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A facile synthesis of α,α′-bis(substituted-benzylidene)-cycloalkanones and substituted-benzylidene heteroaromatics: utility of NaOAc as a catalyst for aldol-type reaction

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Abstract—Utility of NaOAc in glacial HOAc as a catalyst for aldol-type condensation reactions was examined. Reactions of cycloalkanones and selected heteroaromatics with various aldehydes in the presence of NaOAc in glacial HOAc provided α,α′-bis(substituted-benzylidene)-cycloalkanones and substituted-benzylidene heteroaromatics, respectively, in good yields.

1. Introduction

The Claisen–Schmidt reaction (cross-aldol reaction) is a condensation reaction of aldehydes and carbonyl compounds leading to β-hydroxycarbonyl compounds and has been playing important roles in synthetic organic chemistry.[1] Subsequent dehydration of β-hydroxycarbonyl compounds affords α-alkylidene or α-arylidene compounds. Such an introduction of alkylidene or arylidene moieties at the α-position of carbonyl compounds has also been a quite useful synthetic tool in the natural product chemistry.[1a] Similar reaction of selected heteroaromatics with aromatic aldehydes gives arylidene heteroaromatics, which have been used as key intermediates in heterocyclic chemistry.[2]

Although studies on the Claisen–Schmidt reaction have been focused on α-alkylidene- and α-arylidene-carbonyl compounds, interest in α,α′-bisalkylidene- and α,α′-bisarylidene-carbonyl compounds is still increasing. Particularly, α,α′-bis(substituted-benzylidene)cycloalkanones (**3**) have been attracting much attention due to not only their intriguing biological activities such as antiangiogenic,[3] quinine reductase inducer,[4] cytotoxic,[5] and cholesterol-lowering activity,[6] but also their large second-harmonic generation coefficient that is good enough for nonlinear optical materials.[7] They are also the important precursors for the synthesis of pyrimidine derivatives,[8] 2,7-disubstituted tropones,[9] and synthetic intermediates to functionalize α,β-position during the total synthesis of natural products such as cystodytins.[10]

On the other hand, arylidene derivatives of heteroaromatics have been used to functionalize the *peri*-position, especially for the two-step introduction of keto group,[2] and employed for the synthesis of various polydentate ligands[2d,11] as well as biologically interesting compounds.[2f,12]

The Claisen–Schmidt reactions of cycloalkanones leading to α,α′-bis(arylidene)cycloalkanones are originally catalyzed by strong acids[13] and more likely by bases.[14] However, the reactions suffer from reverse and/or side reactions.[15] A variety of metal(II) ions have been introduced to replace acids or bases, but the yields were not satisfactory in most cases.[16] Continuing efforts to find new catalysts have resulted in the introduction of various reagents such as Cp_2ZrH_2,[17a] Cp_2TiPh_2,[17b] BMPTO,[17c] $RuCl_3$,[17d] SmI_3,[17e] $TiCl_3(CF_3SO_3)$,[17f] La^{3+}-immobilized organic solid,[17g] KF–Al_2O_3,[17h] $Mg(HSO_4)_2$,[17i] $FeCl_3$,[17j] $BF_3{\cdot}OEt_2$,[17k] $InCl_3$,[17l] TMSCl/NaI,[17m] TMSCl/Pd–C,[17n] $SOCl_2$,[17o] $Yb(OTf)_3$,[17p] K_2CO_3/PEG-400,[17q] molecular I_2,[17r] and Et_3N in the presence of $LiClO_4$.[17s] In addition, microwave irradiation method was employed to improve yields as well as to reduce reaction time.

Most of the cases, however, suffered from long reaction time, side reactions, and low yields. In some cases, the cost of the catalysts acts as bottleneck for the general use.[17] Disadvantages in the presence of reported catalysts and the importance of the Claisen–Schmidt reaction in synthetic organic chemistry prompted us to evaluate the utility

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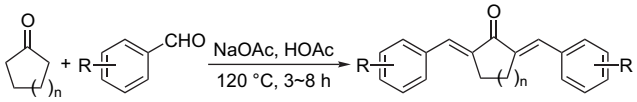
of NaOAc as a catalyst for the introduction of benzylidene moiety on cycloalkanones or heteroaromatics.

