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Synthesis of Tricyclic Quinoline Derivatives from 5- and 6-Aminoindazoles and 5-Aminoindole under Conventional Way and Microwave System

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Abstract: Targeted tricyclic quinolines were prepared from the corresponding aminoindazolic and indolic derivatives as starting materials using two comparative methods; conventional heating and microwave irradiation. We noticed that the syntheses of 5-amino-1-methylindazole and 5-aminoindole were abandoned due to their conversion to fluorescent products one week after free contact with air and acetone. As a result of this finding, we decided to condense the relevant amine with acetone or mesityl oxide to confirm our hypothesis. We show that the amine is converted to the derived quinoline through these condensation processes. Subsequently, this reaction was extended to the aminoindazole derivatives of positions 5 and 6, yielding the appropriate quinoline derivatives. Similarly, 5-aminoindole exhibited the same reactivity. By applying the corresponding NMR and centesimal techniques, the resulting structures were identified.

Keywords: 5- and 6- aminoindazole, 5-aminoindole, quinoline, acetone, mesityl oxide.

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INTRODUCTION

Throughout this century, significant research has been conducted on the synthesis and development of new heterocyclic compounds containing various heteroatoms, namely nitrogen, oxygen, and sulfur; the goal of this work is to produce products with active biological properties that are comparable to those found in nature (1–3). Indazole and quinoline derivatives are pharmacologically important, forming the basic structure of several drugs treating arthritis (4), gynecological disorders, anti-inflammatory (5), the derivatives of isoxazole, thiazoles, and quinoline cyanopyridine, have very good anticancer and antimicrobial activity (6–8). A brief overview of their general preparation methods is necessary; more detailed studies were conducted to synthesize derivatives of quinoline starting from a series of carbonyl (9–19), while scandium ion was used as a catalyst in place of iodine to modify the Skraup reaction in order to increase yield in less time when microwave irradiation was used (13). W.Xiang-Shan and co-worker used a method to obtain quinoline derivatives via three-component reactions of aldehydes, aminoindazole, and thiopyranone (20); recently, a tetrahydro-3H-pyrazolo[4,3-f]quinoline core was synthesized using Povarov multicomponent reaction, the product's proof is its efficiency against cell cancer

(21) (Figure 1), we were then interested on the synthesis of these types of heterocycles with fast, simple, and eco-friendly methods.

