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# Domino routes to substituted benzoindolizines: tandem reorganization of 1,3-dipolar cycloadducts of nitrones with allenic esters/ketones and alternative cycloaddition–palladium catalyzed cyclization pathway

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ABSTRACT

Reactions of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenyl nitrones (**7**) with allenic esters (**8a–c**) and allenic ketones (**18a–d**) furnish benzoindolizines (**9a–k**, **19a–d**) in good yields. The formation of benzoindolizines is postulated to involve regioselective addition of 1,3-dipole to C2–C3 π bond of allenic esters/ketones followed by domino transformation of the cycloadducts, which involve an intramolecular aza Diels–Alder reaction in the intermediate C. DFT calculations of various parameters for diene and dienophile components in the proposed intermediate C have revealed that conformational constraints imposed by the alkyl groups (R=Me, Et) favor intramolecular aza-Diels–Alder cycloaddition. An alternative domino route to benzoindolizines (**9a**,**d**,**g**) involving sequential one-pot cycloaddition of azadienes (**22a–c**) with silyl-enol ether (**23**) followed by palladium(0)-catalyzed Heck coupling reaction has also been developed. Both these approaches represent novel domino routes for the synthesis of benzoindolizines.


## 1. Introduction

Domino processes offer useful one-pot atom economic protocols for the synthesis of a variety of complex molecular frameworks.[1] 1,3-Dipolar cycloadditions of nitrones with olefinic and acetylenic dipolarophiles afford five-membered heterocycles (isoxazolidine/isoxazoline),[2] and have been extensively exploited for the synthesis of a variety of natural products, and scaffolds for biologically active molecules.[3] Available reports on cycloaddition of nitrones with variedly substituted allenes indicate that isoxazolidines (**3**) derived from addition of nitrones (**1**) to allenes (**2**) undergo rearrangement by N–O bond cleavage to yield 3-pyrrolinones (**4**), and in the case of *N*-phenylnitrones the cleavage of N–O bond of isoxazolidines (**3**) leads to benzazepinones (**5**); the latter undergo sequence of retro-Mannich reaction, hydrolysis, and cyclization leading to 2-substituted indoles (**6**, Scheme 1).[4]

We had reported preliminary observations on the formation of benzo[*b*]indolizines (**9**) by tandem reorganization of 1,3-dipolar cycloadducts of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (**7**) with allenic esters (**8**, Scheme 2).[5]

Indolizines form the main framework and constitute common structural core in many naturally occurring alkaloids.[6] Indolizines based molecules are known for their use as synthetic dyes,[7a,b] fluorescent materials,[7c–e] and also as key intermediates for the synthesis of indolizine based molecules.[7f–h] Indolizines both synthetic and natural have also been ascribed with a number of useful biological activities[8–12] such as antibacterial, antiviral, anti-inflammatory (**10**, **11**),[8a,b] testosterone-3α-reductase inhibitors,[8c] 5-HT4 receptor antagonists,[8d] CNS depressants,[8e,f] anti-HIV (**12**),[9] anti-cancer[10] (**13**) and have been used for treating cardiovascular ailments.[11] For instance, aminoalkyloxybenzenesulfonylindolizine compounds such as fantofarone (**14**) and butoprozine (**15**) have been used for the treatment of hypertension, arrhythmia, and angina pectoris.[11] Several oxygenated indolizines have been shown to prevent, due to their strong anti-oxidative effects, the initiation of oxidation processes that lead to DNA damage.[12]

Consequently, synthesis of indolizines has attracted considerable attention and a number of synthetic methodologies have been developed for a variety of indolizines, making use of in particular, transition metal catalyzed reactions.[13] In view of the anticipated pharmacological properties of indolizines with potential therapeutic

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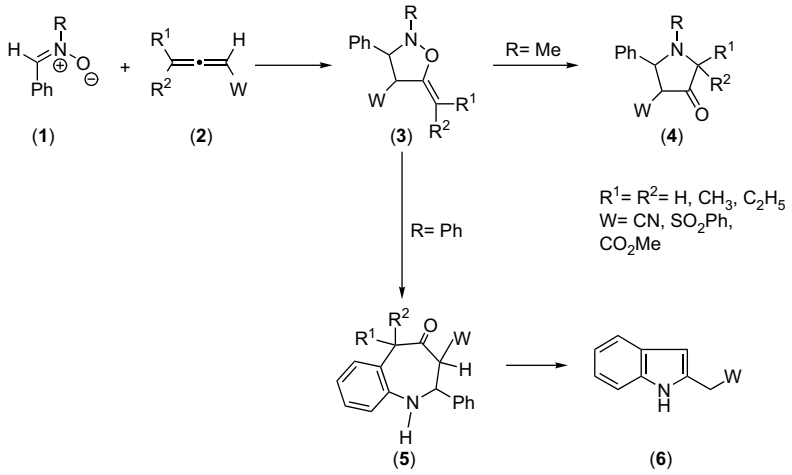
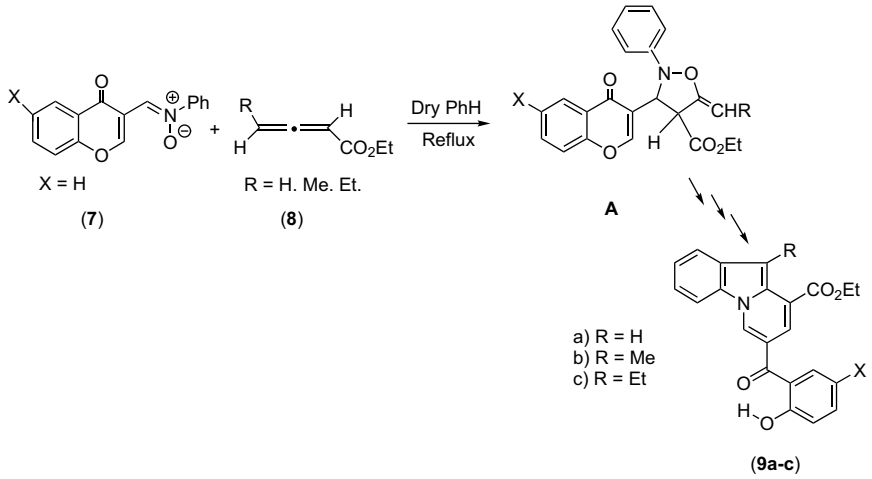



**Scheme 1.**




**Scheme 2.**

applications, it was decided to explore synthesis of variedly substituted benzoindolizines, utilizing the reactions of nitrones with allenic esters and allenic ketones. An alternative one-pot sequential aza-Diels–Alder cycloaddition–Heck coupling route to benzoindolizines has also been developed.