2. Result and discussion

2.1. α,α′-Bis(substituted-benzylidene)cycloalkanones

The Claisen–Schmidt reactions of cyclopentanone (**1a**) and cyclohexanone (**1b**) with benzaldehyde (**2a**)[18] in the presence of an equimolar amount of NaOAc in glacial HOAc smoothly proceeded to afford the corresponding α,α′-bis-(benzylidene)cycloalkanones, **3a** and **3g**, in 83% and 78% yield, respectively (Scheme 1).



1a n = 1 **2** **3**
b n = 2

Scheme 1.

We, thus, examined the catalytic ability of NaOAc by reacting cyclohexanone (**1b**) with benzaldehyde (**2a**) in the presence of various ratios of NaOAc to afford the corresponding α,α′-bis(benzylidene)cyclohexanone (**3g**), and the results are summarized in Table 1. Reactions with 10% molar equivalents of NaOAc gave the desired products in yields comparable to those with stoichiometric amounts of NaOAc. Although reactions with 1% molar equivalent of NaOAc effectively yielded the desired products, somewhat longer time was required to secure the same yields.

We next examined the scope and limitation of this reaction system with selected cycloalkanones and a series of electronically modified aromatic aldehydes in the presence of 10% molar equivalents of NaOAc in glacial HOAc and the results are summarized in Table 2.[19]

The electronic nature of the substituent on the benzene ring did not affect the reaction (compare **3d** vs **3f**, **3h** vs **3m**). Reactions with HOAc or NaOAc alone were also attempted but did not afford the desired products. These results implied that neither HOAc nor NaOAc alone was good enough to catalyze the Claisen–Schmidt reaction. A distinguished advantage of employing NaOAc as a catalyst is that neither the expected (self- and/or mono-condensed products) nor the unexpected side products are obtained from the reaction.

Table 1. Reactions of cyclohexanone (**1b**) with benzaldehyde (**2a**) in the presence of various amounts of NaOAc in glacial HOAc

Entry	NaOAc (mol %)[a]	*t* (h)	*y*[b] (%)
1	100	4	82
2	100	8	83
3	50	4	83
4	50	8	88
5	10	4	83
6	10	8	86
7	1	6	23
8	1	36	84

[a] Relative to benzaldehyde.
[b] Isolated yields of **3g**, which are not optimized.

Table 2. The Claisen–Schmidt reaction of cycloalkanones **1** with aromatic aldehydes **2**

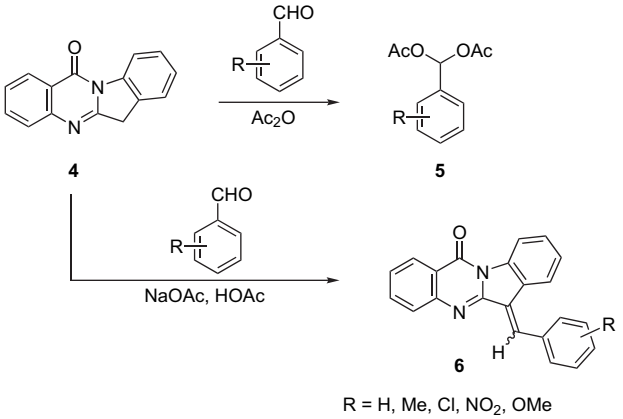
Entry[a]	R	*n*	*t*[b] (h)	*y*[c] (%)	Mp (°C)
3a	H	1	7	86	188–190 (188–189[17c])
3b	2-Br	1	3	85	163–165 (162–163[17e])
3c	3-Cl	1	5	91	175–176
3d	4-F	1	8	93	210 (sub.)
3e	4-Me	1	6	84	230 (sub.) (183–184[17e])
3f	4-OMe	1	4	84	210–211 (210–211[17c])
3g	H	2	7	86	119–120 (117–118[17c])
3h	2-NO_2	2	8	93	158–159
3i	3-Cl	2	4	92	103–105
3j	4-Br	2	6	91	165–168
3k	4-F	2	7	86	158–159 (156–158[17m])
3l	4-Me	2	5	81	165–167 (170.1[20])
3m	4-OMe	2	6	86	202–203 (202–203[17m])

[a] The structures of compounds were confirmed by spectroscopic methods including various NMR (^{1}H, ^{13}C, and DEPT135).
[b] Reaction time, which is not optimized.
[c] Isolated yield, which is not optimized.