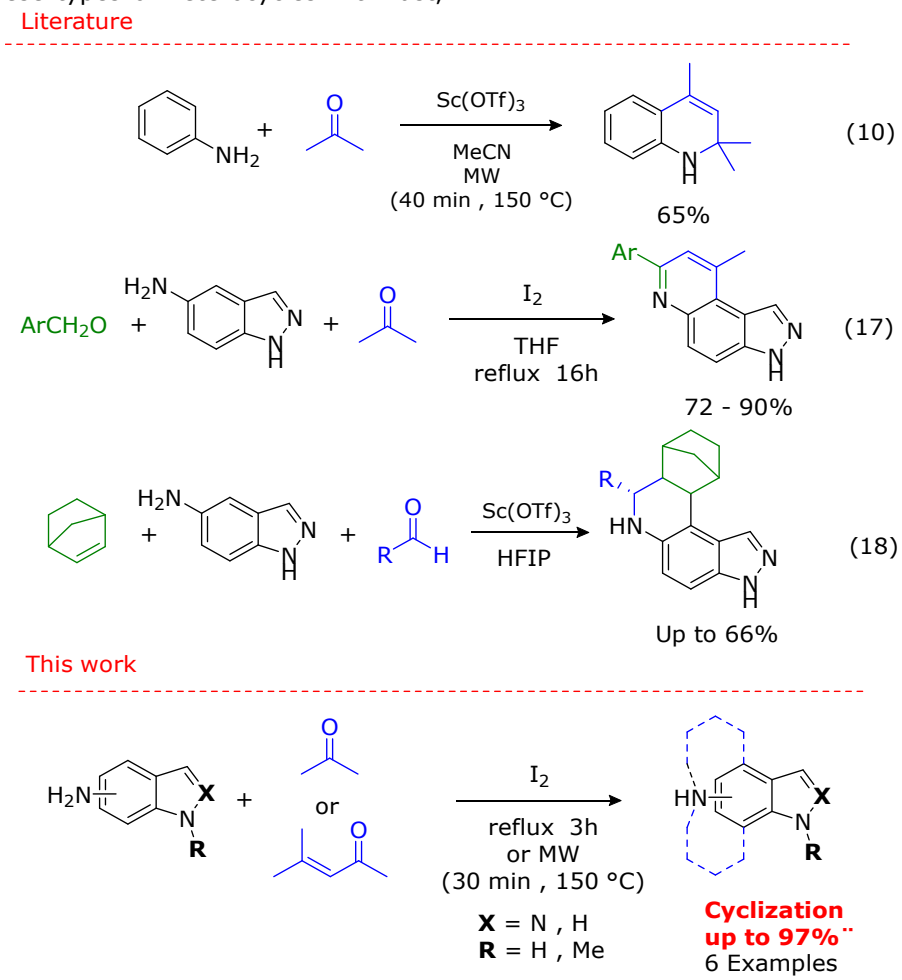


Figure 1: Similar reactions described in the literature.

EXPERIMENTAL SECTION

General Remarks: Melting points were measured on a *Büchi Melting Point* apparatus and are not corrected. Microwave reactor for microwave-assisted extractions: *Monowave 450 from Anton Paar*, The ^{1}H and ^{13}C NMR spectra were measured on a *Bruker Avance 300 Spectrometer* operating at 300 MHz (300 MHz for ^{1}H and 100 MHz for ^{13}C). The chemical shift was recorded as units relative to DMSO-d_6 or $CDCl_3$ as the solvent unless otherwise stated, and *J* values in Hertz. Combustion analyses were performed in the *Microanalysis Laboratory of the National Center for Scientific Research in Vernaison in France*. Separations by chromatography were performed with Merck on "silica gel 60 "(60 – 230 mesh).

Condensation of aminoindazoles into quinoline

Method a

A dry 250 mL bi-necked flask was charged with 2.50 g (17.01 mmol) of 1-methyl-5-aminoindazole, with 5 mol% (0.215 g, 0.850 mmol) of iodine, into a solution of acetone of 200 mL (variable quantity according to the number of mole of amine used). The solution is carried under reflux for 3 hours, the solution was washed with water, the solvent was removed under reduced pressure, and the residue is purified by chromatography on a column with eluent: EtOAc / petroleum Ether (1/1 v/v).

Method b

In sealed tube charged with stirring bar**,** a solution of 5-aminoindazole (0.133 g, 1 mmol) in 5 mL of acetone was added 5 mol% of iodine; the reaction mixture was heated at 150 °C with 400 W during 30 min, the solution was washed with water the solvent was removed under reduced pressure, the residue is purified by chromatography on column with eluent: EtOAc / petroleum ether (1/1 v/v).

Method c

A dry 250 mL bi-necked flask was charged with an equimolar mixture of 1-methyl-5-aminoindazole (2.50 g, 17.01 mmol) and of mesityl oxide (1.67 g,

17.01 mmol) with 5 mol% of iodine (0.215 g, 0.850 mmol), in solution in 200 mL of acetone. The solution is carried under reflux for 3 hours. After filtration and evaporation, the residue is purified by chromatography on the column, eluent: EtOAc / petroleum ether (1/1 v/v).

3,7,7,9-Tetramethyl-6,7-dihydro-3H-pyrazolo[4,3-f] quinoline I method **c** : 3.75 g , 97%, method **a :** 1.33 g, 34%, m.p. 148 °C, ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm) : 7.88 (1*H*, s), 7.23 (1*H*, d, *J* = 8.7 Hz), 6.76 (1*H*, d, *J* = 8.7 Hz), 5.72 (1*H*, s), 5.21 (1*H*, s), 3.92 (3*H*, s), 2.19 (3*H*, s), 1.19 (6*H*, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 138.7, 135.1, 130.3, 128.9, 127.6 (Ar-C), 120.7, 116.5, 109.4, 109.2 (Ar-CH), 50.7 (-NH-$\underline{C}(CH_3)_2$), 35.3 (>N-CH_3), 29.7 (2x-CH_3), 21.7 (-CH_3). Anal. calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.39; H, 7.34; N, 18.52.

