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Facile four-component domino reactions for the synthesis of highly functionalized tetrahydroquinolones

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Abstract: The four-component domino reactions of (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones with anilines, aromatic aldehydes and 1,3-cyclohexanediones in an equimolar ratio in acetic acid afforded functionalized tetrahydroquinolones in good yields. This one-pot transformation involves the formation of two C-C and two C-N bonds in a single synthetic operation.

Keywords: Domino reaction, four-component, (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-one, aniline, tetrahydroquinolinones

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The quinolone moiety is an important scaffold in several biologically active natural products and their analogues are of great importance in biochemistry and pharmaceuticals.[1] Tetrahydroquinolines show a wide range of biological activities.[2-4] In particular, they exhibit anti-allergenic,[2] psychotropic,[5] antioxidant, anti-inflammatory,[6] estrogenic,[7] cerebral anti-ischemic activity in the treatment of Alzheimer's disease, neuroprotectant and platelet anti-aggregatory activity, besides being useful as chemosensitizer in tumor therapy.[8] Oxolinic acid, nalidixic acid, cinoxacin and flumequine drugs possessing quinolone sub-structure are currently employed in the treatment of gram-negative bacteria.[9]

Despite the above biological importance of quinolones and their derivatives, studies on their synthesis are rather limited, which include: (i) a two-step reaction starting from anthranilic acid via the *in situ* generation of 1-methyl/phenyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid methyl esters,[10] (ii) two-component *N*-heterocyclic carbene (NHC)-catalyzed cascade synthesis of 1-substituted 4-aryl-tetrahydroquinoline-2,5-diones from α-bromocinnamic aldehyde and 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone[11] (iii) three-component synthesis of tetrahydroquinolin-5-ones from enaminones, ammonium acetate and cyclic diketones using heterogeneous catalyst, $K_5CoW_{12}O_{40}.3H_2O$[12] and (iv) four-component reactions of cyclic diketones, aromatic aldehyde, ethyl cyanoacetate or ethyl acetoacetate and ammonium acetate in the presence of ceric ammonium acetate and metal nanoparticles such as Ni or Pd.[13,14] These methods, however, suffer from one or more disadvantages such as costly reactants/catalysts, low or inconsistent yields, low intrinsic structural variability of the reactants etc. Consequently, we were prompted to report in this Letter an expedient four-component approach for the synthesis of novel 3-aroyl-1,4-diaryl-4,6,7,8-tetrahydroquinolin-5(1*H*)-ones in good yields (Scheme 1). This method, endowed with high intrinsic structural variability, is amenable for a large library synthesis. This investigation forms a part of our exploratory research embarked on the synthesis of novel biologically relevant heterocycles employing multi-component domino/sequential/ green transformations.[15] It is pertinent to note that multi-component reactions (MCRs) have advantages such as high bond forming efficiency, convergence, operational simplicity, reduction in waste generation and hence conform to the principles of green chemistry.

The enamino ketones, *viz.* (*E*)-1-(4-aryl)-3-(dimethylamino)prop-2-en-1-ones **1** required for the present work were readily prepared by a literature method.[16] We started our study by examining the model four-component reaction of an equimolar mixture of (*E*)-3-(dimethylamino)-1-*p*-tolylprop-2-en-1-one **1**, 4-isopropylbenzaldehyde **2**, 4-chloroaniline **3** and cyclohexane-1,3-dione **4** affording **5f** (Table 1). Initially, the reaction was investigated in different solvents as well as under solvent- and catalyst-free conditions (Table 1) with a view to finding optimal conditions to maximize the yield of the product. The reaction in ethanol using various catalysts such as CAN, *p*-TSA, L-proline and iodine afforded a lower yield of **5f**, while the reaction in AcOH solvent, which could also play the role of a catalyst, at reflux furnished a higher yield of the product in short reaction time (Table 1, entry 7). The above reaction in the presence of TFA, HCOOH, glycol in aq. acetic acid, aq. HCl and aq. H_2SO_4 (Table 1, entries 9-14) failed to proceed or afforded a low yield of the product, despite allowing long reaction times. The reaction when performed in the absence of any catalyst in DMF, ethanol and water failed to afford the product, while the reaction in water in the presence of K-10 montmorillonite clay and *p*-TSA (20 mol%) (Table 1, entries 17 and 18) diminished the yield of the product. Hence the reaction in AcOH under reflux emerged as the ideal reaction conditions for this transformation.