2.2. Substituted-benzylidene heteroaromatics

The arylidene derivatives of heteroaromatics have been generally prepared by condensing heteroaromatics with aromatic aldehyde in the presence of Ac_2O.[2] A serious drawback of this method, which should be overcome, is the tedious work-up procedures due to self-aldol condensation of aldehydes.[2c,11c]

Our initial attempts to prepare 6-(substituted-benzylidene)-indolo[2,1-*b*]quinazolin-12(5*H*)-ones (**6**) by the reactions of indolo[2,1-*b*]quinazolin-12(5*H*)-one (**4**) with benzaldehydes in the presence of Ac_2O afforded benzaldehyde-1,1-diacetates (**5**)[21] instead of the desired product **6** (Scheme 2). However, the reactions in the presence of NaOAc in glacial acetic acid afforded **6** in fairly good yields as the mixtures of (*E*)- and (*Z*)-isomer and the results are summarized in Table 3. These isomers were separable either by careful column chromatography or by preparative HPLC. The electronic nature as well as the position of substituents did not seem to affect the reaction. The utility of NaOAc in HOAc was further pursued with 2,3-cycloalkano[*b*]pyridines (**7**) and 2,3-polymethylenequinazolin-4(3*H*)-ones (**9**) and the results are summarized in Table 3.



Scheme 2.

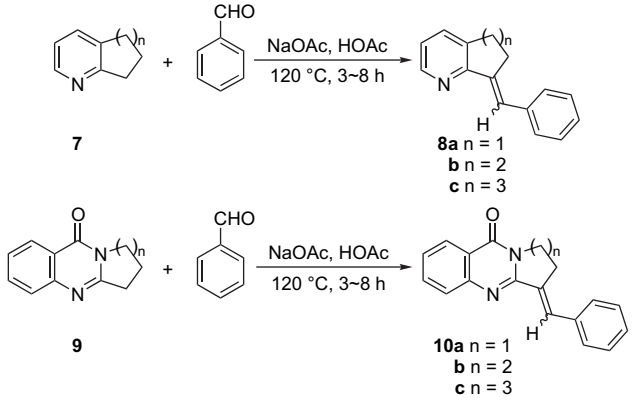
Reactions proceeded smoothly to yield the corresponding benzylidene derivatives **8** and **10**, respectively, in good

Table 3. Preparation of the benzylidene heteroaromatics

Entry[a]	R	*n*	*t*[b] (h)	*y*[c] (%)	Ratio[d] (*E*:*Z*)
6a	H	—	8	89	1.2:1[e]
6b	2-OMe	—	6	67	13:1
6c	3-OMe	—	4	61	7:1
6d	4-OMe	—	7	67	4.5:1
6e	2-NO_2	—	8	78	*E* only
6f	3-NO_2	—	4	80	*Z* only
6g	4-NO_2	—	6	79	*E* only
6h	2-Cl		6	65	11:1
6i	3-Cl		5	70	11:1
6j	4-Cl		7	76	2:1
8a	—	1	7	85	*E* only
8b	—	2	3	87	*E* only
8c	—	3	5	91	n.d[f]
10a	—	1	3	87	*E* only
10b	—	2	6	96	*E* only
10c	—	3	8	90	3.1:1

[a] The structures of compounds were confirmed by spectroscopic methods including various NMR (^{1}H, ^{13}C, and DEPT135).
[b] Reaction times, which are not optimized.
[c] Isolated yields, which are not optimized.
[d] Determined by either ^{1}H NMR or HPLC unless noted.
[e] Ratio of isolated products.
[f] Not determined.

yields (Table 3, Scheme 3). It should be noted that cyclopentano-system (**9a**) and cyclohexano-system (**9b**) afforded only (*E*)-isomers (**10a**,**b**), confirmed by ^{1}H NMR experiments while cycloheptano-system (**9c**) afforded the mixture of (*E*)-**10c** and (*Z*)-**10c** isomers in a ratio of 3.1:1. Such distribution might be explained by the severe steric hindrance between phenyl and lone pair electrons of nitrogen of the *possible* (*Z*)-isomer in the more flatter cyclopentano-derivative (**10a**) and cyclohexano-derivative (**10b**) resulting in the exclusive formation of the (*E*)-isomers, but in the case of the more flexible cycloheptano-derivative (**10c**) such a steric hindrance can be relieved enough to afford the mixture of (*E*)- and (*Z*)-isomer.



Scheme 3.