7,7,9-Trimethyl-6,7-dihydro-3H-pyrazolo[4,3-f] quinoline III, method **b**: 0,96 g, 45%, method **c** : (1.33 g, 10 mmol) of 5-aminoindazole, mesityl oxide (0.98 g, 10 mmol), iodine 5 mol% and 100 mL of acetone: 0.6 g, 28%, ^{1}H-NMR (300 MHz ,DMSO-d_6, δ, ppm): 12.42 (1*H*, s), 7.69 (1*H*, s), 6.92 (1*H*, d, *J* = 8.7 Hz), 6.47 (1*H*, d, *J* = 8.7 Hz), 5.38 (1*H*, s), 4.94 (1*H*, s), 1.96 (3*H*, s), 0.94 (6*H*, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 139.5, 138.6, 129.1, 127.3, 125.1 (Ar-C), 120.1, 116.7, 110.2, 109.2 (Ar-CH), 50.8 (-NH-$\underline{C}(CH_3)_2$), 29.8 (2x-CH_3), 21.7 (-CH_3).

(1,3-Dimethyl-buta-1,3-dienyl)-(1H-indazol-5-yl)-amine IV , method **c** : (1.33 g, 10 mmol) of 5-aminoindazole, mesityl oxide (0.98 g, 10 mmol), iodine 5 mol % and 100 mL of acetone : 0.51 g, 24%, ^{1}H-NMR (300 MHz ,DMSO-d_6, δ, ppm): 12.66 (1*H*, s), 7.95 (1*H*, s), 7.09 (1*H*, d, *J* = 8.7 Hz), 6.57 (1*H*, d, *J* = 8.8 Hz), 5.50 (2*H*, d, *J* = 8.3 Hz), 5.21 (1*H*, s), 4.89 (1*H*, d, *J* = 5.1), 3.72 (1*H*, s), 3.33 (3*H*, s), 1.00 (3*H*, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 143.6, 138.4, 135.2 (Ar-C), 120.4,118,3, 118.4, 106.9 (Ar-CH), 125.4 (-N-$\underline{C}(CH_3)$=C-), 125.2 (H_2C=$\underline{C}(CH_3)$-), 105.8 ($H_2\underline{C}$=C(CH_3)-), 74.3 (-N-C(CH_3)=$\underline{C}$-), 27.1, 21.5 (-CH_3).

7,7,9-Trimethyl-6,7-dihydro-1H-pyrazolo[3,4-f] quinoline V, method **c**: a mixture of (1 g, 7.220 mmol) of 6-aminoindazole, mesityl oxide (0.737 g, 7.220 mmol), iodine 5 mol % (0.361 mmol , 0,091 g) and 100 mL of acetone, 1.130 g, 74%, m.p. 190°C, ^{1}H-NMR (300 MHz ,DMSO-d_6, δ, ppm): 12.06 (1*H*, s), 7.69 (1*H*, s), 7.28 (1*H*, d, *J* = 8.4 Hz) 6.48 (1*H*, d, *J* = 8.5 Hz), 6.16 (1*H*, s), 5.10 (1*H*, s); 2.25 (3*H*, s), 1.21 (6*H*, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 143.5, 142.2, 138.6, 127.3, 125.4 (Ar-C), 120.4, 117.84, 116.9, 110.1 (Ar-CH), 50.7 (-NH-$\underline{C}(CH_3)_2$), 29.8 (2x-CH_3), 21.3 (-CH_3).

1,7,7,9-Tetramethyl-6,7-dihydro-1H-pyrazolo[3,4-f] quinoline VI, method **a**: (0.147 g ,1 mmol) of 1-methyl-6-aminoindazoline in 10 mL of acetone, with 5 mol % of iodine give 49%, 0.136 g. A mixture of 1-methyl 6-aminoindazole (0.195 g, 1.326 mmol), mesityl oxide (0.131 g, 1.326 mmol), in 30 mL of methanol, acetone and glacial acetic acid (1/1/1 v/v/v), activated by 10 mol% Pd/C, 0.135 g, 48%, m.p. 92°C, ^{1}H-NMR (300 MHz ,DMSO-d_6, δ, ppm): 8.16 (1*H*, s), 7.68 (1*H*, d, *J* = 7.5 Hz), 6.79 (1*H*, d, *J* = 8.5 Hz), 5.40 (1*H*, d, *J* = 4.7 Hz), 4.23 (3*H*, s), 2.74 (3*H*, s), 1.58 (6*H*, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 144.9, 144.3, 139.0, 136.9, 133.9 (Ar-C), 120.9, 117.2, 112.1, 99.9 (Ar-CH), 50.9 (-NH-$\underline{C}(CH_3)_2$), 39.3 (>N-CH_3), 29.4 (2x-CH_3), 27.5 (-CH_3).