With the above results in hand, the scope of the reaction was investigated under the optimal conditions established above using (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones, cyclohexane-1,3-diones, anilines and aromatic aldehydes bearing different substituents in the aryl rings (Table 2). Typically, the reaction of an equimolar mixture of eanamino ketone **1**, aromatic aldehyde **2**, aniline **3** and cyclohexane-1,3-dione **4** in AcOH (15 ml) at 120 ^{o}C for 4-6 h afforded a library of novel 3-aroyl-1,4-diaryl-4,6,7,8-tetrahydroquinolin-5(1*H*)-ones **5** in good yields (73-96%; Table 2), considering the four-components involved in this reaction.[17]

The structure of the product **5** is in accord with combustion as well as one- and two-dimensional NMR spectroscopic data as illustrated for a representative example **5f** (vide supporting information). A single crystal X-ray crystallographic study (Figure 3) of **5b** confirms the structure arrived at from NMR spectroscopic data.[18] The X-ray structure of **5b** further discloses (i) a half chair conformation for the cyclohexenone ring and a non planar conformation for the dihdyropyridine ring and (ii) that the N-aryl, C-aryl and C-aroyl rings are twisted out-of-plane

from the general plane of the dihdyropyridine ring to minimize steric interactions.

The plausible mechanistic pathway for the formation of **5** through four-component, one pot, domino reaction is depicted in Scheme 2. Presumably, acetic acid catalyzes the formation of arylidenecyclohexane-1,3-dione **6** from the reaction of cyclohexane-1,3-diones with aromatic aldehyde. This intermediate **6** undergoes Michael addition with (*E*)-1-phenyl-3-(phenylamino)prop-2-en-1-one **7,** formed by the reaction of **1** with aniline via an addition-elimination mechanism, leading to the formation of the Michael adduct **9** via intermediate **8**. Subsequent annulation of Michael adduct followed by dehydration affords the quinolone **5**.

In conclusion, we have described a facile protocol employing domino reactions to access the hitherto unreported tetrahydroquinolones from simple, readily available starting materials in a one pot operation in good yields. This methodology has several advantages such as convergence, multi-component domino protocol possessing high intrinsic variability amenable for combinatorial synthesis employing simple starting materials affording good yields of product.

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17. General procedure for the synthesis of tetrahydroquinolinones **5**

An equimolar mixture of (*E*)-1-(4-aryl)-3-(dimethylamino)prop-2-en-1-one **1** (1 mmol), 1,3-diketone (1 mmol), aniline (1 mmol) and aromatic aldehyde (1 mmol) in acetic acid (15 ml) was heated at 120 °C for 4-6 h. The reaction progress was monitored by thin layer chromatography. After completion of the reaction, the solvent was removed and the product was purified by flash column chromatography on silica gel using petroleum ether–ethyl acetate mixture (4:1 v/v) as eluent to obtain pure tetrahydroquinolinones **5**.

Analytical data for a few representative tetrahydroquinolinones **5** are given below.

1-(4-chlorophenyl)-4-(4-isopropylphenyl)-3-(4-methylbenzoyl)-4,6,7,8-tetrahydroquinolin-5(1*H*)-one 5f

Isolated as pale yellow solid Yield :73% m.p.=220 ºC ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.20 (d, 6H, *J* = 6.9 Hz), 1.86-1.98 (m, 2H), 2.09-2.20 (m, 1H), 2.26-2.44 (m, 3H), 2.33 (s, 3H), 2.78-2.87 (m, 1H), 5.48 (s, 1H), 6.97 (s, 1H), 7.09-7.14 (m, 4H), 7.22-7.23 (m, 2H), 7.33 (d, 2H, *J* = 8.1 Hz), 7.40 (d, 2H, *J* = 7.8 Hz), 7.44 (d, 2H, *J* = 8.7 Hz) ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 21.3, 21.4, 23.9, 27.4, 33.6, 34.4, 36.9, 115.9, 119.7, 126.4, 127.6, 128.1, 128.6, 128.8, 130.2, 134.7, 136.3, 140.3, 141.2, 141.4, 143.2, 146.5, 150.1, 194.2, 195.7 Anal. Calcd for $C_{32}H_{30}ClNO_2$ C, 77.48; H, 6.10; N, 2.82% found C, 77.57; H, 6.01; N, 2.75%