3. Conclusion

Aldol-type condensation reactions of cycloalkanones **1** and selected heteroaromatics **4**, **7**, and **9** with various aromatic aldehydes in the presence of NaOAc in glacial HOAc afforded α,α′-bis(substituted-benzylidene)cycloalkanones (**3**) and substituted-benzylidene heteroaromatics **6**, **8**, and **10**, respectively, in good yields. The advantages of employing NaOAc in glacial acetic acid include high yields, simplicity of operation, and no expected/unexpected by-products. Experiments to determine an optimal amount of NaOAc for the best result as well as to select the best acetate salts are in progress and will be due in the near future.

4. Experimental

4.1. General

Melting points were recorded on a Fisher–Jones melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded using KBr pellets for solids and neat for liquids on FT/IR-300 E (Jasco) spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker 250 spectrometer (250 MHz for ^{1}H NMR and 62.5 MHz for ^{13}C NMR) or Bruker 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) and are reported in parts per million (ppm) from the internal standard tetramethylsilane. Cyclohexanone and cyclopentanone were redistilled just before the reactions. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on LCQ advantage-trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA). Elemental analyses were carried out on a Hewlett–Packard Model 185B elemental analyzer.

4.2. Representative procedure for the preparation of α,α′-bis(benzylidene)cyclopentanones (3): α,α′-bis-(benzylidene)cyclopentanone (3a)

A mixture of cyclopentanone (**1a**, 0.42 g, 5.0 mmol), benzaldehyde (**2a**, 1.06 g, 10.0 mmol), and anhydrous NaOAc (82 mg, 1.0 mmol) in glacial HOAc (5 mL) was heated at 120 °C for 8 h under N_2 atmosphere. The reaction mixture was poured into crushed ice, the solid formed was collected and washed with *n*-hexane to give 216 mg (86%) of α,α′-bis(benzylidene)cyclopentanone (**3a**). The spectral data are identical to those of literature.[17m]

The spectral data and analytical data of the *unknown* compounds are given below.

4.2.1. 2,5-Bis(3-chlorobenzylidene)cyclopentanone (3c). Yellow needles: mp 175–176 °C. IR (KBr): *ν* 1621, 1560, 1186, 671 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): *δ* 7.52 (t, *J*=1.2 Hz, 2H), 7.48 (s, 2H), 7.43–7.41 (m, 2H), 7.35–7.32 (m, 4H), 3.08 (s, 4H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): *δ* 195.9, 138.1, 137.3, 134.7, 132.6, 130.1, 130.0, 129.4, 128.9, 26.3. MS *m*/*z* (rel intensity): 331.2 (25), 329.3 (M+1, 40), 293.2 (100). MS (ESI) calcd for $C_{19}H_{14}Cl_2O$: 329 $[M+H]^+$, found: 329. Anal. Calcd for $C_{19}H_{14}Cl_2O\cdot 0.5H_2O$: C, 67.47; H, 4.47. Found: C, 67.51; H, 4.45.

4.2.2. 2,5-Bis(4-fluorobenzylidene)cyclopentanone (3d). Yellow needles: mp 210 °C (sublimed). IR (KBr): *ν* 1638, 1618, 617 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) *δ* 7.58–7.55 (m, 6H), 7.13–7.08 (m, 4H), 3.07 (s, 4H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): *δ* 196.1, 163.5 (J_{C-F}=208 Hz), 136.64, 136.60, 132.7 (J_{C-F}=8.5 Hz), 132.0 (J_{C-F}=3 Hz), 116.1 (J_{C-F}=22 Hz), 26.3. MS *m*/*z* (rel intensity): 297.3 (M+1,

40), 279.1 (72), 201.1 (72), 173.1 (90), 109.1 (100). Anal. Calcd for $C_{19}H_{14}F_2O$: C, 77.01; H, 4.76. Found: C, 76.97; H, 4.74.

4.2.3. 2,6-Bis(2-nitrobenzylidene)cyclohexanone (3h). Yellow needles: mp 158–159 °C. IR (KBr) ν 1638, 1617, 1519 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.11 (dd, J=8.2, 0.8 Hz, 2H), 7.96 (s, 2H), 7.63 (dd, J=7.5, 0.8 Hz, 2H), 7.49 (td, J=7.7, 0.8 Hz, 2H), 7.35 (d, J=7.6 Hz, 2H), 2.58 (overlapped t, J=5.6 Hz, 4H), 1.70 (quintet, J=5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 188.6, 148.2, 137.2, 134.0, 133.1, 131.9, 131.1, 129.0, 124.9, 27.8, 22.7. MS *m/z* (rel intensity): 365.1 (100), 331.2 (18). Anal. Calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.16; H, 4.05; N, 7.96.

