Acetate-Promoted Aldol-Type Reaction: Scope and Reactivity of Acetates and Aldehydes

Dong Hyeon Kim, A. F. M. Motiur Rahman, Byeong-Seon Jeong, Eung Seok Lee, and Yurngdong Jahng*

*College of Pharmacy, Yeungnam University, Gyeongsan 712-749, Korea. *E-mail: ydjahng@ynu.ac.kr*
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Potential of acetates and related compounds in glacial acetic acid as a catalyst for aldol-type condensation reactions was examined. Reactions of cycloalkanones or selected heteroaromatics with aldehydes in presence of 10 mol% of various acetates in acetic acid afforded α,α'-bis(substituted-benzylidene)cycloalkanones and substituted-benzylidene-mackinazolinones, respectively, in good yields. Among the compounds tested, ammonium acetate is the best and effective especially towards the reactions of mackinazolinone and aliphatic aldehydes to afford 6-alkylidene-mackinazolinones.

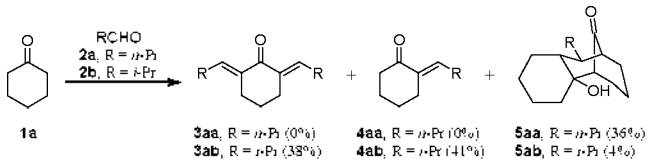
Key Words: Ammonium acetate, Aldol, 2,5-Bis-benzylidenecyclopentanone, 2,6-Bis-benzylidenecyclohexanone, Mackinazolinone

Introduction

The compounds with α,α'-bis(alkylidene)- and α,α'-bis(arylidene)-compounds such as α,α'-bis(benzylidene)cycloalkanones (7)[1] have been attracting much attention due to not only their intriguing biological activities such as anti-angiogenic,[2] quinine reductase inducer,[3] cytotoxic,[4] and cholesterol-lowering activity,[5] but also their potentials for nonlinear optical materials.[6] They are also the important precursors for the synthesis of pyrimidine derivatives,[7] 2,7-disubstituted tropones,[8] and synthetic intermediates to functionalize α,β-position during the synthesis of natural products[9] and theoretically interesting carbocycles[10] as well as heterocycles.[11] Arylidene-heteroaromatics have also been used to functionalize the *peri*-position, especially for the two-step introduction of keto group,[12] and employed for the synthesis of precursors for various polydentate ligands[12e,13] as well as biologically interesting compounds.[12f,14]

The α,α'-bis(arylidene)cycloalkanones were originally prepared from cycloalkanones and aromatic aldehydes in the presence of strong acids[15] and more likely bases,[16] which was named as the Claisen-Schmidt reaction. Such reactions, however, suffer from reverse and/or side reactions.[17] Coordination complexes with a variety of metals have been introduced to replace acids or bases, but the yields were not satisfactory in most cases.[18] Continuing efforts to find new catalysts have resulted in the introduction of various reagents such as Cp_2ZrH_2,[19a] Cp_2TiPh_2,[19b] BMPTO,[19c] $RuCl_3$,[19d] SmI_3,[19e] $TiCl_3(CF_3SO_3)$,[19f] La^{3+}-immobilized organic solid,[19g] KF-Al_2O_3,[19h] $Mg(HSO_4)_2$,[19i] $FeCl_3$,[19j] $BF_3\cdot OEt_2$,[19k] $InCl_3$,[19l] TMSCl/NaI,[19m] TMSCl/Pd-C,[19n] $SOCl_2$,[19o] $Yb(OTf)_3$,[19p] K_2CO_3/PEG-400,[19q] molecular I_2,[19r] and Et_3N in the presence of $LiClO_4$.[19s] In addition, microwave irradiation method was employed to improve yields as well as to reduce reaction time.[20]

On the other hand, catalysts for the Claisen-Schmidt reaction of aliphatic aldehydes toward aldehydes or ketones to lead 2-alkylidene-aldedhydes or ketones are very limited.[19a,d,l,m,p] Even though such cases are applicable to the preparation of 2-alkylidene-aldehydes or ketones, studies revealed that these were not suitable for α,α'-bis(alkylidene) cycloalkanones.[21] Previous studies revealed that the reaction of cyclopentanone with propionaldehyde in the presence of 0.5 M NaOH afforded 2,5-bis(ethylidene)cyclopentanone in 19% yield[21a] while the reaction of cyclohexanone with butyraldehyde afforded 3,4-tetramethylene-2-propylbicyclo [3.3.1]nonan-4-ol-9-one (**5aa**) instead of the expected 2,6-bis(butylidene)cyclohexanone (**3aa**) or 2-butylidenecyclohexanone (**4aa**).[21b] On the other hand, the reaction of cyclohexanone with isobutyraldehyde afforded a mixture of 2,6-bis(isobutylidene)cyclohexanone (**3ab**), 2-isobutylidenecyclohexanone (**4ab**), and 3,4-tetramethylene-2-isopropylbicyclo-[3.3.1]nonan-4-ol-9-one (**5ab**).[21b]