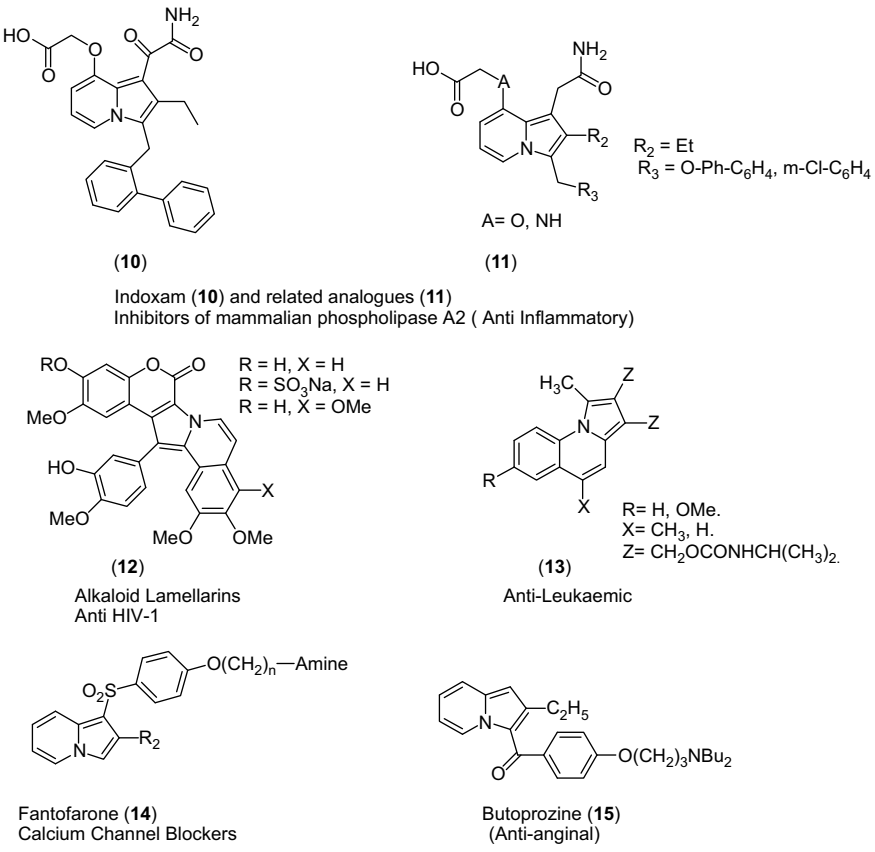
## 2. Result and discussion

Substituted nitrones (**7**) were synthesized from 6-substituted-3-formyl chromones by reported method.[14] Initially, the reactions of nitrone (**7**) were carried out with allenic esters (**8**) by refluxing the solution of addends (1:1.2 molar, respectively) in dry benzene. The obtained substituted benzoindolizines (**9a–h**, 29–59%, Scheme 3) were isolated by column chromatography over silica gel and characterized on the basis of spectroscopic ($^1$H NMR, $^{13}$C NMR, IR, mass) and microanalytical data. The structure of **9f** was confirmed by X-ray crystallography (Fig. 1).[15] Varied amounts (25–40%) of nitrone rearrangement product (**17**)[14,16] were also isolated from the reactions. The results of the reactions between nitrones (**7**) and allenic esters (**8**) are summarized in Table 1.

Further, the investigations were extended to reactions of nitrone (**7**) with allenic ketones (**18**). The solutions of addends (**7** and **18**; 1:1.2 molar, respectively) were stirred in dry benzene at ambient temperature till the completion of reaction (TLC) and obtained benzoindolizines (**19a–d**, 28–42%, Scheme 4) were isolated by column chromatography over silica gel and characterized spectroscopically. Further elution lead to the isolation of nitrone rearranged product (**17**).[14,16] The results are summarized in Table 2.

In order to prevent the excessive rearrangement of nitrones (**7**) to **17**,[14,16] the reactions with allenic esters were also performed at room temperature but it takes longer time for completion of reaction (3–5 days) with slight improvements in yield and consequent decrease in the yields of nitrone rearranged products (**17**). The reactions with allenic ketones could not be carried out under refluxing conditions as they undergo excessive polymerization, drastically reducing the yield of indolizines.

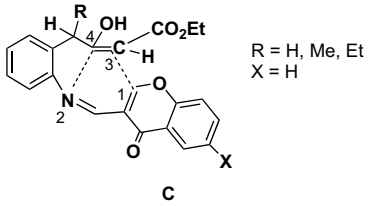
Mechanistically, the formation of the benzoindolizines can be explained on the basis of the domino process as outlined in Scheme 5. It is postulated that indolizines are derived from initial regioselective addition of nitrones (**7**) to the activated C2–C3 $\pi$ bond of allenic esters (**8**)/allenic ketones (**18**), followed by homolytic scission of N–O bond of the formed isoxazolidines (**A**) and the recyclization of the diradical intermediate onto the *ortho* position of the *N*-phenyl ring leads to the formation of **B**. 1,3 H-shift in **B** results in tetrahydrobenzazepinone (**B1**) and the latter undergoes retro-Mannich ring opening to yield the intermediate (**C**). Intramolecular aza-Diels–Alder reaction in **C** followed by subsequent loss of water and opening of the chromone ring results in the formation of benzoindolizines (**9**, **19**). The 2-substituted indoles were formed in some cases by the hydrolysis of C=N in the intermediate **C**, followed by cyclization (Scheme 5).

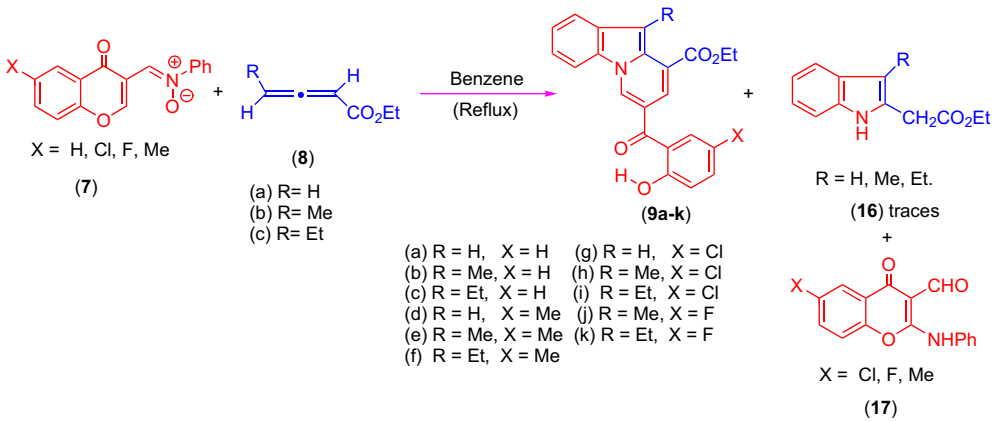



**Some representative biologically active indolizines**

It is observed that alkyl substitution on allenic moiety (**8a**→**8b**) leads to improved yields of benzoindolizines with reduced reaction times and further improvement of yields and shortening of reaction times occur as the size of alkyl substituent increases from methyl to ethyl (**8b**→**8c**, Table 1). Thinking that intramolecular aza-Diels–Alder cycloaddition in intermediate **C** is a crucial step for the formation of benzoindolizines (**9a**–**k**), DFT calculations were carried out at B3LYP/6-31G* level for azadiene and dienophilic components in intermediate **C**. The results of calculations are shown in Tables 3–5. The calculation of activation energy for cycloaddition in **C** leading to **D** revealed (Table 3) that the activation energy decreases as R in **C** changes from H, through $CH_3$, to $C_2H_5$, which parallels the enhanced yield of benzoindolizines (**9b**,**c**) with reduced reaction times.

Fukui functions ($f^+$, $f^0$, $f^-$) for reacting atoms in the intermediate **C** have been calculated and given in Table 4. Keeping the azadiene part constant (X=H), parameters such as energies of HOMO and LUMO (in Hartrees), chemical hardness ($\eta$), chemical potential ($\mu$), and global electrophilicity ($\omega$, Table 5, all values in eV) for dienophile part in intermediate **C** (R=H, Me, Et) were also computed. All the calculations were carried out at B3LYP/6-31G* level.




**Scheme 3.**

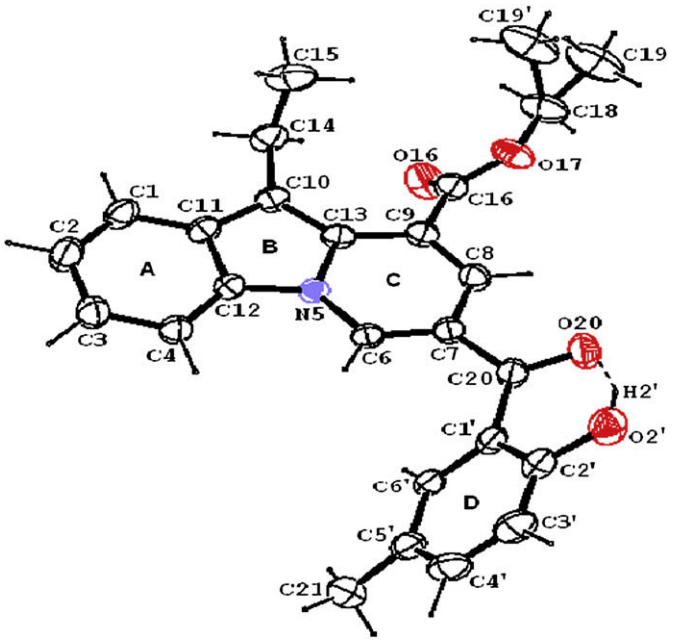



**Figure 1.** ORTEP view of **9f**.

**Table 1**
Product yields and reaction times for reactions of nitrones (**7**) with allenic esters (**8**)

| Sr. no. | R | X | Benzoindolizines | %Yield (reaction time, h) |
|---|---|---|---|---|
| 1 | H | H | **9a** | 35 (22) |
| 2 | Me | H | **9b** | 55 (16) |
| 3 | Et | H | **9c** | 60 (14) |
| 4 | H | Me | **9d** | 32 (21) |
| 5 | Me | Me | **9e** | 49 (15) |
| 6 | Et | Me | **9f** | 59 (12) |
| 7 | H | Cl | **9g** | 29 (20) |
| 8 | Me | Cl | **9h** | 45 (15) |
| 9 | Et | Cl | **9i** | 50 (13) |
| 10 | Me | F | **9j** | 40 (17) |
| 11 | Et | F | **9k** | 45 (15) |

The insignificant change in these parameters in the series (R=H, Me, Et) reveals that the observed change in the reactivity is purely due to conformational restrictions imposed by the alkyl groups. This fact is corroborated by the decreasing distance between the reacting atoms in intermediate **C** as well as in the putative transition states, in their optimized geometries (Fig. 2). It is observed that there is reduction in distance with increase in the size of the substituents in dienophile component of intermediate **C** (R=H→Me→Et), consequently, resulting in decrease of activation energy, which contributes to higher yields of benzoindolizines on going from **9a** to **9c** and also from **9d** to **9f** (X=Me), from **9g** to **9i** (X=Cl), and from **9j** to **9k** (X=F, Table 1).