4.2.4. 2,6-Bis(3-chlorobenzylidene)cyclohexanone (3i). Yellow needles: mp 103–105 °C. IR (KBr): ν 1628, 1609, 1574, 1490, 1472, 1170, 782, 681 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.68 (t, J=1.2 Hz, 2H), 7.40 (s, 2H, benzylidene H), 7.32–7.28 (m, 6H), 2.87 (t, J=5.6 Hz, 4H), 1.77 (quintet, J=5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 189.7, 137.5, 136.9, 135.5, 134.2, 124.8, 129.6, 128.6, 128.5, 28.2, 22.6. MS *m/z* (rel intensity): 345.1 (8), 343.1 (18), 325.1 (100). Anal. Calcd for $C_{20}H_{16}Cl_2O$: C, 69.98; H, 4.70. Found: C, 70.03; H, 4.75.

4.2.5. 2,6-Bis(4-bromobenzylidene)cyclohexanone (3j). Yellow needles: mp 165–168 °C. IR (KBr) ν 1637, 1616, 1269, 1162 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.68 (s, 2H), 7.51 (dm, J=8.1 Hz, 4H), 7.30 (dm, J=8.0 Hz, 4H), 2.86 (t, J=5.6 Hz, 4H), 1.78 (quintet, J=5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 189.9, 136.4, 135.8, 134.6, 131.8, 131.6, 122.9, 28.3, 22.7. MS *m/z* (rel intensity): 437.7 (30), 435.1 (55), 433.4 (100), 381.6 (65). Anal. Calcd for $C_{20}H_{16}Br_2O$: C, 55.59; H, 3.73. Found: C, 55.54; H, 3.75.

4.3. Representative procedure for the preparation of benzylidene heteroaromatics 6, 8, and 10: 6-benzylideneindolo[2,1-*b*]quinazolin-12(5*H*)-one (6a)

A mixture of indolo[2,1-*b*]quinazolin-12(6*H*)-one (**4**) (1.17 g, 5.0 mmol), benzaldehyde (**2a**) (1.06 g, 10.0 mol), and NaOAc (0.082 g, 1.0 mmol) in 10 mL of glacial acetic acid was refluxed for 8 h. The resulting mixture was poured into 10% NaOH (40 mL) and extracted with CH_2Cl_2 (30 mL×3). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave a greenish yellow solid, which was purified by silica gel column chromatography eluting with CH_2Cl_2. The early eluants (R_f=0.65) afforded the (*E*)-isomer (1.61 g, 50%) as yellow needles: mp 161–162 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.69 (d, J=8.1 Hz, 1H), 8.44 (d, J=7.9 Hz, 1H), 8.35 (s, 1H), 7.84–7.78 (m, 3H), 7.72–7.67 (m, 2H), 7.54–7.43 (m, 5H), 7.15 (t, J=7.7 Hz, 1H). Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 82.03; H, 4.35; N, 8.70. The latter fractions (R_f=0.55) afforded the (*Z*)-isomer (1.35 g, 42%): mp 146–147 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (d, J=8.1 Hz, 1H), 8.59 (dd, J=8.0, 0.8 Hz, 1H), 8.43 (dd, J=8.0, 0.8 Hz, 1H), 7.80–7.74 (m, 3H), 7.70 (d, J=7.6 Hz, 2H), 7.54–7.43 (m, 5H), 7.35 (t, J=8.0, 0.8 Hz, 1H), 7.26 (s, 1H). Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.95; H, 4.37; N, 8.71.

4.3.1. 6-(2-Methoxybenzylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6b). Yellow needles as a mixture of (*E*)- and (*Z*)-isomer in a ratio of 13:1. (*E*)-Isomer: ^1H NMR ($CDCl_3$, 250 MHz): δ 8.69 (d, 1H, J=8.0 Hz), 8.43 (d, J=7.0 Hz, 1H), 8.42 (s, 1H), 7.80 (t, J=8.0 Hz, 1H), 7.77 (d, J=7.8 Hz, 2H), 7.74 (t, J=7.8 Hz, 1H), 7.50 (t, J=7.6 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.42 (t, J=8.0 Hz, 1H), 7.14 (t, J=7.8 Hz, 1H), 7.04 (t, J=7.8 Hz, 1H), 7.01 (d, J=7.8 Hz, 1H), 3.90 (s, 3H). MS (ESI) calcd for $C_{23}H_{16}N_2O_2$: 353 $[M+H]^+$, found: 353. (*Z*)-Isomer: ^1H NMR ($CDCl_3$, 250 MHz): δ 9.02 (d, J=7.8 Hz, 1H), 8.60 (d, J=7.6 Hz, 1H), 8.15 (s, 1H), 8.03 (d, J=8.0 Hz, 1H), 7.87 (d, J=7.8 Hz, 1H), 7.83–7.68 (m, 3H), 7.52–7.39 (2H), 7.14 (t, J=7.8 Hz, 1H), 7.04 (t, J=7.8 Hz, 1H), 7.01 (d, J=7.8 Hz, 1H), 3.92 (s, 3H). MS (ESI) calcd for $C_{23}H_{16}N_2O_2$: 353 $[M+H]^+$, found: 353.