Condensation of aminoindole into quinoline
In the presence of acetone
A dry 250 mL bi-necked flask was charged with 1.45 g (10.98 mmol) of 5-aminoindole, with 5 mol % (0.14 g, 0.549 mmol) of iodine, into a solution of 100 mL of acetone (variable quantity according to the number of moles of amine used). The solution is carried under reflux for 3 hours. After evaporation, the residue is purified by chromatography on the column, eluent: CH_2Cl_2 / n-pentane (1/1 v/v). Compound **II** is isolated with a 42% yield, 0.98 g.

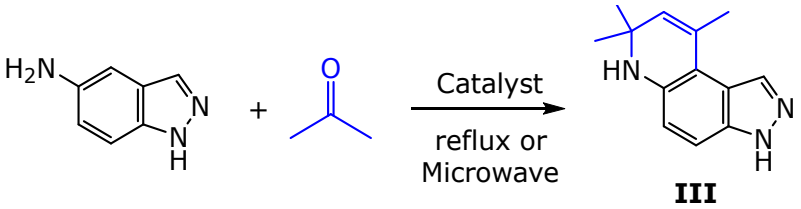
In the presence of mesityl oxide
A dry 250 mL bi-necked flask was charged with an equimolar mixture of 5-aminoindole (0.265 g, 2.023 mmol) and of mesityl oxide (0.198 g, 2.023 mmol) with 5 mol% of iodine (0.026 g, 0.101 mmol), in solution in 50 mL of acetone. The solution is carried under reflux for 3 hours. After filtration and evaporation, the residue is purified by chromatography on the column, eluent: CH_2Cl_2/ n-pentane (1/1 v/v). Compound **II** is isolated with a 50% yield, 0.215 g.

7,7,9-Trimethyl-6,7-dihydro-3H-pyrrolo[3,2-f] quinoline II, m.p. 118°C, ^{1}H-NMR (300 MHz ,DMSO-d_6, delta, ppm): 10.71 (1*H*, s), 7.14 (1*H*, d, *J* = 2.3 Hz), 7.04 (1*H*, d, *J* = 8.3 Hz), 6.48 (1*H*, d, *J* = 8.5 Hz), 6.44 (1*H*, sbr), 5.17 (1*H*, s), 2.20 (3*H*, s), 1.17 (6*H*, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 137.5, 130.9, 130.1, 127.3, 124.7 (Ar-C), 124.5, 113.2, 111.7, 110.9, 100.9 (Ar-CH), 50.6 (-NH-$\underline{C}(CH_3)_2$), 29.4 (2x-CH_3), 22.3 (-CH_3).

RESULTS AND DISCUSSION

Test of Catalysts
The treatment of 5-aminoindazole with different catalysts in acetone under reflux and microwave afforded to the corresponding quinoline **III** in good yield (Scheme 1).

Our first study focused on the absence of a catalyst; any progress was found neither under reflux nor a microwave system (Table 1, Entry **1**). The same reaction was carried out with iodine in different amounts 5 mol%, 10 mol%, and 20 mol %, the given result in yield is the same 45% (Table 1, Entry **2**), showing that a higher amount of catalyst has no influence on the reaction. Some transition metals were also used to catalyze our reaction under the same conditions, copper (CuI, CuCl, $CuSO_4$), iron ($FeCl_3$), manganese (MnO), and bismuth ($BiCl_3$) in their salt form give fewer interesting results (0-25%) as shown in (Table 1, Entry **3-8**). $ZnCl_2$ performs the reaction as iodine does and led us to the desired product **III** with a 45% yield (Table 1, Entry **10**). I_2 was chosen instead of $ZnCl_2$ to catalyze the reaction because of its non-toxic, inexpensive, and eco-friendly nature (22–27).



III

Scheme 1: Cyclization of 5-aminoindazole with acetone under different conditions.

Table 1: Optimization of yield for **III** using different catalysts under reflux.