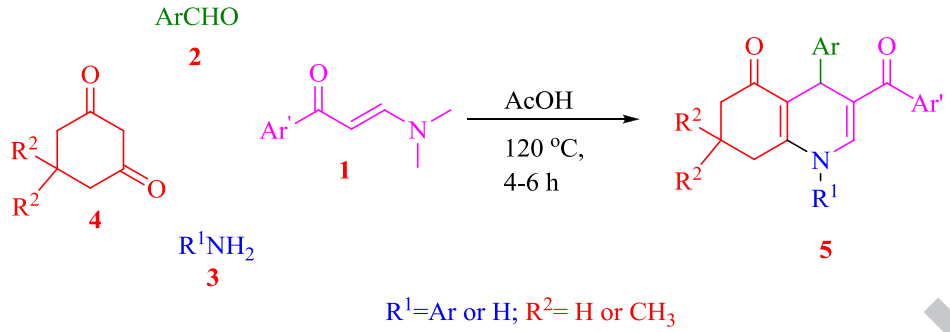
3-(4-chlorobenzoyl)-4-(4-isopropylphenyl)-1-(4-methoxyphenyl)-7,7-dimethyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one 5k

Isolated as yellow gummy solid. Yield :93% ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.91 (s, 3H), 0.98 (s, 3H), 1.19 (d, 6H, *J* = 6.9 Hz), 2.99-2.15 (m, 2H), 2.21 (s, 2H), 2.81-2.85 (m, 1H), 3.86 (s,

3H), 5.42 (s, 1H), 6.93- 6.99 (m, 3H), 7.09-7.18 (m, 4H), 7.30-7.35 (m, 4H), 7.40-7.42 (m, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 23.9, 27.4, 29.0, 32.5, 33.6, 34.5, 40.7, 50.4, 55.5, 114.5, 115.2, 118.9, 126.3, 127.6, 128.3, 128.5, 129.8, 134.3, 136.8, 137.6, 142.8, 143.2, 146.5, 149.2, 159.7, 193.1, 195.6 Anal. Calcd for $C_{34}H_{34}ClNO_3$ C, 75.61; H, 6.35; N, 2.59 % Found C, 75.68; H, 6.44; N, 2.51 %

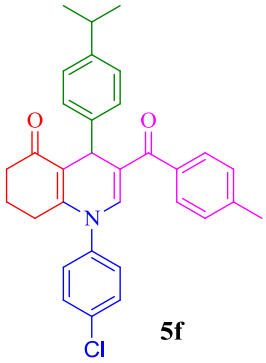
3-benzoyl-7,7-dimethyl-4-(4-nitrophenyl)-1-*p*-tolyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one 5n Isolated as pale yellow gummy solid. Yield: 89% ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.85 (s, 3H), 0.96 (s, 3H), 2.01-2.12 (m, 2H), 2.15-2.25 (m, 2H), 2.39 (s, 3H), 5.52 (s, 1H), 7.06- 7.12 (m, 3H), 7.23-7.32 (m, 4H), 7.36-7.43 (m, 2H), 7.60-7.63 (m, 2H), 8.10-8.13 (m, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 21.1, 27.2, 29.1, 32.6, 35.7, 40.7, 50.3, 113.4, 117.5, 123.6, 127.0, 128.3, 128.3, 128.9, 130.9, 131.1, 138.7, 139.4, 143.6, 146.4, 149.9, 153.3, 193.9, 195.6. Anal. Calcd for $C_{31}H_{28}N_2O_4$ C, 75.59; H, 5.73; N, 5.69 % Found C, 75.66; H, 5.68; N, 5.61%

18. Crystallographic data (excluding structure factors) for 3-benzoyl-1-(4-methoxyphenyl)-4-*p*-tolyl-4,6,7,8-tetrahydroquinolin-5(*1H*)-one **5b** in this Letter have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 941193 Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].