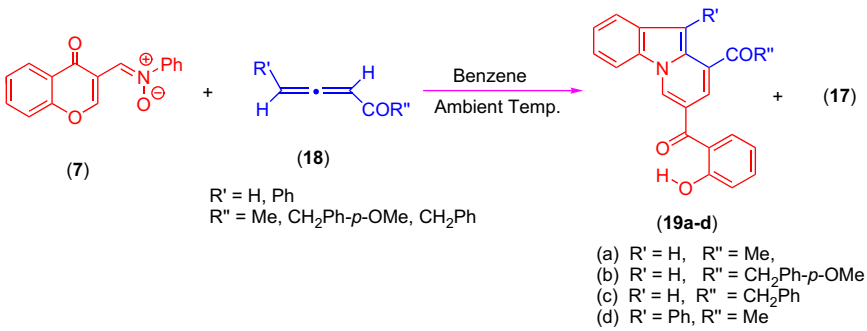
**Table 2**
Product yields and reaction times for reactions of nitrone (**7**) with allenic ketones (**18**)

| Sr. no. | R′ | R″ | Benzoindolizines | %Yield (reaction time, days) |
|---|---|---|---|---|
| 1 | H | $CH_3$ | **19a** | 34 (6) |
| 2 | H | $CH_2Ph$-*p*-$OCH_3$ | **19b** | 28 (6) |
| 3 | H | $CH_2Ph$ | **19c** | 39 (5) |
| 4 | Ph | $CH_3$ | **19d** | 42 (5) |

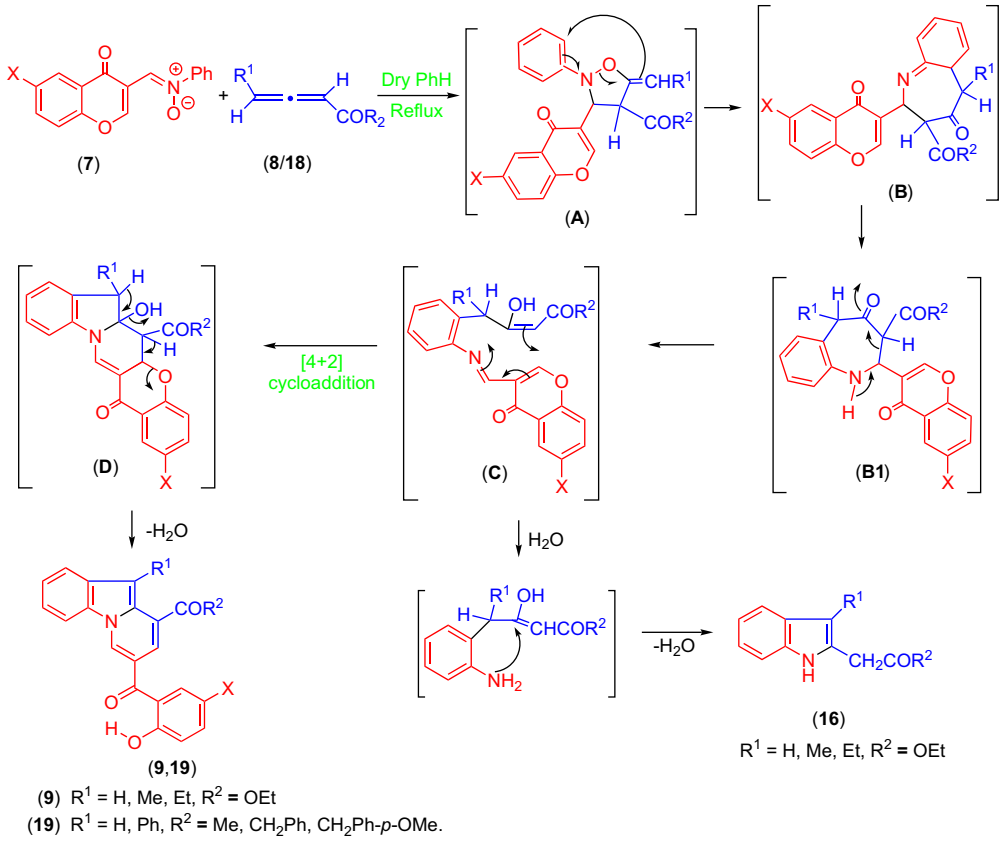
As the proposed mechanism (Scheme 5) involves an intramolecular (4+2) cycloaddition reaction, hence it was realized that an alternative intermediate (**H**) can be easily approached utilizing a convenient strategy involving tandem intramolecular aza-Diels–Alder reaction of silyl-enol ether and azadienes, which can be subsequently subjected to Heck coupling using palladium acetate as a catalyst to obtain substituted benzoindolizines (Scheme 6).

Hence, it was decided to use the sequential one-pot cycloaddition of azadienes (**22**) with silyl-enol ether (**23**) followed by intramolecular palladium(0)-catalyzed Heck coupling reaction to synthesize benzoindolizines (**9a**,**d**,**g**). The variedly substituted azadienes (**22**) were prepared by heating a solution of 3-formylchromone (**20**, X=H, Me, Cl) with *o*-iodoaniline (**21**, 1:1 molar, respectively) in dry toluene. The ethyl 3-trimethylsiloxy-2-butenoate (**23**) was synthesized by the reported method.[17] The in situ generated azadienes (**22**, X=H, Me, Cl) were subjected to cycloaddition reaction with ethyl 3-trimethylsiloxy-2-butenoate (**23**, 1:1.2 mol equiv) followed by intramolecular Heck coupling reaction using catalytic amount of $Pd(OAc)_2$ (5–10 mol %) in the presence of slight excess of triethylamine as a base, by heating their solution in dry toluene at 90 °C. After completion of reaction (TLC), the product benzoindolizines (**9a**,**d**,**g**, 18–25%, Scheme 7) were purified through column chromatography and their structures were established by spectroscopic analysis. The relative yields and reaction times of benzoindolizines (**9a**,**d**,**g**) are given in Table 6.

Mechanistically, the formation of the benzoindolizines (**9a**,**d**,**g**) by palladium catalyzed domino transformations can be explained on the basis of the pathway summarized in Scheme 8. The cascade reactions begin with aza Diels–Alder reaction of 3-[(2-iodo-phenylimino)-methyl]-chromen-4-one (**22**) with ethyl 3-trimethylsiloxy-2-butenoate (**23**, silyl-enol ether). The initially formed (4+2) cycloadduct leads to the formation of intermediate (**H** or **H′**) either through direct thermal elimination of trimethyl silanol in the presence of base or by its hydrolysis followed by the loss of $H_2O$. The intermediate **H** subsequently undergoes intramolecular Heck coupling in the presence of palladium acetate and a base, followed by the opening of chromone ring leading to the formation of benzoindolizines (**9a**,**d**,**g**). Alternatively, the intermediate **H′** could also undergo opening of chromone ring prior to the intramolecular Heck coupling (Scheme 8).