Entry	Catalyst	Time (h)	yield% [b]
1 [a]	-	3	ND [a]
2 [a]	**I_2**	**3**	**45** [a]
3	CuI	3	Trace
4	CuCl	3	20
5	$CuSO_4$	3	ND
6	$BiCl_3$	3	25
7	$FeCl_3$	3	25
8	MnO	3	ND
9	$PdCl_2$	3	23
10 [a]	**$ZnCl_2$**	**3**	**45** [a]

[a] Reaction tested under microwave system (30 min,150 °C,400 W), [b] isolated yield, ND: not detected

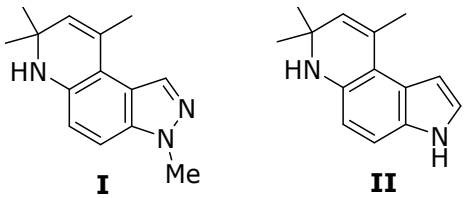
Optimization of the conditions for microwave irradiation

The choice of the optimal condition reaction under microwave irradiation was studied, the same substrate has been condensed in the presence of acetone catalyzed by iodine, starting with temperature from 100 °C during 30 min of reaction, we observed a formation of compound **III** with 20% of yield, after increasing the heating we reached 150 °C corresponding to 45% of yield, some impurities were spotted above this temperature, we then fixed it and changed the time of reaction, after 5 min under irradiation no evolution was observed, the structure **III** begins to be formed from the 15th min, the isolated yield indicates 12% and start increasing until 45% and stabilizes after 30 min of reaction. The reaction under reflux was privileged compared to microwave irradiation because it requires less drastic conditions insight of the power and temperature needed to get our desired structures.

Formation of quinolines

Having noted, we observed a transformation of 5-amino-1-methylindazole and the 5-aminoindole bunged with the free air into quinoline **I** and **II** (Figure 2).

Test reaction of condensation on the products transformed lead to the same structure of quinoline **I** and **II** in both cases, even with acetone or mesityl oxide.

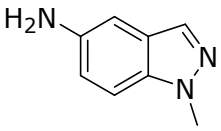
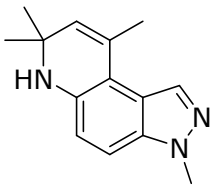
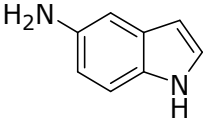
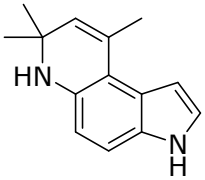
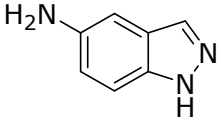
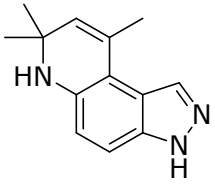
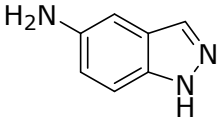


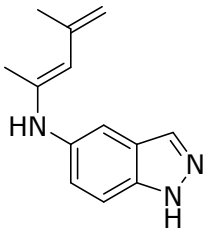
I **II**

Figure 2. Quinolines **I** and **II** formed from 5-amino-1-methylindazole and the 5-aminoindole respectively.

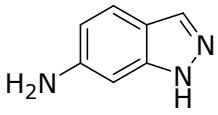
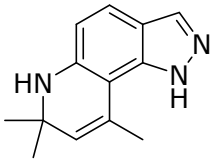
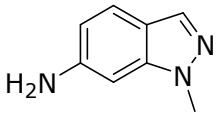
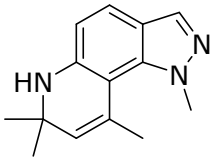
After 3 hours in refluxing the 5-amino-1-methylindazole with acetone in the catalytic medium of iodine, we observed the formation of the product **I** with a yield of 34%. However, the 5-amino-1- methylindazole treated with mesityl oxide in the presence of iodine led to a similar product of structure **I** with a yield of 97% (Table 2, Entry **1**). After carrying out the proton and carbon 13 NMR spectra, a study of spectral fragmentation of mass shows the presence of a molecular mass of 227 amu and a chemical ionization of the peak [M + 1] + is equal to 228 amu (M + H+) and two other significant peaks of fragmentation M/Z = 29 for ion NCH_3] + and M/Z = 41 for ion HCN] +. The addition of the 5-aminoindole with acetone in the presence of a catalytic quantity of iodine under reflux led to the same structure **II**, which is obtained with a reaction yield of 42%. However, the action of mesityl oxide on the 5-aminoindole, under the same conditions, gives us the structure **II** with a yield of 50%, as shown in (Table 2 (Entry **2**). We realized that the reaction of 5-aminoindazole in the presence of acetone produces the compound **III** with 45% of yield (Table 2, Entry **3**), then we observed the formation of another product IV in addition to our predicted one **III** by using mesityl oxide under identical conditions, the two current structures were formed in competition with less difference in yield 24% and 28% respectively (Table 2, Entries **3-4**). For this phenomenon, two mechanisms were suggested, a different attack of the mesityl oxide on 5- aminoindazole (Scheme 3, 4). However, the condensation of the 6-aminoindazole with mesityl oxide led to the compound **V** with an output of 74%, illustrating a more interesting result against the condensation with acetone which gives a 27% yield (Table 2, Entry **5**). The structure **VI** was formed with 49% in yield under the same conditions as the previously formed quinolines; in order the increase this last and to observe the best condensation, the 6-amino-1-methylindazole condenses with mesityl oxide in the presence of a mixture of the solvent of $CH_3OH/CH_3COCH_3/CH_3CO_2H$ catalyzed by Pd / C (12), the competitor's condition shows any evolution in yield and give 48% of quinoline **VI** (Table 2, Entry **6**).