The Claisen condensation between ketones and aldehydes or aldehydes itself, thus, have not been widely considered as a practical method because under basic conditions they often undergo self-condensation leading to complex product mixtures.[1a] To overcome such limit, several indirect methods such as employing silyl enol ether,[22] 2-formylketone,[23] enamine,[24] lithiated imine,[25] and lithiated enamine,[26] have been designed, but sometimes long reaction sequence and expensive reagents are the bottle-necks for the general use.

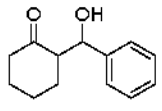
Disadvantages of the present catalysts and importance of the Claisen-Schmidt reaction in synthetic organic chemistry lead us to find sodium acetate in glacial acetic acid as a new catalytic system for the introduction of benzylidene moiety on cycloalkanones as well as heteroaromatics.[27] Concerning the catalytic activity of acetates in acetic acid, a couple of previous studies such as reaction of chloral with methyl ketones with sodium acetate in acetic acid to afford the corresponding aldol adduct, 1,1,1-trichloro-2-hydroxyethyl ketones, in 41-59%

yield.[28] and one-pot Kröhnke synthesis of annulated pyridines employed ammonium acetate/acetic acid system to generate 2,6-bis(substituted-benzylidene)cycloalkanones from (substituted)benzaldehydes to cyclic ketones have been reported.[29] However, no systematic studies on the catalytic activity of acetates in the aldol condensation have been pursued as yet. We, thus, herein described the scope and reactivity of acetates as catalysts for aldol-type reactions.

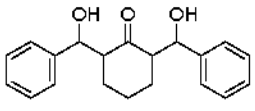
Results and Discussion

The Claisen-Schmidt reactions of cyclohexanone (**1a**) with benzaldehyde (**6**) in the presence of 10 mol% of acetates or related compounds in glacial acetic acid were first examined and results are summarized in Table 1.

Reactions proceeded smoothly to afford 2,6-dibenzylidenecyclohexanone (**7**) in 83-95% yields. The reaction with ammonium acetate gave the best result which was comparable to that with sodium acetate,[27] to afford the desired product in 95% yield in 8 h of reaction time. On the other hand, the reactions with sodium propanoate and triethylammonium acetate required 36 h and 72 h, respectively, to complete the reaction (entries 4 and 3) and reactions with piperidinium acetate, acetamide or sodium L-prolinate required even longer reaction time (120 h). Thus ammonium acetate can be a good candidate for the aldol-type condensation catalyst. It should be noted that the reaction in the presence of sodium L-prolinate, of which the free acid has been used as enantioselective catalyst for the Claisen-Schmidt reaction to lead β-hydroxycarbonyl compounds,[30] also led bis(benzylidene)cyclohexanone in 86% yield after 120 h. Although early study claimed that the ratios between the aldol addition product and the Claisen-Schmidt product were highly dependent on the pH, the pH range was very narrow, in which the Claisen-Schmidt products were the only ones in the pH range of 11.0-11.4 while the aldol adducts were the major under the pH range 9.8-10.5.[31] The present study showed that no trace of initial aldol-adduct, β-hydroxycarbonyl compound **8** and/or bis-β-hydroxycarbonyl compound **9** was observed.



8



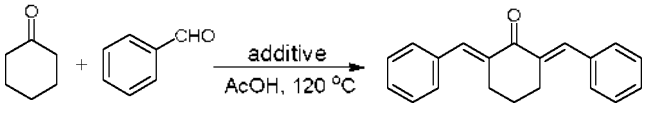
9

Effect of reaction temperature. To find an optimized reaction condition, we examined the effect of reaction temperature for the Claisen-Schmidt reaction. Although the reaction with ammonium acetate below 60 °C required over 72 h, reaction at 120 °C required less than 8 h for the completion. Previous studies on sodium acetate[27] as well as present study revealed that 120 °C can be the choice of reaction temperature. Since the β-hydroxycarbonyl compounds **8** and/or **9** are the expected intermediates, the reactions were pursued at room temperature. However, no identifiable products were isolated in each case.