**Scheme 4.**




**Scheme 5.**

**Table 3**
Calculated activation energies for cycloaddition in **C** leading to **D** at B3LYP/6-31G* level

| X | R | Reaction time (h) | Activation energy (kJ/mol) |
|---|---|---|---|
| H | H | 22 | 103.6 |
| H | $CH_3$ | 16 | 99.2 |
| H | $C_2H_5$ | 14 | 96.0 |

**Table 4**
Fukui function values for the reacting atoms of intermediate **C**

| Fukui functions | X | R | 4C | 3C | 2N | 1C |
|---|---|---|---|---|---|---|
| $f^+$ | H | H | 0.004 | 0.002 | 0.062 | 0.099 |
| | H | $CH_3$ | 0.005 | 0.001 | 0.062 | 0.101 |
| | H | $C_2H_5$ | 0.004 | 0.001 | 0.061 | 0.100 |
| $f^0$ | H | H | 0.002 | 0.012 | 0.063 | 0.066 |
| | H | $CH_3$ | 0.002 | 0.012 | 0.062 | 0.066 |
| | H | $C_2H_5$ | 0.002 | 0.009 | 0.064 | 0.066 |
| $f^-$ | H | H | 0.001 | 0.023 | 0.064 | 0.032 |
| | H | $CH_3$ | 0.001 | 0.023 | 0.063 | 0.032 |
| | H | $C_2H_5$ | 0.001 | 0.019 | 0.067 | 0.032 |

**Table 5**
Theoretical parameters calculated for dienophile part of intermediate **C** (X=H)

| Parameters | R | | |
|---|---|---|---|
| | H | $CH_3$ | $C_2H_5$ |
| $\epsilon_{HOMO}$ (Hartrees) | −0.21699 | −0.21617 | −0.21566 |
| $\epsilon_{LUMO}$ (Hartrees) | −0.06636 | −0.06589 | −0.06498 |
| Chemical hardness ($\eta$, eV) | 2.049 | 2.045 | 2.050 |
| Chemical potential ($\mu$, eV) | −3.855 | −3.838 | −3.818 |
| Electrophilicity ($\omega$, eV) | 3.626 | 3.601 | 3.556 |

## 3. Conclusions

A method for the synthesis of novel substituted benzoindolizines (**9a–k**) by the reaction of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrones (**7**) with allenic esters (**8**) is elaborated. Further, the reactions of nitrone (**7**) have been extended to allenic ketones (**18**) to obtain variedly substituted benzoindolizines (**19a–d**). The DFT calculations of the parameters such as Fukui functions ($f^+$, $f^0$, $f^-$), energies of HOMO and LUMO, chemical hardness ($\eta$), chemical potential ($\mu$), and global electrophilicity ($\omega$) for dienophile component in the intermediate **C** and activation energies of transition states for the intramolecular cycloaddition in intermediate **C** leading to **D**, in the proposed domino pathway at B3LYP/6-31G* level have been carried out, which revealed that conformational restrictions in **C** may be responsible for improved yields of indolizines along with reduced reaction times, observed in the case of allenic esters bearing alkyl substituents. It is observed that there is reduction in distance with increase on the size of the substituents R in intermediate **C**, consequently, resulting in decrease of activation energy.

An alternative route to benzoindolizines (**9a**,**d**,**g**) involving cycloaddition of azadienes (**22a–c**) with silyl-enol ether (**23**) followed by palladium(0)-catalyzed Heck coupling reaction is also developed. Both these approaches represent novel domino routes for the synthesis of benzoindolizines.

## 4. Experimental

### 4.1. General information

All melting points are uncorrected and measured in open glass-capillaries on a Veego (make) MP-D digital melting point apparatus. Bruker AC-200 FT (200 MHz) and JEOL AL-300FT

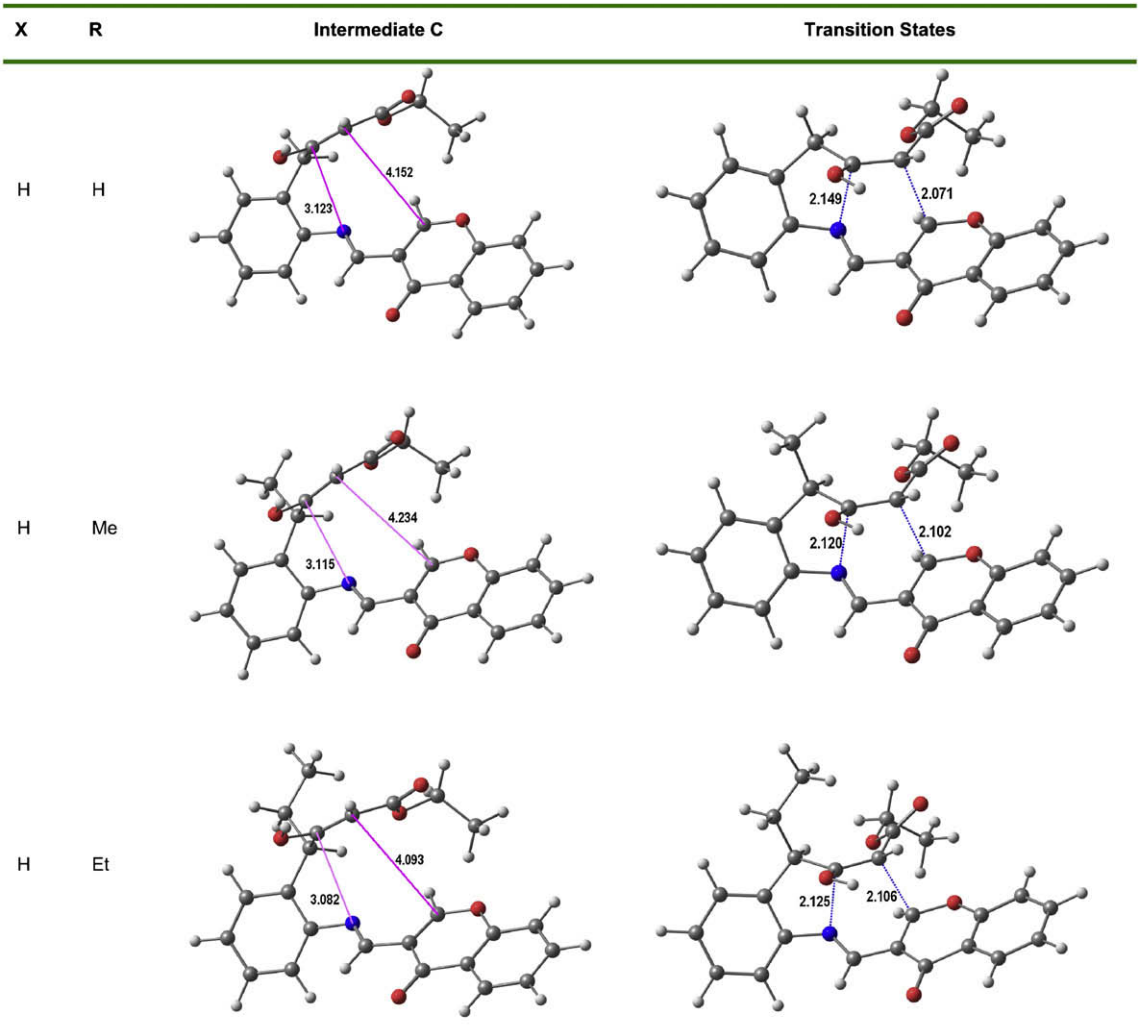
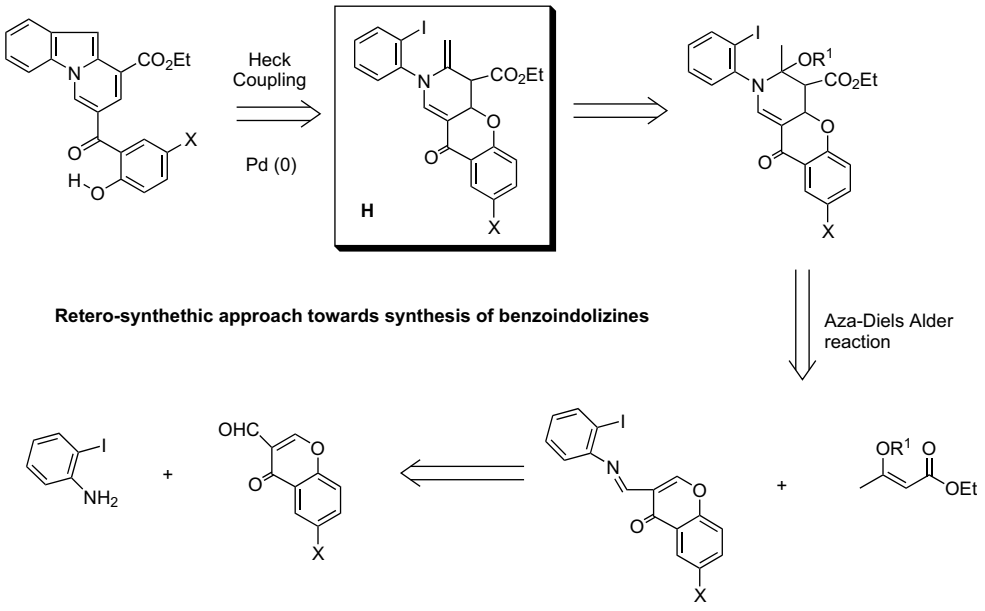
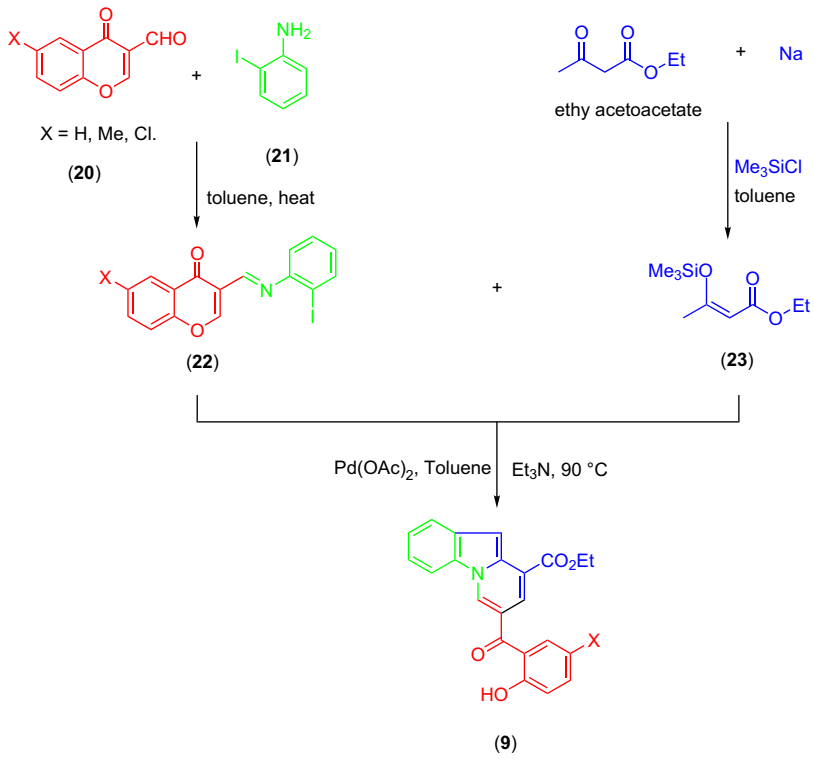