Table 2. Formation of quinoline derivatives using acetone and mesityl oxide.

Entry [a]	Amine	Product	Yield using acetone [b]	Yield using mesityl oxide [b]
1		 **I**	34%	97%
2 [c]		 **II**	42% [c]	50%
3 [c]		 **III**	45% [c]	28%
4			ND	24%



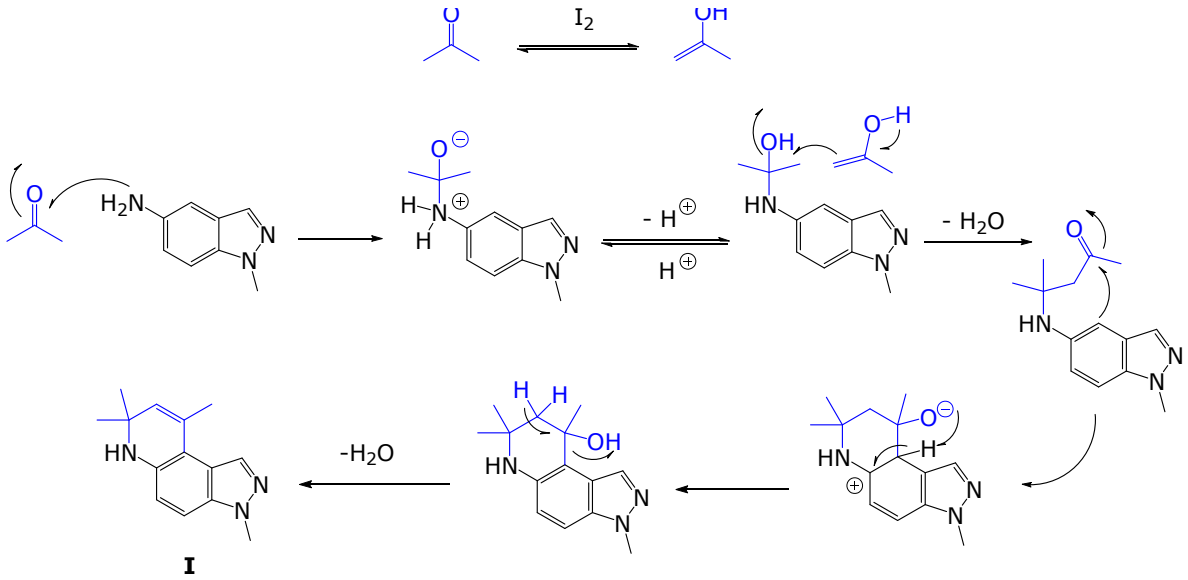
IV

5 [c]		 **V**	27% [c]	74%
6 [d]		 **VI**	49%	48% [d]

[a] Reaction condition: solvent: acetone, reflux (3h), 5 mol% I_2 as the catalyst.
[b] Isolated yield, ND: not detected.
[c] Reaction was also tested under microwave irradiation (150 °C, 400 W, 30 min).
[d] Reaction condition : solvent : $CH_3OH/CH_3COCH_3/CH_3CO_2H$,reflux (3h), 10 mol% Pd / C (12) as catalyst.

Proposed mechanisms

The mechanism proposed is shown in (Scheme 2), iodine participates in equilibrium form of acetone into enol, the amine attacks the carbonyl functional group then a Diels-Alder reaction naturally takes place spawning dehydration. Finally, structure **I** is produced following a cyclization step.