Effects of aliphatic aldehydes. We, next examined the reactions of **1** with aliphatic aldehydes in the presence of ammonium acetate in glacial acetic acid, and results are summarized in Table 3. Reactions of cyclohexanone (**1a**) with 2 equiv of isopropyl aldehyde, acetaldehyde, and cyclohexanecarbaldehyde afforded the corresponding 2,6-bis(alkylidene)cyclohexanones, **3ab, 3ac,** and **3af**, in 78, 35, and 65% yield, respectively. It should be noted that the reaction of **1a** with acetaldehyde yielded a mixture of bis- (**3ac**) and monocondensed (**4ac**) product in 26% and 36% yield, respectively. The stereochemistry of the products was assigned as *E* based on the literature values of olefinic H's which were resonanced in the range of δ 6.62-6.92 for (*E*)-isomer and δ 5.46-5.60 for (*Z*)-isomer.[32] Reactions of the other aliphatic aldehydes did not lead to any isolable desired products as reported.[21b] but yielded 12-18% of 2-alkylidene-alkanal as a self-condensed product and 25-35% of as yet unidentified mixtures of products. On the other hand, reactions of cyclopentanone (**1b**) afforded desired 2,5-bis(alkylidene)cyclopentanones in 35 83% yield. The difference of reactivity of cyclohexanone *vs* cyclopentanone may be due to the difference of ring flexibility.

It should be noted that the reactions of aldehydes with a

Table 1. Reactions of cyclohexanone with benzaldehyde in the presence of various additives in glacial acetic acid

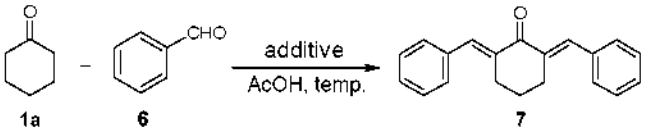


1a **6** **7**

Entry	additive[a]	time (h)	yield (%)[b]
1	ammonium acetate	8	95
2	piperidinium acetate	120	90
3	triethylammonium acetate	72	83
4	sodium propanoate	36	86
5	acetamide	120	84
6	sodium L-prolinate	120	86

[a]Reaction was run in the presence of 10 mol% additive relative to cyclohexanone. [b]Isolated yields which are not optimized.

Table 2. Effect of reaction temperature on the reaction of cyclohexanone (**1a**) with benzaldehyde (**6**) in the presence of various additives in glacial acetic acid

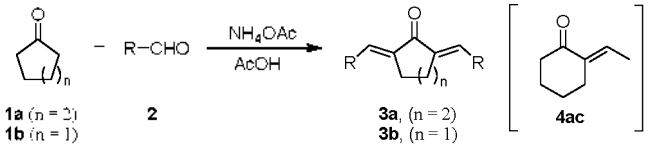


1a **6** **7**

Entry	additive[a]	temp (°C)	yield (%)[b]
1	ammonium acetate	r.t.	N.R.[c]
2	ammonium acetate	60	72
3	ammonium acetate	120	95
4	piperidinium acetate	r.t.	N.R.[c]
5	piperidinium acetate	120	42
6	sodium L-prolinate	r.t.	N.R.[c]
7	sodium L-prolinate	60	18
8	sodium L-prolinate	120	34

[a]Reaction was run in the presence of 10 mol% additive relative to benzaldehyde and quenched after 8 h. [b]Isolated yields which are not optimized. [c]No product was detectable after 5 days.

Table 3. The Claisen-Schmidt reaction of cycloalkanone **1** with aliphatic aldehydes **2**



1a (n = 2)
1b (n = 1)

2

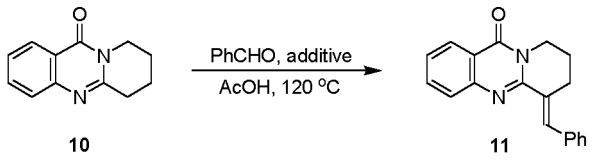
3a, (n = 2)
3b, (n = 1)

4ac

Entry	compound	R	yield (%)[a]	mp (°C)
1	**3aa**	*n*-Pr	0	
2	**3ab**	*i*-Pr	78	colorless oil
3	**3ac**	Me	35	130 (0.5 mmHg)
4	**3ad**	Et	0	
5	**3ae**	*n*-C_5H_{11}	0	
6	**3af**	C_6H_{11}	65	colorless oil
7	**3ba**	*n*-Pr	43	yellow oil [lit.[33] bp 80 (0.08 mHg)]
8	**3bb**	*i*-Pr	83	colorless oil
9	**3bc**	Me	35	59–61 [lit.[34] mp 61]
10	**3bd**	Et	37	colorless oil
11	**3be**	*n*-C_5H_{11}	42	colorless oil
12	**3bf**	C_6H_{11}	72	126–127 [lit.[35] mp 127]

[a]Isolated yields which are not optimized.