**Figure 2.** Optimized geometries of **C** and transition states in **C** in going from **C** to **D** (X=H) at B3LYP/6-31G* level (the distances are given in Å).




**Scheme 6.**




**Scheme 7.**

(300 MHz) spectrometers were used to record $^{1}$H NMR and $^{13}$C NMR (50 and 75 MHz) spectra. Chemical shifts ($\delta$) are reported as downfield displacements from TMS used as internal standard and coupling constants ($J$) are reported in hertz. IR spectra were recorded with Shimadzu FT-IR-8400S spectrophotometer on KBr pellets. Mass spectra, EI and ESI methods, were recorded on Shimadzu GC–MS-QP-2000A and Bruker Daltonics Esquire 300 mass spectrometers, respectively. Elemental Analyses were carried out using Vario EL-III elemental analyzer and are reported in percent atomic abundance.

Reagents were purchased from commercial suppliers and purified/distilled/crystallized before use. Hexane, petroleum ether, and ethyl acetate used in column chromatography were distilled before use; petroleum ether employed was the fraction boiling in the range of 40–60 °C. Benzene was dried over sodium-benzophenone. *C*-(4-Oxo-4*H*[1] benzopyran-3-yl)-*N*-phenylnitrone and its 6-substituted derivatives (**7**) were prepared according to the reported procedure[14] and allenic esters (**8**) were prepared by the method of Lang and Hansen.[18] Penta-3,4-diene-2-one and its derivatives (**18**) were prepared by reported methods.[19] All the calculations were performed using Gaussian 98 package.[20] The molecules have been optimized at B3LYP/6-31G* level. All of them were found to be minimum on the potential energy surface with zero imaginary frequency. Global reactivity indexes were calculated using the working equations available in the literature. Local reactivity indices, Fukui functions, have been calculated using the DMOL program implemented in Cerius2 package employing Hershfeld populations scheme.

**Table 6**
Product yields and reaction times for the formation of benzoindolizines (**9a**,**d**,**g**)

| S. no. | X | Benzoindolizines | % Yield (reaction time, h) |
|---|---|---|---|
| 1 | H | **9a** | 27 (15) |
| 2 | $CH_3$ | **9d** | 34 (12) |
| 3 | Cl | **9g** | 25 (17) |

### 4.2. General procedure for the reaction of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrones (7) with allenic esters (8)

A solution of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrones (**7**, 200 mg) and allenic esters (**8**, 1.2 mol equiv) in 20 mL dry benzene was refluxed under nitrogen atmosphere till the completion of reaction (TLC). Benzene was removed under vacuum and the benzoindolizines (**9a**–**k**) were purified by column chromatography (silica gel, 60–120 mesh, eluent hexane/EtOAc 9.5:0.5). Further elution with increasing concentration of EtOAc in hexane afforded the rearranged products (**17**) of nitrone (25–40%) and in some cases indoles (**16**, <5%) were also obtained and detected by $^{1}$H NMR of some column fractions.

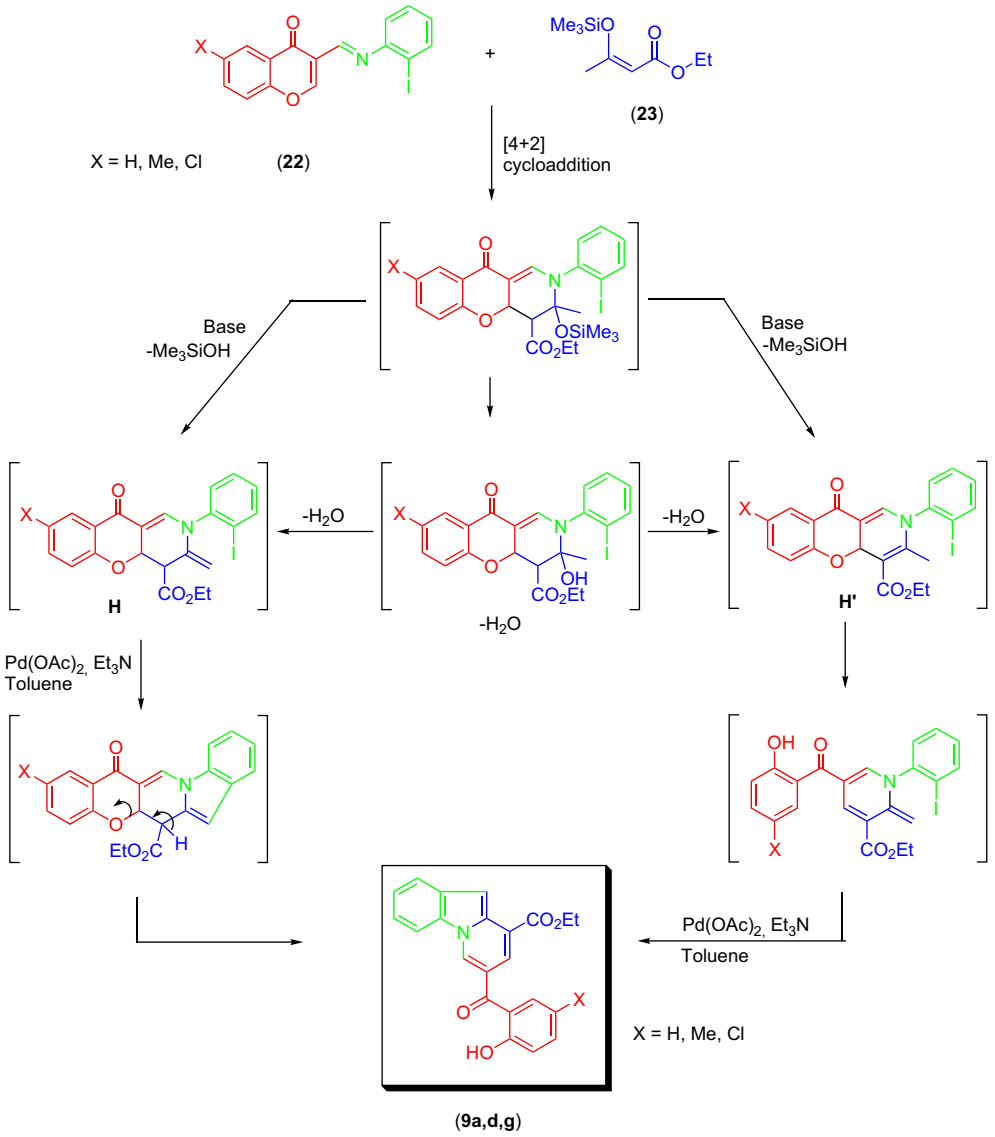
### 4.3. General procedure for the reaction of azadienes (22) and ethyl 3-trimethylsiloxy-2-butenoate (23)

