected by further reducing the cyclohexanone in the process up to the catalytic level (10 mol%).

This finding led us to conclude that the cyclohexanone supported the catalyst in the process rather than acting as a solvent. Conversely, acetone was only able to yield 12% of 6a, while benzophenone and acetophenone were unable to produce any of the product at all (entry 9–11, Table 2.1). Next, we carried out the reaction using the TBHP reduced equivalent, and we were able to determine that 0.7 equiv. as opposed to stoichiometric TBHP, in this instance the reaction did not even create minor impurity, yielding the highest yield of 6a (87%). As a result, we determined that the ideal conditions for this reaction were I2 (10 mol%), cyclohexanone (10 mol%), and TBHP (0.7 equiv.) (entry 14, Table 2.1). A reduced yield of 6a was seen when H2O2 was used in lieu of TBHP, whereas DTBP produced no
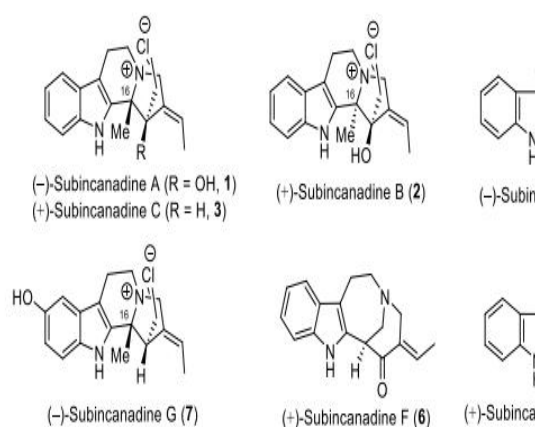
product at all (entries 12–13, Table 2.1). Only 63% of the yield was achieved when the reaction was tested at 80 ºC (entry 16, Table 2.1). Furthermore, the product could not be obtained by substituting I2 with other Lewis/ Brønsted acid catalysts (entry 17–19, Table 2.1). The product was not obtained when KI was used in place of I2 (entry 20, Table 2.1).

Unless otherwise noted, 5a (1.5 mmol, 176 mg) in 2 mL of solvent at room temperature was used in all processes. Column chromatography was used to purify the products, and the yields listed are for the isolated compounds. [b] Cyclohexanone (10 mol%) was used. Benzoic acid is known as BA. [d] The reaction was conducted in an oil bath at 80 ºC. After determining the ideal reaction conditions, we looked into the range of substrates. Scheme 2.5 summarises the optimised conditions for the reaction involving a range of indoles. We are happy that several replacements at the indole's nitrogen atom and on its aromatic ring were all consistent with the reaction. We found that the reaction either yielded no yield at all or a decreased yield when the indole nucleus included electron-withdrawing compounds. For instance, the former produced 17% when 5-nitroindole or 7-

azaindole were treated under the ideal reaction conditions.

3 METHODOLOGY

There are two parts in this chapter. The first part describes the entire synthesis of (±)/(+)-subincanadine E and how the enantioselective first synthesis led to the identification of its absolute configuration. The azabicyclodecane architecture and its use in the enantioselective synthesis of (+)-subincanadine F are discussed in the second part along with the regioselective and stereoselective reductive aziridinium ring cleavage that results in it. Each section has been adequately concluded with references, some chosen NMR spectra, fully tabulated analytical and spectral data, and thorough experimental protocols. From the bark of the Brazilian medicinal plant Aspidosperma subincanum mart, subincanadines A–G (1–7) were isolated in 0.002% yield; among these, (+)-subincanadines E (5) and F (6) carry distinct 1-azabicyclo[5.2.2]undecane and 1-azabicyclo[4.3.1] decane moieties.

(−)-Subincanadine A (R = OH, **1**)
(+)-Subincanadine C (R = H, **3**)

(+)-Subincanadine B (**2**)

(−)-Subin

(−)-Subincanadine G (**7**)

(+)-Subincanadine F (**6**)

(+)-Subinca

correspondingly. From the perspective of biological activity, (+)-subincanadine E (5) shows the strongest cytotoxicity against human epidermoid carcinoma KB cells (IC50, 4.4 μg/mL) and murine lymphoma L1210 cells (IC50, 2.40 μg/mL), as well as (+)-subincanadine F (6), which also shows strong cytotoxicity against these two types of cells in vitro (IC50, 4.80 μg/mL). Due of their restricted availability from natural sources, these compounds' intriguing biological activity and intriguing molecular structures have drawn quick attention and turned them into synthetic targets.