4.3.2. 6-(3-Methoxybenzylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6c). Yellow needles as a mixture of (*E*)- and (*Z*)-isomer in a ratio of 7:1. (*E*)-Isomer: ^1H NMR ($CDCl_3$, 250 MHz): δ 8.67 (d, J=7.8 Hz, 1H), 8.42 (d, J=8.0 Hz, 1H), 8.29 (s, 1H), 7.84 (d, J=7.8 Hz, 1H), 7.80 (s, 1H), 7.78–7.75 (m, 1H), 7.52–7.48 (m, 1H), 7.43 (t, J=7.8 Hz, 1H), 7.40 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 7.14 (t, J=7.5 Hz, 1H), 6.97 (dd, J=8.0, 2.0 Hz, 1H), 3.84 (s, 3H). MS (ESI) calcd for $C_{23}H_{16}N_2O_2$: 353 $[M+H]^+$, found: 353. (*Z*)-Isomer: ^1H NMR ($CDCl_3$, 250 MHz): δ 8.71 (d, J=7.8 Hz, 1H), 8.64 (d, J=8.0 Hz, 1H), 7.78–7.75 (m, 2H), 7.66 (s, 1H), 7.52–7.48 (m, 2H), 7.43 (t, J=7.8 Hz, 1H), 7.40 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 7.14 (t, J=7.5 Hz, 1H), 7.04 (dd, J=8.0, 2.0 Hz, 1H), 3.98 (s, 3H). MS (ESI) calcd for $C_{23}H_{16}N_2O_2$: 353 $[M+H]^+$, found: 353.

4.3.3. 6-(4-Methoxybenzylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6d). Yellow needles as a mixture of (*E*)- and (*Z*)-isomer in a ratio of 4.5:1. (*E*)-Isomer: mp 234–235 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.72 (d, J=8.1 Hz, 1H), 8.44 (d, J=7.9 Hz, 1H), 8.31 (s, 1H), 7.97 (d, J=7.7 Hz, 1H), 7.79–7.76 (m, 2H), 7.70 (d, J=8.5 Hz, 2H), 7.52–7.41 (m, 2H), 7.19 (td, J=7.8, 1.0 Hz, 1H), 7.01 (d, J=8.5 Hz, 2H), 3.89 (s, 3H). MS (ESI) calcd for $C_{23}H_{16}N_2O_2$: 353 $[M+H]^+$, found: 353. (*Z*)-Isomer: ^1H NMR ($CDCl_3$, 250 MHz): δ 8.72 (d, J=8.1 Hz, 1H), 8.44 (d, J=7.9 Hz, 1H), 8.31 (s, 1H), 7.97 (d, J=7.7 Hz, 1H), 7.82–7.78 (m, 2H), 7.70 (d, J=8.5 Hz, 2H), 7.52–7.41 (m, 2H), 7.19 (td, J=7.8, 1.0 Hz, 1H), 7.04 (d, J=8.5 Hz, 2H), 3.92 (s, 3H). MS (ESI) calcd for $C_{23}H_{16}N_2O_2$: 353 $[M+H]^+$, found: 353.

4.3.4. (*E*)-6-(2-Nitrophenylmethylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6e). Yellow needles as an (*E*)-isomer only: mp 267–268 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.67 (d, J=8.1 Hz, 1H), 8.51 (s, 1H), 8.43 (d, J=7.9 Hz, 1H), 8.34 (d, J=8.0 Hz, 1H), 7.85–7.76 (m, 4H), 7.70–7.65 (m, 1H), 7.53 (ddd, J=8.5, 8.0, 1.0 Hz, 1H), 7.43 (ddd, J=8.0, 7.8, 1.0 Hz, 1H), 7.08–7.05 (m, 2H). Anal. Calcd for $C_{22}H_{15}N_3O_3$: C, 71.93; H, 3.57; N, 11.44. Found: C, 71.92; H, 3.59; N, 11.42.