A solution of 3-formylchromone (**20**, 200 mg) was refluxed with *o*-iodoaniline (**21**, 1.0 mol equiv) in dry toluene using Dean Stark water separator till the completion of reaction (TLC). To the resulting solution of in situ generated azadiene (**22**) in dry toluene at 90 °C were added ethyl 3-trimethylsiloxy-2-butenoate (**23**, 1:1.4 mol), and triethylamine (0.25 ml, excess) and $Pd(OAc)_2$ (5–10 mol %). The heating of the mixture was continued at 90 °C, till the completion of reaction as observed by TLC and formed benzoindolizines (**9a**,**d**,**g**) were isolated through column chromatography (silica gel 60–120 mesh, eluent hexane/EtOAc 9.5:0.5), further elution afforded an intangible mass.

All the benzoindolizines were obtained as red and orange red crystalline compounds, recrystallized from $CCl_4$/hexane (1:9).

*4.3.1. 1-Ethoxycarbonyl-3-(2′-hydroxybenzoyl)-benzo[b]-indolizine (**9a**)*

Red needles ($CCl_4$/hexane, 1:9); mp 114–115 °C; yield (35%); $R_f$=0.54 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3060, 3015, 1715, 1624,




**Scheme 8.**

1600, 1483, 1458, 1422, 1352, 1333, 1304, 1288, 1265, 1213, 1198 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$=1.41 (t, $J$=7.11 Hz, 3H), 4.40 (q, $J$=7.11 Hz, 2H), 6.88 (t, $J$=7.53 Hz, 1H), 7.03 (d, $J$=8.24 Hz, 1H), 7.25–7.51 (m, 4H), 7.63 (dd, $J$=1.35 and 7.91 Hz, 1H), 7.76 and 7.80 (overlapping doublets, $J$=7.62 and 8.02 Hz, 1H each), 8.11 (s, 1H), 8.93 (s, 1H), 11.47 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$=14.4, 61.5, 97.9, 110.6, 117.5, 118.8, 119.1, 119.3, 120.1, 121.6, 121.9, 125.2, 128.0, 130.5, 131.3, 131.9, 132.4, 133.9, 136.2, 162.6, 164.6, 195.1; MS (70 eV, EI): $m/z$: 360 ($M^+$+1), 359 ($M^+$); elemental analysis calcd (%) for $C_{22}H_{17}NO_4$ (359.12): C 73.53, H 4.77, N 3.90. Found: C 73.34, H 4.68, N 3.80.

*4.3.2. 1-Ethoxycarbonyl-3-(2′-hydroxybenzoyl)-10-methyl-benzo[b]indolizine (**9b**)*

Red needles ($CCl_4$/hexane, 1:9); mp 123–124 °C; yield (55%); $R_f$=0.68 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3068, 1720, 1628, 1609, 1530, 1483, 1428, 1230, 1028 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$=1.44 (t, $J$=7.16 Hz, 3H), 2.55 (s, 3H), 4.45 (q, $J$=7.16 Hz, 2H), 6.98 (t, $J$=7.60 Hz, 1H), 7.09 (d, $J$=8.28 Hz, 1H), 7.37–7.52 (m, 4H), 7.68–7.86 (m, 3H), 8.93 (s, 1H), 11.50 (s, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$=10.6, 14.4, 61.4, 105.1, 110.2, 116.4, 118.7, 118.9, 119.4, 119.6, 121.1, 123.3, 124.7, 125.7, 128.3, 130.0, 131.5, 132.3, 135.8, 162.7, 165.8, 195.0; MS (70 eV, EI): $m/z$: 374 ($M^+$+1), 373 ($M^+$); elemental analysis calcd (%) for $C_{23}H_{19}NO_4$ (373.13): C 73.98, H 5.13, N 3.75. Found C 73.38, H 5.03, N 3.67.

*4.3.3. 1-Ethoxycarbonyl-3-(2′-hydroxybenzoyl)-10-ethyl-benzo[b]indolizine (**9c**)*

Red needles ($CCl_4$/hexane, 1:4); mp 68–69 °C; yield (60%); $R_f$=0.73 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3052, 1726, 1632, 1607, 1529,1487, 1427, 1222, 1029 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$=1.29 (t, $J$=7.40 Hz, 3H), 1.46 (t, $J$=7.11 Hz, 3H), 3.08 (q, $J$=7.40 Hz, 2H), 4.46 (q, $J$=7.11 Hz, 2H), 6.94 (t, $J$=7.54 Hz, 1H), 7.09 (d, $J$=8.30 Hz, 1H), 7.37–7.52 (m, 4H), 7.63 (overlapping dd and s, 1H each), 7.83 (d, $J$=7.74 Hz, 1H), 8.92 (s, 1H), 11.50 (s, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$=14.5, 15.3, 18.1, 61.5, 110.0, 112.0, 116.3, 118.6, 118.7, 119.4, 119.5, 122.0, 123.1, 124.6, 125.4, 127.0, 130.2, 131.3, 131.5, 133.6, 135.7, 162.6, 165.8, 195.3; MS (70 eV, EI): $m/z$: 388 ($M^+$+1), 387 ($M^+$); elemental analysis calcd (%) for $C_{24}H_{21}NO_4$ (387.15): C 74.40, H 5.46, N 3.62. Found C 74.23, H 5.37, N 3.54.

*4.3.4. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-methyl-benzoyl)-benzo[b]indolizine (**9d**)*

Red needles ($CCl_4$/hexane, 1:9); mp 160–162 °C; yield (32%); $R_f$=0.58 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 2924, 2854, 1713, 1628, 1543, 1458, 1365, 1311, 1288, 1257, 1196 $cm^{-1}$; $^1H$ NMR (300 MHz,

$CDCl_3$): $\delta$=1.49 (t, $J$=7.2 Hz, 3H), 2.33 (s, 3H), 4.48 (q, $J$=7.2 Hz, 2H), 7.01 (d, $J$=8.4 Hz, 1H), 7.33–7.50 (m, 5H), 7.86 and 7.89 (overlapping doublets, $J$=9.3 and 8.7 Hz, 2H), 8.21 (s, 1H), 9.01 (s, 1H), 11.38 (s, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=14.5, 20.6, 61.2, 97.9, 110.5, 117.5, 118.7, 119.0, 119.9, 121.7, 121.8, 125.1, 127.9, 128.1, 130.5, 131.3, 131.5, 132.4, 133.7, 137.0, 160.8, 164.3, 195.5; MS (ESI): $m/z$: 396.0 $(M+Na)^+$; elemental analysis calcd (%) for $C_{23}H_{19}NO_4$ (373.13): C 73.98, H 5.13, N 3.75. Found C 73.67, H 5.08, N 3.69.

#### 4.3.5. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-methyl-benzoyl)-10-methyl-benzo[b]indolizine (**9e**)

Red needles ($CCl_4$/hexane, 1:9); mp 180–181 °C; yield (49%); $R_f$=0.64 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3062, 1728, 1635, 1574, 1543, 1458, 1319, 1296, 1265, 1227 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=1.45 (t, $J$=7.15 Hz, 3H), 2.35 (s, 3H), 2.58 (s, 3H), 4.50 (q, $J$=7.14 Hz, 2H), 7.05 (d, $J$=8.44 Hz, 1H), 7.37–7.54 (m, 4H), 7.82–7.89 (m, 3H), 8.94 (s, 1H), 11.37 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=10.4, 14.2, 20.5, 61.6, 105.1, 110.2, 116.4, 118.4, 119.0, 119.5, 122.1, 122.9, 124.6, 125.7, 127.7, 128.1, 129.8, 131.4, 132.0, 133.6, 136.9, 160.2, 165.9, 195.5; MS (ESI): $m/z$: 410.0 $(M+Na)^+$; elemental analysis calcd (%) for $C_{24}H_{21}NO_4$ (387.15): C 74.40, H 5.46, N 3.62. Found C 74.28, H 5.41, N 3.56.