Scheme 1. Synthesis of functionalized tetrahydroquinolinones **5**

Table 1 Optimization of reaction conditions for the preparation of compound **5f**

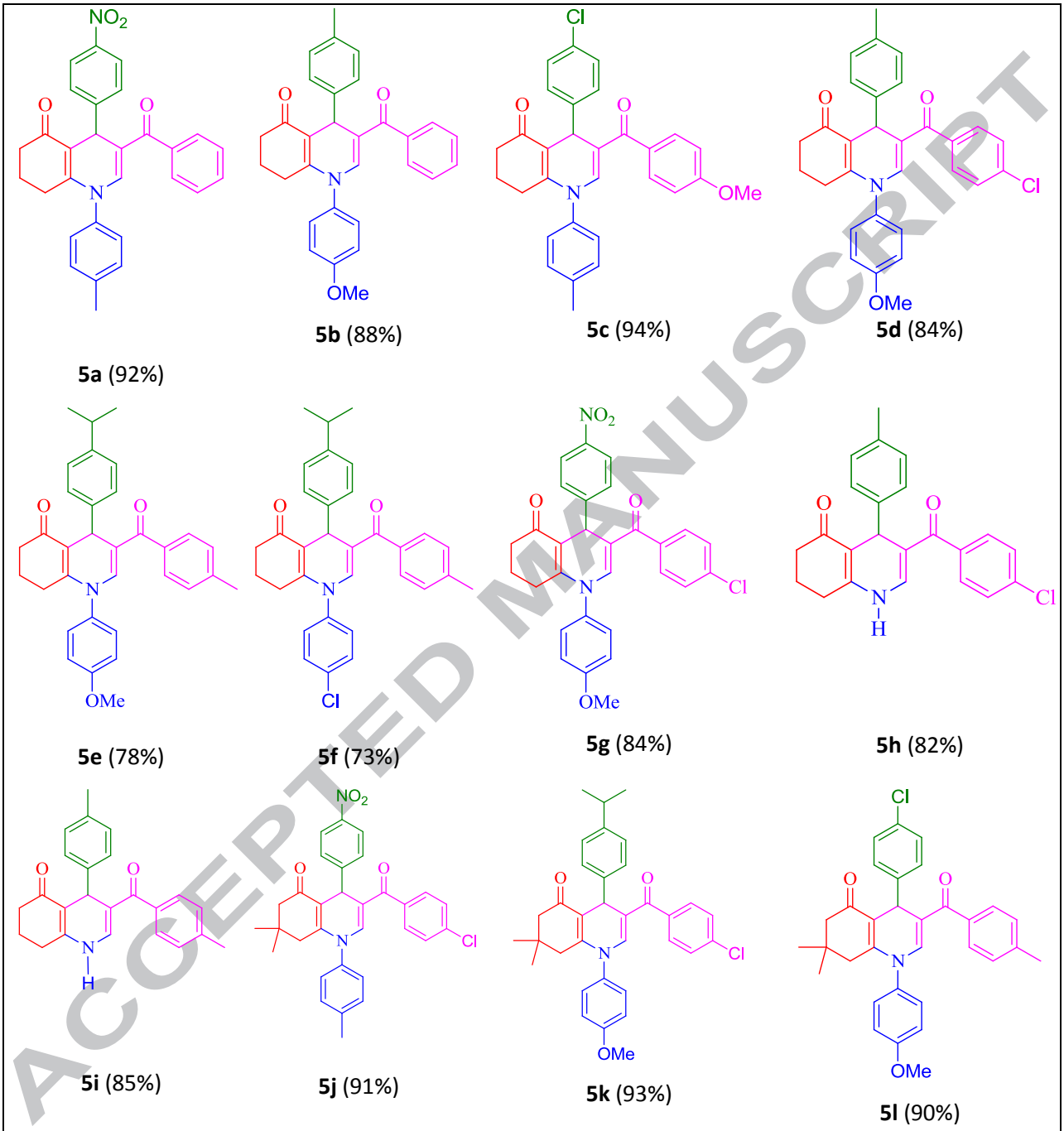


5f

Entry	Solvent	Catalyst (mol%)	Temp. (^{o}C)	Time (h.)	Yield (%)[a]
1	Solvent-free	-	120	5	-[b]
2	EtOH	L-proline (20)	80	12	68
3	EtOH	CAN (20)	80	12	42
4	EtOH	*p*-TSA (20)	80	12	48
5	EtOH	Iodine (20)	80	12	44
6	EtOH	-	80	10	-[b]
7	HOAc	-	120	6	73
8	DMF	AcOH (20)	120	10	46
9	aq. HOAc[c]	-	110	12	56
10	aq. H_2SO_4[d]	-	110	8	-[b]
11	aq. HCl[e]	-	110	8	-[b]
12	TFA	-	110	10	44
13	HCOOH	-	123	10	32
14	Glycol	-	120	10	10
15	DMF	-	120	10	-[b]
16	Water	-	100	6	-[b]
17	Water	K-10 Montmorillonite[f]	100	12	37
18	Water	*p*-TSA (20)	100	12	65