In 2014, Bennasar et al. reported a synthetic approach to the bridged indole alkaloid subincanadine E framework, based on the combination of ring-closing metathesis (RCM) and Heck cyclization. Based on this approach, Zai and

coworkers successfully synthesised the first total synthesis of (±)-subincanadine E in 2015.2a Please refer to chapter 1; scheme 4 and page no. 9 for details. The ring closure on the strained 1-azabicyclo[5.2.2]undecane framework of the subincanadine E by using the corresponding vinyl halide Heck coupling was systematically pursued after the construction of the tricyclic nine-membered central ring via RCM-based route, but sadly it was unsuccessful (please see chapter 1; scheme 5 and page no. 10). Subincanadine E, also known as pericine, was first isolated from Picralima nitida by Stöckigt and colleagues in 1982.3 More recently, Kam and colleagues have proposed that the (S)-subincanadine E is a common biogenetic precursor of five structurally unprecedented monoter penoid indole alkaloids: valparicine (8), apparicine (9), 4 arboridinine (10), 5a (+)-arborisidine (11) and (−)-arbornamine

4 RESULTS

Hexahydro-3H-indolizino(8,7-b)indol-3-one (31) is represented by 11b-Allyl-1,2,5,6,11,11b. A solution of allylmagnesium chloride in THF (2 M, 1.37 mL, 2.75 mmol) was added dropwise in an argon environment to a

stirred solution of compound 13 (300 mg, 1.25 mmol) in dry THF (10 mL). After 1.5 hours of stirring at the same temperature, the reaction mixture was allowed to cool to 0 degrees Celsius for a further 1.5 hours. At 0 °C, saturated aqueous NH4Cl solution was used to quench the process. The reaction mixture was vacuum-concentrated, and the resultant residue was dissolved in 50 millilitres of EtOAc. After being cleaned with brine and water, the organic layer was dried over Na2SO4. Lactamol 30 was produced by concentrating the organic layer in a vacuum, and it was immediately used in the next stage. Two N HCl (0.30 mL) was added to a stirred solution of lactamol 30 in THF (10 mL) at 0 °C. The reaction mixture was then agitated for five hours to enable it to reach 25 °C. At 0°C, saturated aqueous NaHCO3 was used to quench the reaction, and 3 × 15 mL of EtOAc was used to extract the reaction mixture. After being mixed, the organic layer was brine-washed and dried.

beyond Na2SO4. Compound (±)-31 was produced as a yellow solid (280 mg, 85%) by purifying the residue obtained from the concentration of the organic layer in vacuo and purifying it again using column chromatography (silica gel,

60–120 mesh, PE–EtOAc, 50:50). Mp 191−193 °C; 1H NMR (CDCl3, 400 MHz) δ 2.70–2.96 (m, 4H), 3.32 (dt, J = 12.5 and 5.5 Hz, 1H), 4.62 (dd, J = 13.4 and 6.1 Hz, 1H), 5.15 (d, J = 13.4 Hz, 1H), 5.19 (d, J = 6.1 Hz, 1H), 5.68 (sext, J = 6.7 Hz, 1H), 6.21 (d, J = 6.1 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.35 (t, J = 5.5 Hz, 1H), 7.36 (d, J = 6.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H); 13C NMR (CDCl3, 100 MHz) δ 21.8, 35.9, 41.9, 67.0, 107.9, 111.1, 118.8, 119.8, 119.9, 122.4, 126.5, 126.8, 131.0, 132.9, 136.3, 150.1, 171.6; ESIMS (m/z) 265 [M+H] + ; HRMS (ESI) calcd for C17H17N2O 265.1335, found 265.1337; IR (CHCl3) vmax 3459, 1678 cm-1 .

5-allylidenepyrrolidin-2-one (E)-1-[2-(1H-Indol-3-yl)ethyl] (34). A dropwise mode solution of allylmagnesium chloride in THF (2 M, 2.10 mL, 4.20 mmol) was added to a stirred solution of compound 32 (500 mg, 2.10 mmol) in dry THF (15 mL) under argon atmosphere. The reaction mixture was allowed to reach 0 °C for the following 1.5 hours after being agitated for 1.5 hours at the same temperature. Saturated aqueous NH4Cl solution was used to quench the process. The reaction mixture was vacuum-concentrated, and

the resultant residue was dissolved in 50 millilitres of EtOAc. After being cleaned with brine and water, the organic layer was dried over Na2SO4. Lactamol 33 was produced by the concentration of organic layer in vacuo and was used immediately for the next stage. After adding 2 N HCl (0.50 mL) at 0 °C to a stirred solution of lactamol 33 in THF (12 mL), the reaction mixture was agitated for 20 minutes.
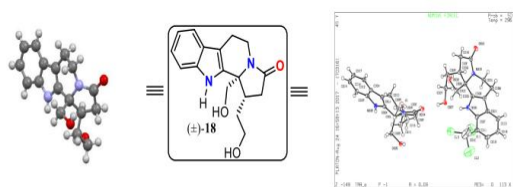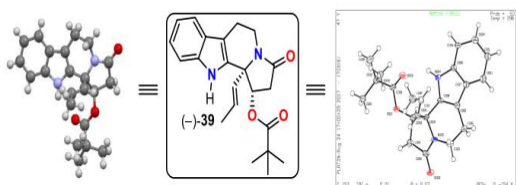

Figure 3. X-ray crystal structures of compound (±)-18.