#### 4.3.6. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-methyl-benzoyl)-10-ethyl-benzo[b]indolizine (**9f**)

Orange red needles ($CCl_4$/hexane, 1:9); mp 116–118 °C; yield (59%); $R_f$=0.69 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3055, 1720, 1628, 1589, 1466, 1312, 1288, 1227 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=1.31 (t, $J$=7.42 Hz, 3H), 1.46 (t, $J$=7.13 Hz, 3H), 2.33 (s, 3H), 3.10 (q, $J$=7.42 Hz, 2H), 4.48 (q, $J$=7.12 Hz, 2H), 7.03 (d, $J$=8.44 Hz, 1H), 7.35–7.56 (m, 4H), 7.78 (s, 1H), 7.87 (fused d, $J$=8.24 Hz, 2H), 8.93 (s, 1H), 11.35 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.2, 15.2, 18.0, 20.5, 61.6, 110.3, 111.9, 116.3, 118.3, 119.0, 119.5, 122.0, 123.0, 124.5, 125.5, 126.9, 128.0, 130.1, 131.1, 131.3, 133.6, 136.8, 160.2, 166.1, 195.4; MS (ESI): $m/z$: 424.05 $(M+Na)^+$; elemental analysis calcd (%) for $C_{25}H_{23}NO_4$ (401.16): C 74.79, H 5.77, N 3.49. Found C 74.48, H 5.64, N 3.43.

#### 4.3.7. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-chloro-benzoyl)-benzo[b]indolizine (**9g**)

Red needles ($CCl_4$/hexane, 1:9); mp 144–145 °C; yield (29%); $R_f$=0.59 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3078, 2978, 1713, 1620, 1458, 1311, 1257, 1219 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.49 (t, $J$=7.05 Hz, 3H), 4.49 (q, $J$=7.1 Hz, 2H), 7.08 (d, $J$=8.7 Hz, 1H), 7.40–7.51 (m, 4H), 7.69 (d, $J$=2.4 Hz, 1H), 7.86 and 7.91 (overlapping doublets, $J$=7.5 and 8.4 Hz, 2H), 8.17 (s, 1H), 9.01 (s, 1H), 11.41 (s, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=14.4, 61.4, 98.4, 110.6, 116.9, 119.9, 120.4, 120.9, 121.7, 122.1, 123.8, 125.3, 127.4, 130.6, 130.7, 131.4, 132.3, 134.0, 135.9, 161.1, 164.3, 194.6; MS (ESI): $m/z$: 416.18 $(M+Na)^+$; elemental analysis calcd (%) for $C_{22}H_{16}ClNO_4$ (393.08): C 67.10, H 4.10, N 3.56. Found C 66.82, H 4.03, N 3.50.

#### 4.3.8. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-chloro-benzoyl)-10-methyl-benzo[b]indolizine (**9h**)

Red needles ($CCl_4$/hexane, 1:9); mp 144–146 °C; yield (45%); $R_f$=0.63 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3055, 1728, 1635, 1574, 1512, 1465, 1311, 1288, 1227, 1188 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.47 (t, $J$=7.05 Hz, 3H), 2.55 (s, 3H), 4.46 (q, $J$=7.1 Hz, 2H), 7.06 (d, $J$=9.0 Hz, 1H), 7.38–7.52 (m, 3H), 7.69 (d, $J$=2.4 Hz, 1H), 7.75 (d, $J$=1.5 Hz, 1H), 7.81 and 7.86 (overlapping doublets, $J$=7.8 Hz each, 2H), 8.93 (s, 1H), 11.37 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=10.6, 14.4, 61.6, 105.9, 110.3, 115.9, 119.7, 120.1, 120.4, 122.5, 123.3, 123.7, 124.9, 125.3, 127.7, 130.2, 130.6, 132.3, 133.9, 135.6, 161.0, 165.5, 194.2; MS (ESI): $m/z$: 429.97 $(M+Na)^+$; elemental analysis calcd (%) for $C_{23}H_{18}ClNO_4$ (407.09): C 67.73, H 4.45, N 3.43. Found C 67.52, H 4.41, N 3.41.

#### 4.3.9. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-chloro-benzoyl)-10-ethyl-benzo[b]indolizine (**9i**)

Red needles ($CCl_4$/hexane, 1:9); mp 136–138 °C; yield (50%); $R_f$=0.65 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3063, 1720, 1620, 1527, 1458, 1419, 1311, 1265, 1234, 1188, 1142 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.29 (t, $J$=7.35 Hz, 3H), 1.47 (t, $J$=7.05 Hz, 3H), 3.07 (q, $J$=7.4 Hz, 2H), 4.46 (q, $J$=7.1 Hz, 2H), 7.05 (d, $J$=8.7 Hz, 1H), 7.24 (s, 1H), 7.30–7.50 (m, 2H), 7.70 (dd, $J$=1.5 and 2.7 Hz, 2H), 7.84 (t, $J$=9.15 Hz, 2H), 8.92 (s, 1H), 11.37 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.4, 15.4, 18.2, 61.7, 110.4, 112.7, 115.9, 119.8, 120.2, 120.4, 122.5, 123.6, 123.7, 124.9, 125.1, 130.4, 130.6, 132.9, 133.9, 134.9, 135.6, 161.0, 165.7, 194.2; MS (ESI): $m/z$: 444.5 $(M+Na)^+$; elemental analysis calcd (%) for $C_{24}H_{20}ClNO_4$ (421.11): C 68.33, H 4.78, N 3.32. Found C 68.16, H 4.71, N 3.23.

#### 4.3.10. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-fluoro-benzoyl)-10-methyl-benzo[b]indolizine (**9j**)

Red needles ($CCl_4$/hexane, 1:9); mp 122–124 °C; yield (40%); $R_f$=0.73 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3064, 1710, 1598, 1478, 1466, 1420, 1266, 1227, 1188 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.46 (t, $J$=7.2 Hz, 3H), 2.53 (s, 3H), 4.46 (q, $J$=7.2 Hz, 2H), 7.06 (d, $J$=9.0 Hz, 1H), 7.23–7.30 (m, 1H), 7.33 (s, 1H), 7.39(sd, $J$=7.15 Hz, 1H), 7.49 (t, $J$=7.5 Hz, 1H), 7.73 (s, 1H), 7.79 and 7.84 (overlapping doublets, $J$=8.1 Hz each, 1H each), 8.90 (s, 1H), 11.20 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=10.5, 14.3, 61.7, 105.7, 110.3, 115.9, 116.4, 116.7, 118.9, 119.0, 119.6, 119.9, 120.1, 122.3, 123.1, 123.3, 123.4, 124.9, 125.1, 127.7, 130.1, 132.2, 133.8, 153.2, 156.4, 158.6, 160.3, 165.7, 194.4; MS (ESI): $m/z$: 414.1 $(M+Na)^+$; elemental analysis calcd (%) for $C_{23}H_{18}FNO_4$ (391.12): C 70.58, H 4.64, N 3.58. Found C 70.46, H 4.57, N 3.52.

#### 4.3.11. 1-Ethoxycarbonyl-3-(2′-hydroxy-5′-fluoro-benzoyl)-10-ethyl-benzo[b]indolizine (**9k**)

Red needles ($CCl_4$/hexane, 1:9); mp 143–145 °C; yield (45%); $R_f$=0.76 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3078, 1736, 1651, 1589, 1481, 1419, 1265, 1188, 1149 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.22 (t, $J$=7.5 Hz, 3H), 1.39 (t, $J$=7.05 Hz, 3H), 3.01 (q, $J$=7.4 Hz, 2H), 4.40 (q, $J$=7.0 Hz, 2H), 7.01 (d, $J$=9.0 Hz, 1H), 7.17–7.46 (m, 4H), 7.65 (s, 1H), 7.77 and 7.80 (overlapping doublets, $J$=0.9, 7.2 Hz, 2H), 8.86 (s, 1H), 11.13 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.2, 15.3, 18.1, 61.5, 110.4, 112.4, 115.9, 116.3, 116.6, 118.9, 119.6, 120.0, 122.3, 122.7, 123.3, 124.8, 125.0, 126.9, 130.2, 131.4, 140.5, 158.6, 168.9, 194.2; MS (ESI): $m/z$: 428.1 $(M+Na)^+$; elemental analysis calcd (%) for $C_{24}H_{20}FNO_4$ (405.14): C 71.10, H 4.97, N 3.45; Found C 70.86, H 4.91, N 3.37.