[a] Yield calculated from crude NMR spectrum, conversion based on starting material to product; [b] No reaction occurred; [c] HOAc (17 mmol in 3 ml); [d] H_2SO_4 (5 mmol in 2.5 ml); [e] HCl (12 mmol in 3 ml); 20 mg of K-10 Montmorillonite in equimolar amount (1 mmol) of reactants

Table 2. Synthesis of functionalized tetrahydroquinolin-5(1*H*)-ones **5**



5a (92%)

5b (88%)

5c (94%)

5d (84%)

5e (78%)

5f (73%)

5g (84%)

5h (82%)

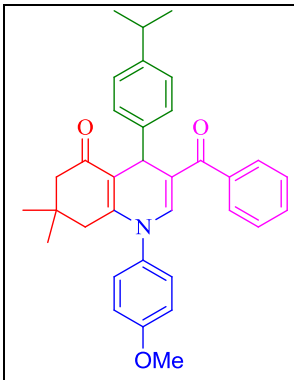
5i (85%)

5j (91%)

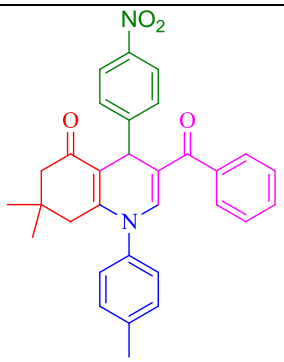
5k (93%)

5l (90%)

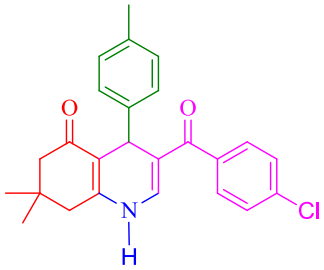
Table 1 continued



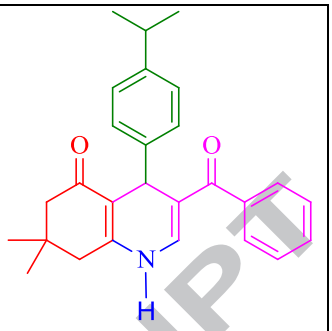
5m (93%)



5n (89%)



5o (88%)



5p (85%)

[a] Yield after filtration through a pad of silica gel.