Table 4. Reactions of mackinzaolinone (**10**) with benzaldehyde (**6**) in the presence of various additives in glacial acetic acid



10 **11**

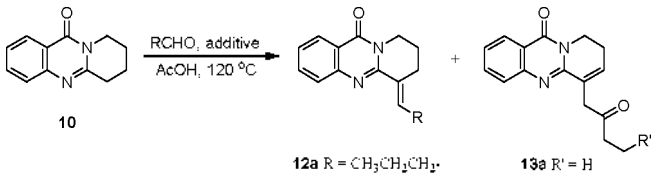
Entry	additive[a]	time (h)	yield (%)[b]
1	ammonium acetate	4	86
2	ammonium acetate	8	95
3	piperidinium acetate	4	< 10
4	piperidinium acetate	120	90
5	triethylammonium acetate	4	< 10
6	triethylammonium acetate	72	86
7	sodium propanoate	8	46
8	sodium propanoate	36	86
9	acetamide	4	86
10	acetamide	72	90
11	sodium L-prolinate	4	12
12	sodium L-prolinate	8	40
13	acetic anhydride	4	18
14	acetic anhydride	72	95

[a]Reaction was run in the presence of 10 mol% additive relative to benzaldehyde. [b]Isolated yields which are not optimized.

substituent at α-position proceeded smoothly to yield the corresponding 2,ω-bis(alkylidendene)derivatives in 65-83% yields (entries 2, 6, 8, and 12). Although a direct synthesis of 2,ω-bis(alkylidene)cycloalkanones from cycloalkanones and alkyl aldehydes are known impractical,[1a,22-26] the present method can be applicable for the direct preparation of 2,5 bis(alkylidene)cyclopentanones, especially from aldehydes with a substituent at the α-position.

Effects of acetates on benzylidene-heteroaromatics. The

Table 5. Reaction mackinazolinone (**10**) with aliphatic aldehydes with 10 mol% additives in acetic acid



10

12a R = $CH_3CH_2CH_2$-
12b R = $(CH_3)_2CH$-
12c R = CH_3CH_2-
12d R = $CH_3CH_2CH_2CH_2$-
12e R = $CH_3CH_2CH_2CH_2CH_2$-
12f R = cyclohexyl-

13a R' = H
13d R' = CH_3-
13e R' = CH_3CH_2-

entry	R	additive	yield (%)[a] (**12**:**13**)[b]
1	*n*-Pr	ammonium acetate	71 (25:46)
2	*n*-Pr	sodium acetate	66 (22:44)
3	*n*-Pr	sodium propanoate	68 (17:51)
4	*n*-Pr	acetamide	63 (14:49)
5	*i*-Pr	ammonium acetate	70 (**12b** only)
6	Et	ammonium acetate	67 (**12c** only)
7	*n*-Bu	ammonium acetate	91 (83:8)
8	*n*-C_5H_{11}	ammonium acetate	70 (23:47)
9	cyclohexyl	ammonium acetate	96 (**12f** only)

[a]Isolated yields which are not optimized. [b]ratios of isolated products.

effect of acetates in glacial acetic acid on the reaction of 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (mackinazolinone, **10**), was examined and results are summarized in Table 4. Reaction at 120 °C with ammonium acetate completed in 8 h while reactions with sodium propanoate, triethylammonium acetate, acetamide, and acetic anhydride required longer reaction time up to 120 h. As described above, ammonium acetate can be a better catalyst for aldol-type condensation reactions.

Effects of aliphatic aldehydes on alkylidene-heteroaromatics. Previous study revealed that the arylidene derivatives of selected heteroaromatics were effectively prepared by condensing with aromatic aldehyde in the presence of 10 mol% of sodium acetate in glacial acetic acid.[27] However, no systematic study on aliphatic aldelydes has been pursued as yet. We, thus, examined the reactivity of aldehydes towards mackinazolinone (**10**) and results are summarized in Table 5.

The reactions with propionaldehyde, isobutyraldehyde and cyclohexanecarbaldelyde led the corresponding alkylidene derivatives (**12b,c,f**) in 67-96% yields (entries 5, 6, and 9), which was superior to the 22-33% yields reported previously.[14a] However, the reactions with butyraldehyde, pentanal and hexanal yielded mixtures of two compounds **12** and **13**. Reactions of butyraldehyde in presence of various acetates (entries 1-4) in glacial acetic acid afforded the corresponding alkylidene derivatives **12a** in 14-25% yields along with an unexpected **13a** in 44-51% yields. Similarly, reactions with pentanal in the presence of ammonium acetate (entry 7) afforded **12d** and **13d** in 83% and 8% yields, respectively, while hexanal yielded **12e** and **13e** in 23% and 47% yield, respectively. It should be noted that attempts (data not shown) to react **10** with aliphatic aldehydes under the refluxing acetic anhydride for 72 h provided the products in only < 8% yield, which is not consistent with results described above for the

reactions with aromatic aldehydes (Table 4, entry 14).