4.3.5. 6-(3-Nitrophenylmethylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6f). Yellow needles as (*Z*)-isomer

only: mp 310 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 10.69 (t, J=1.2 Hz, 1H), 8.67 (d, J=8.2 Hz, 1H), 8.43 (dd, J=8.2, 1.3 Hz, 1H), 8.31 (dd, J=8.2, 0.8 Hz, 1H), 8.26 (d, J=8.2 Hz, 1H), 8.03 (d, J=8.2 Hz, 1H), 7.86–7.80 (m, 2H), 7.71 (s, 1H), 7.65 (t, J=8.2 Hz, 1H), 7.60–7.49 (m, 2H), 7.38 (t, J=8.0 Hz, 1H). MS (ESI) calcd for $C_{23}H_{13}N_3O_3$: 368 $[M+H]^+$, found: 368. Anal. Calcd for $C_{22}H_{15}N_3O_3$: C, 71.93; H, 3.57; N, 11.44. Found: C, 71.82; H, 3.60; N, 11.42.

4.3.6. 6-(4-Nitrophenylmethylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6g). Yellow needles as an (*E*)-isomer only: mp 282–283 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.65 (d, J=7.8 Hz, H1), 8.63 (dm, J=8.7 Hz, 2H, H3′ and H5′), 8.43 (d, J=8.0 Hz, 1H, H4), 8.34 (dm, J=8.0 Hz, 2H, H2′ and H6′), 7.81–7.72 (m, 3H), 7.68 (s, 1H), 7.56 (td, J=8.0, 1.0 Hz, 1H), 7.52 (t, J=8.0 Hz, 1H), 7.38 (t, J=7.5 Hz, 1H). (ESI) calcd for $C_{23}H_{13}N_3O_3$: 368 $[M+H]^+$, found: 368. Anal. Calcd for $C_{22}H_{15}N_3O_3$: C, 71.93; H, 3.57; N, 11.44. Found: C, 71.89; H, 3.56; N, 11.45.

4.3.7. 6-(2-Chlorophenylmethylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6h). Yellow needles as a mixture of (*E*)- and (*Z*)-isomer in a ratio of 11:1. (*E*)-Isomer: mp 218–219 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.67 (d, J=8.1 Hz, H1), 8.43 (dd, J=7.5, 1.0 Hz, H4), 8.32 (s, 1H), 7.85–7.78 (m, 2H), 7.72 (dd, J=8.0, 1.0 Hz, 1H), 7.56–7.36 (m, 6H), 7.11 (td, J=8.0, 1.0 Hz, 1H). MS (ESI) calcd for $C_{22}H_{13}ClN_2O$: 357 $[M+H]^+$, found: 357. (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.64 (d, J=8.1 Hz, H1), 8.41 (dd, J=7.5, 1.0 Hz, H4), 7.95 (s, 1H), 7.85–7.78 (m, 2H), 7.72 (dd, J=8.0, 1.0 Hz, 1H), 7.56–7.36 (m, 7H). MS (ESI) calcd for $C_{22}H_{13}ClN_2O$: 357 $[M+H]^+$, found: 357.

4.3.8. 6-(3-Chlorophenylmethylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6i). Yellow needles as a mixture of (*E*)- and (*Z*)-isomer in a ratio of 11:1. (*E*)-Isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.69 (d, J=8.3 Hz, H1), 8.42 (d, J=8.3 Hz, H4), 8.25 (s, 1H), 7.80–7.78 (dm, J=7.5 Hz, 1H), 7.72 (d, J=8.1 Hz, 1H), 7.64 (d, J=7.5 Hz, 1H), 7.56–7.48 (m, 3H), 7.43 (t, J=7.8 Hz, 1H), 7.41 (overlapped d, J=8.3 Hz, 2H). MS (ESI) calcd for $C_{22}H_{13}ClN_2O$: 357 $[M+H]^+$, found: 357. (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 9.22 (s, 1H), 8.60 (d, J=8.1 Hz, H1), 8.43 (d, J=7.5 Hz, H4), 8.05 (m, 1H), 7.92 (dm, J=7.8 Hz, 1H), 7.79 (dm, J=7.5 Hz, 1H), 7.72 (d, J=8.1 Hz, 1H), 7.56–7.48 (m, 3H), 7.43 (t, J=7.8 Hz, 1H), 7.41 (overlapped d, J=8.3 Hz, 2H). MS (ESI) calcd for $C_{22}H_{13}ClN_2O$: 357 $[M+H]^+$, found: 357.