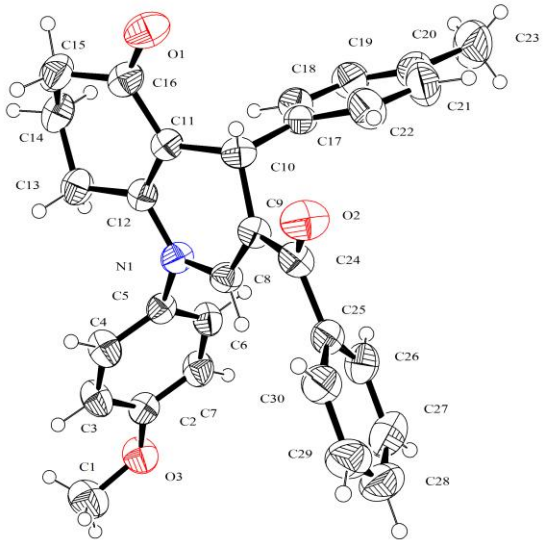
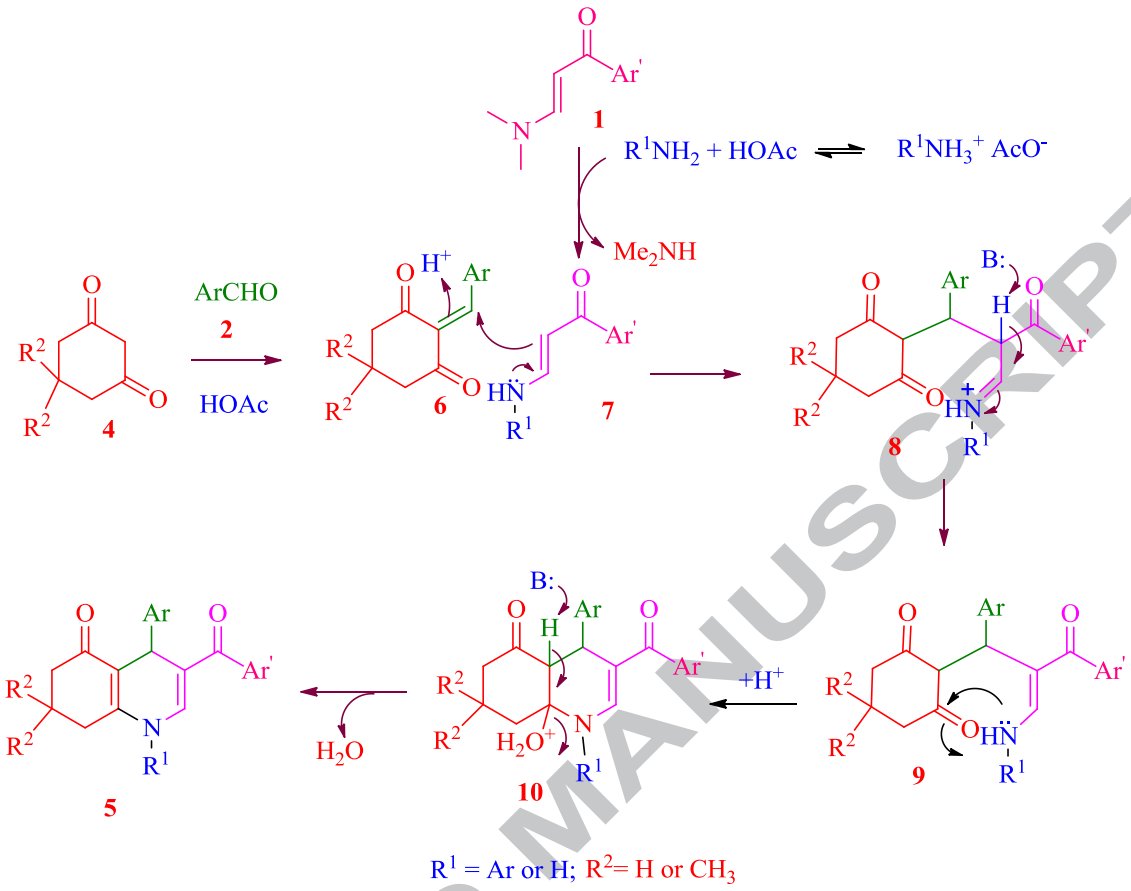


Figure 1. ORTEP diagram of **5b**



Scheme 2. Plausible mechanism for the formation of functionalized tetrahydroquinolinones **5**

Graphical abstract

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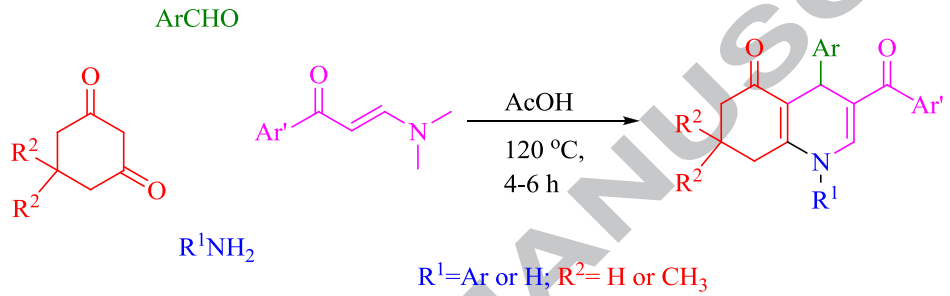

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