#### 4.3.12. 2-(Carboethoxymethyl)indole (**16a**)

Viscous oil; yield (5%); $R_f$=0.64 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 1732, 1532, 1555, 1537, 1508, 1488, 1468, 1458, 1450, 1432, 1409, 1378, 1355, 1242 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=1.28 (t, $J$=7.07 Hz, 3H), 3.82 (s, 2H), 4.20 (q, $J$=7.07 Hz, 2H), 6.35 (s, 1H), 7.01–7.50 (m, 4H), 8.68 (s, 1H, NH); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=14.1, 33.9, 61.3, 101.7, 110.7, 119.7, 120.0, 121.6, 126.4, 132.8, 135.8, 170.6; MS (70 eV, EI): $m/z$: 204 ($M^+$+1), 203 ($M^+$); elemental analysis calcd (%) for $C_{12}H_{13}NO_2$ (203.09): C 70.92, H 6.45, N, 6.89. Found C 70.78, H 6.42, N 6.86.

#### 4.3.13. 2-(Carboethoxymethyl)-3-methylindole (**16b**)

Viscous oil; yield (~1%); $R_f$=0. 71 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 1732, 1532, 1555, 1537, 1508, 1488, 1468, 1458, 1450, 1432, 1409, 1378, 1355, 1242 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=1.24 (t, $J$=7.10 Hz, 3H), 2.48 (s, 3H), 3.82 (s, 2H), 4.20 (q, $J$=7.10 Hz, 2H), 7.09–7.46 (m, 3H), 7.49 (d, $J$=7.30 Hz, 1H), 8.71 (s, 1H, NH); MS (70 eV, EI): $m/z$: 218 ($M^+$+1), 217 ($M^+$); elemental analysis calcd (%) for $C_{13}H_{15}NO_2$ (217.11): C 71.87, H 6.96, N 6.45. Found C 71.59, H 6.89, N 6.38.

*4.3.14. 2-(Carboethoxymethyl)-3-ethylindole (**16c**)*

Viscous oil; yield (<1%); $R_f$=0. 74 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 1732, 1572, 1555, 1537, 1508, 1488, 1468, 1458, 1450, 1432, 1409, 1378, 1355, 1242 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$=1.16 (t, $J$=7.43 Hz, 3H), 1.25 (t, $J$=7.12 Hz, 3H), 2.64 (q, $J$=7.43 Hz, 2H), 3.66 (s, 2H), 4.16 (q, $J$=7.12 Hz, 2H), 6.99–7.30 (m, 3H), 7.43 (d, $J$=7.25 Hz, 1H), 8.71 (s, 1H, NH); MS (70 eV, EI): $m/z$: 232 ($M^+$+1), 231 ($M^+$); elemental analysis calcd (%) for $C_{14}H_{17}NO_2$ (231.13) C 72.70, H 7.41, N 6.06. Found C 72.52, H 7.34, N 5.98.

### 4.4. General procedure for the reaction of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (7) with allenic ketones (18)

A solution of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (**7**, 200 mg) and allenic ketones (**18**, 1.5 mol equiv) in 20 mL dry benzene was stirred at ambient temperature under nitrogen atmosphere till the completion of reaction (TLC). Benzene was removed under vacuum and the benzoindolizines (**19a–d**) were purified by column chromatography (silica gel, 60–120 mesh, eluent hexane/ EtOAc 9.5:0.5). Further elution with increasing concentration of EtOAc in hexane afforded the rearranged product (**17**) of nitrones (30–45%).

*4.4.1. 1-Acetyl-3-(2′-hydroxybenzoyl)benzo[b]indolizine (**19a**)*

Red needles ($CCl_4$/hexane, 1:4); mp 144–145 °C; yield (34%); $R_f$=0.63 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 1684, 1632, 1611, 1601, 1530, 1487, 1431, 1226, 1034, 936 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$=2.70 (s, 3H), 6.99 (t, $J$=7.64 Hz, 1H), 7.14 (d, $J$=8.34 Hz, 1H), 7.30–7.54 (m, 4H), 7.72 (overlapping d and s, 1H each), 7.82 (d, $J$=7.98 Hz, 1H), 8.12 (s, 1H), 9.00 (s, 1H), 11.48 (s, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$=26.9, 99.4, 110.5, 116.9, 118.7, 118.9, 120.7, 121.8, 122.1, 125.2, 127.5, 128.4, 129.7, 130.2, 131.6, 133.2, 134.5, 136.2, 162.5, 195.7, 195.9; MS (70 eV, EI): $m/z$: 329 ($M^+$); elemental analysis calcd (%) for $C_{21}H_{15}NO_3$ (329.11): C 76.58, H 4.59, N 4.25; Found C 76.46, H 4.51, N 4.21.

*4.4.2. 1-p-Methoxybenzylcarbonyl-3-(2′-hydroxybenzoyl)-benzo[b]indolizine (**19b**)*

Red needles ($CCl_4$/hexane, 1:3); mp 178–179 °C; yield (28%); $R_f$=0.57 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3099, 1677, 1632, 1602, 1528, 1486, 1222, 1158, 1027 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$=3.80 (s, 3H), 4.32 (s, 2H), 6.90 (d, $J$=8.80 Hz, 2H), 6.94 (t, $J$=7.08 Hz, 1H), 6.99 (d, $J$=8.19 Hz, 1H), 7.15 (d, $J$=8.59 Hz, 2H), 7.43–7.55 (m, 3H), 7.62 (dd, $J$=8.70 & 1.48 Hz, 1H), 7.76 (overlapping d and s, 1H each), 7.88 (t, $J$=7.67 Hz, 1H), 8.21 (d, $J$=1.04 Hz, 1H), 9.05 (s, 1H), 11.49 (s, 1H); MS (70 eV, EI): $m/z$: 436 ($M^+$+1), 435 ($M^+$), 369, 355, 112, 58; elemental analysis calcd (%) for $C_{28}H_{21}NO_4$ (435.15): C 77.23, H 4.86, N 3.22. Found C 77.16, H 4.81, N 3.17.

*4.4.3. 1-Benzylcarbonyl-3-(2′-hydroxybenzoyl)benzo[b]-indolizine (**19c**)*

Red needles ($CCl_4$/hexane, 1:3); mp 161–162 °C; yield (29%); $R_f$=0.62 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 3068 (OH), 1675, 1628, 1602, 1525, 1482, 1427, 1218, 1162, 1030, 931 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 4.38 (s, 2H), 6.98 (t, $J$=7.86 Hz, 1H), 7.15 (d, $J$=8.88 Hz, 1H), 7.28–7.58 (m, 8H), 7.60 (dd, $J$=8.80 and 1.23 Hz, 1H), 7.73 (s, 1H), 7.88 (overlapping ds, $J\sim$7.31 Hz, 2H), 8.21 (d, $J$=1.28 Hz, 1H), 9.05 (s, 1H), 11.49 (s, 1H); MS (EI): $m/z$: 406 ($M^+$+1), 405 ($M^+$), 356, 355, 284, 283, 269, 241, 58; elemental analysis calcd (%) for $C_{27}H_{19}NO_3$ (405.14): C 79.98, H 4.72, N 3.45. Found C 79.76, H 4.67, N 3.40.

*4.4.4. 1-Acetyl-3-(2′-hydroxybenzoyl)-10-phenyl-benzo[b]indolizine (**19d**)*

Red needles ($CCl_4$/hexane, 1:3); mp 201–202 °C; yield 42%; $R_f$=0.69 ($CHCl_3$/hexane, 9:1); IR (KBr): $\nu_{max}$ 1696, 1632, 1611, 1530, 1483, 1431, 1342, 1226, 1034 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.89 (s, 3H), 6.95 (t, $J$=7.61 Hz, 1H), 7.14 (d, $J$=8.20 Hz, 1H), 7.24–7.62 (m, 8H), 7.72 and 7.68 (overlapping doublets, $J$=7.97 and 7.63 Hz, 2H), 7.90–7.97 (m, 2H), 9.01 (s, 1H), 11.57 (s, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 28.9, 107.1, 110.5, 116.3, 118.8, 119.9, 120.1, 122.6, 123.7, 125.3, 126.9, 127.2, 127.4, 127.5, 128.5, 129.4, 129.8, 130.4, 131.6, 132.2, 133.5, 135.9, 162.7, 195.5, 198.9; MS (EI): $m/z$: 405 ($M^+$); elemental analysis calcd (%) for $C_{27}H_{19}NO_3$ (405.14): C 79.98, H 4.72, N 3.45. Found C 79.84, H 4.65, N 3.39.

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### Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.076.

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