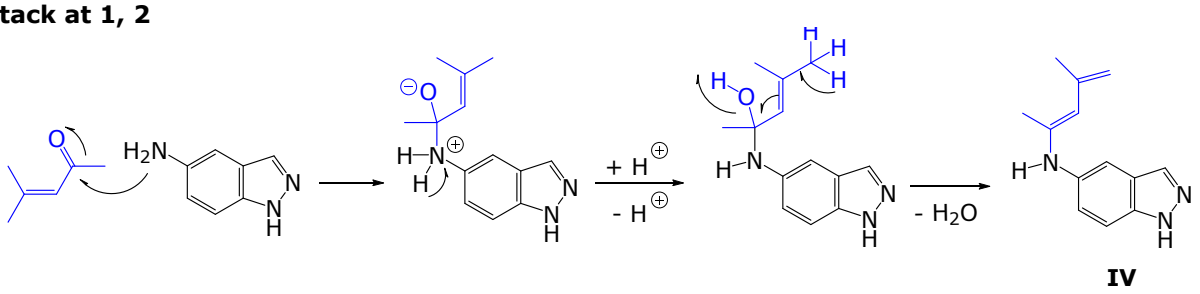


I

Scheme 2. The suggested mechanism for obtaining structure **I** using acetone.

The two structures **IV** and **V** were formed because of the considerable difference of amine's attack on mesityl oxide. Structure **IV** was undoubtedly formed when the amine reacts favorably with the carbonyl function disadvantaging the cyclization (Scheme 3).

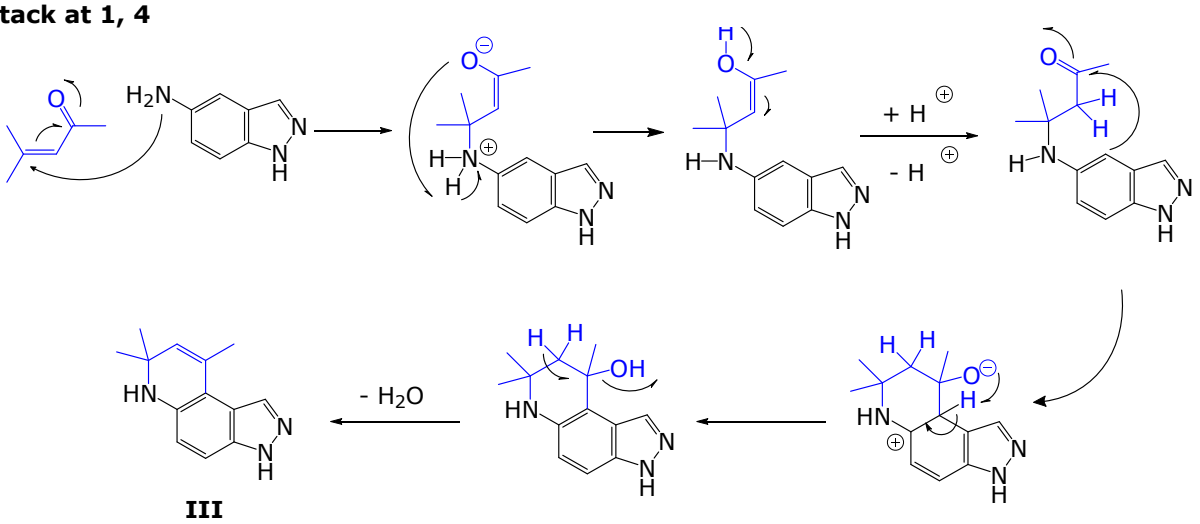
Attack at 1, 2



Scheme 3. The mechanism suggested obtaining structure **IV** using mesityl oxide.

On the other hand, the amine reacts correctly with the aliphatic alkene vacating place to the cyclization naturally done by the carbonyl function (Scheme 4).

Attack at 1, 4



Scheme 4. The mechanism suggested obtaining structure **III** using mesityl oxide.

CONCLUSION

In conclusion, a simple and eco-friendly approach has been demonstrated to synthesize different quinolines with a different yield up to 97% starting from indazolic and indolic structures by condensation using acetone and mesityl oxide in a catalytic medium of iodine, the conventional way and the microwave system of the condensation reaction generate the same results, on this cause that the reflux reaction was chosen as the leading precursor to obtain our final structures in order to avoid the energy consumption at elevated temperature which can assist polymerization.

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