At 0°C, saturated aqueous NaHCO3 was used to quench the reaction, and 3 × 20 mL of EtOAc was used to extract the aqueous layer. After being mixed, the organic layer was brine-washed and then dried over Na2SO4. Compound 34 was produced as a white solid (428 mg, 78%), by first concentrating the organic layer in vacuo and then purifying the residue using column chromatography (silica gel, 60–120 mesh, PE–EtOAc,

50:50). Mp 105−107 °C; 1H NMR (CDCl3, 200 MHz) δ 2.40–2.60 (m, 2H), 2.70–2.90 (m, 2H), 3.04 (t, J = 8.2 Hz, 2H), 3.83 (t, J = 7.7 Hz, 2H), 4.98 (d, J = 10.2 Hz, 1H), 5.08 (d, J = 16.8 Hz, 1H), 5.60 (d, J = 11.0 Hz, 1H), 6.30–6.55 (m, 1H), 7.08 (d, J = 2.2 Hz, 1H), 7.05–7.30 (m, 2H), 7.36 (d, J = 7.1 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 8.23 (s, 1H); 13C NMR (CDCl3, 50 MHz) δ 21.7, 22.5, 28.6, 40.7, 102.6, 111.2, 112.5, 112.8, 118.5, 119.4, 121.96, 122.00, 127.4, 131.6, 136.2, 142.5, 175.7; ESIMS (m/z) 289 [M+Na]+ ; HRMS (ESI) calcd for C17H18N2ONa 289.1311, found 289.1314; IR (CHCl3) vmax 3423, 1681, 1601 cm−1 .

(E)-11b-hexahydro-3H-indolizino(8,7-b)indol-3-one-1,2,5,6,11,11b-(Prop-1-en-1-yl) (35). 2 N HCl (0.50 mL) was added to a stirred solution of compound 34 (400 mg, 1.50 mmol) in THF (10 mL) at 0 °C. The reaction mixture was then agitated for three hours to enable it to reach 25 °C. At 0°C, saturated aqueous NaHCO3 was used to quench the reaction, and 3 × 20 mL of EtOAc was used to extract the reaction mixture. After being mixed, the organic layer was brine-washed and then dried over Na2SO4. Compound 35 was produced as a white solid (328 mg, 82%), after the

organic layer was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 40:60). Mp 177−179 °C; 1H NMR (CDCl3, 500 MHz) δ 1.70 (d, J = 6.8 Hz, 3H), 2.25 (q, J = 10.9 Hz, 1H), 2.39–2.51 (m, 2H), 2.69 (td, J =17.4 and 9.5 Hz, 1H), 5.80 (dd, J = 15.4 and 5.2 Hz, 1H), 2.85–2.94 (m, 1H), 3.09 (dt, J = 16.9 and 5.5 Hz, 1H), 4.44 (dd, J = 13.1 and 6.1 Hz, 1H), 5.42 (qd, J = 15.4 and 6.4 Hz, 1H), 5.70 (d, J = 15.3 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 8.63 (s, 1H); 13C NMR (CDCl3, 125 MHz) δ 17.4, 21.1, 30.4, 32.1, 34.9, 63.3, 108.0, 111.0, 118.4, 119.6, 122.0, 126.5, 127.3, 131.2, 134.9, 136.2, 173.2; ESIMS (m/z) 267 [M+H] + ; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1494; IR (CHCl3) vmax 3419, 1677 cm−1 .

5 CONCLUSION

According to Beversdorf, micro propagation is the "in-vitro regeneration of plants from organs, tissues, cells, or protoplasts" and "the true-to-type propagation of a specific genotype utilising in-vitro culture techniques." (Read and Debergh). True-to type propagation offers important benefits for very heterozygous plants, such dioecious papaya genotypes, for which conventional plant breeding has not been able to generate stable lines. In order to quickly multiply before new varieties, like pineapple and strawberry, are released and before they can be propagated normally, micro propagation has also been used. In order to keep stock free of illness, it also acts as a germplasm repository. However, the micropropagation technique used might sometimes affect the ability to develop plants in vitro devoid of genetic off-types.

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