4.3.9. 6-(4-Chlorophenylmethylidene)indolo[2,1-*b*]quinazolin-12(5*H*)-one (6j). Yellow needles as a mixture of (*E*)- and (*Z*)-isomer in a ratio of 2:1. (*E*)-Isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.69 (d, J=8.5 Hz, 1H), 8.43 (dd, J=7.9, 1.0 Hz, H4), 8.25 (s, 1H), 7.79–7.75 (m, 2H), 7.64 (dm, J=8.4 Hz, 2H), 7.56–7.45 (m, 4H), 7.46 (dm, J=8.4 Hz, 2H), 7.17 (td, J=7.7, 0.8 Hz, 1H). MS (ESI) calcd for $C_{22}H_{13}ClN_2O$: 357 $[M+H]^+$, found: 357. (*Z*)-Isomer: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.65 (d, J=8.5 Hz, H1), 8.56 (d, J=8.5 Hz, H4), 7.79–7.75 (m, 2H), 7.74 (s, 1H), 7.74 (dm, J=8.4 Hz, 2H), 7.56–7.45 (m, 3H), 7.46 (dm, J=8.4 Hz, 2H), 7.38 (td, J=7.7, 0.8 Hz, 1H). MS (ESI) calcd for $C_{22}H_{13}ClN_2O$: 357 $[M+H]^+$, found: 357.

4.3.10. 8-Benzylidenecyclopenta[*b*]pyridine (8a). White needles: mp 74–75 °C [lit.[2d] mp 74.5–75.5 °C].

4.3.11. 8-Benzylidenecyclohexa[*b*]pyridine (8b). White needles: mp 65–66 °C (lit.[2c] mp 66–67 °C).

4.3.12. 9-Benzylidenecyclohepta[*b*]pyridine (8c). Pale yellow oil: bp 142–148 °C (0.3 mm). [lit.[2e] bp 110–148 °C (0.3 mm)].

4.3.13. 6-Benzylidene-7,8-dihydropyrrolo[2,1-*b*]quinazolin-10(6*H*)-one (10a). Yellow needles: mp 176–178 °C [lit.[2f] mp 176–178 °C].

4.3.14. 6-Benzylidene-7,8-dihydropyrido[2,1-*b*]quinazolin-11(6*H*)-one (10b). Pale yellow needles: mp 139–140 °C [lit.[2f] mp 139–140 °C].

4.3.15. 6-Benzylidene-7,8,9,10-tetrahydroazepino[2,1-*b*]-quinazolin-12(6*H*)-one (10c). Pale yellow needles as an (*E*)-isomer (*E*-**10c**) (68%). Mp 160–161 °C [lit.[2f] mp 160–161 °C]. Concentration of mother liquor afforded yellow needles as a (*Z*)-isomer (*Z*-**10c**) (22%). Mp 139–141 °C [lit.[2f] mp 139–141 °C].

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18. Reactions of cyclopentanone (**1a**) and cyclohexanone (**1b**) with cyclohexanecarbaldehyde gave 2,5-bis(cyclohexylmethylidene)cyclopentanone (42%)[17s] and 2,6-bis(cyclohexylmethylidene)cyclohexanone (30%),[22] respectively, as isolated and characterized products along with 38–46% of as yet unidentified mixtures of products in both reactions.
19. Reactions of an equimolar mixture of cyclopentanone (**1a**) or cyclohexanone (**1b**) and benzaldehyde (**2a**) were separately examined to afford 2,5-bis(benzylidene)cyclopentanone or 2,6-bis(benzylidene)cyclohexanone as the only isolable product in 38–42% of yield.
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22. Colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.52 (d, J=9.7 Hz, 2H), 2.51–2.45 (m, 4H), 2.13–2.05 (m, 2H), 1.85–1.55 (m, 14H), 1.24–1.09 (m, 8H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): d 185.57, 144.25, 134.41, 40.20, 36.71, 31.73, 26.64, 23.72, 23.35. MS (ESI) calcd for $C_{20}H_{18}O$: 275 $[M+H]^+$, found: 275.