The structures of **13** were determined by spectroscopic methods including various NMR techniques such as HMBC and DEPT-135. Reaction mechanism for the formation of **13** remained to be clarified.

Conclusion

Effects of acetates as well as other factors on the aldol-type condensation reactions of cycloalkanones and mackinazolinone with various aldehydes were examined. Catalytic amount (10 mol% relative to aldehyde) of ammonium acetate in glacial acetic acid was good enough to lead best results at 120 °C. Reactions of cyclopentanone with aliphatic aldehydes led the corresponding 2,5-bis(alkylidene)cyclopentanones in 35-83% yield while reactions of cyclohexanone were proceeded only with acetaldehyde, isobutyraldehyde and cyclohexanecarbaldehyde. Best results in the introduction of alkylidene moiety at the *peri*-position of carbocycle-fused heterocycles were achieved when ammonium acetate was employed as a catalyst.

Experimental

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 performed 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 as a parts per million (ppm) from the internal standard tetramethylsilane (TMS). Cyclohexanone was 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 taken on Hewlett-Packard Model 185B elemental analyzer.

General procedure for the preparation of 3, 7, 11 and 12. A mixture of cyclohexanone (5.0 mmol), aldehyde (10.0 mmol) and anhydrous acetate or related salts (1.0 mmol) in glacial acetic acid (15 mL) was heated under the conditions described in Table 1, 2, and 3. The reaction mixture was poured into crashed ice, and work up as usual afforded an oily material, which was chromatographed on silica gel eluting with CH_2Cl_2:hexanes (1:1) to give analytically pure α,α'-bis(alkylidene)cycloalkanones **3** and 2,6-bis(benzylidene)cyclohexanones **7** except for **7a** described specifically. The spectral and analytical data of the *unknown* compounds are given below.

2,6-Bis(ethylidene)cyclohexanone (3ac): A mixture of cyclohexanone (0.52 g, 5.0 mmol), acetaldehyde (0.66 g, 15.0 mmol) and anhydrous ammonium acetate (77 mg, 1.0 mmol, 10% equiv) in glacial acetic acid (5 mL) was heated at 60 °C for 8 h under N_2 atmosphere in a sealed tube. The reaction mixture was poured to crashed ice and extracted with Et_2O (30 mL × 3). Combined organic layers were washed with water, brine and dried over $MgSO_4$. Evaporation of the solvent afforded an oily material which was distilled under reduced pressure.

The early fractions afforded **(*E*)-2-ethylidenecyclohexanone (4ac)** as colorless oil (0.16 g, 26% yield), bp 76-80 °C (14 mmHg) [lit.[36] bp 87-89 °C (18 mmHg)]; IR (KBr) υ 1670, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.68 (1H, qt, J = 7.5, 2.0 Hz), 2.41 (2H, t, J = 5.9 Hz), 2.37 (2H, t, J = 6.5 Hz), 1.72 (3H, d, J = 7.5 Hz), 1.12-1.11 (4H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 200.87, 137.03, 134.17, 39.96, 26.23, 23.36, 23.21, 13.40.

The latter fractions afforded **2,6-bis(ethylidene)cyclohexanone (3ac)** as colorless oil (0.26 g, 35% yield): bp 130 °C (0.5 mmHg); IR (KBr) υ 1668, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.85 (2H, qm, J = 7.5 Hz), 2.45 (4H, t, J = 5.9 H), 1.72 (6H, d, J = 7.5 Hz), 1.12-1.11 (2H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 188.99, 136.67, 135.15, 25.89, 21.98, 13.78; MS (ESI) calcd for $C_{10}H_{15}O$ $[M+H]^-$: 151, found 151.

2,6-Bis(cyclohexylmethylidene)cyclohexanone (3ae): Colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.52 (2H, d, J = 9.7 Hz), 2.51-2.45 (4H, m), 2.13-2.05 (2H, m), 1.85-1.55 (14H, m), 1.24-1.09 (8H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 185.57, 144.25, 134.41, 40.20, 36.71, 31.73, 26.64, 23.72, 23.35; MS (ESI) calcd for $C_{20}H_{31}O$ $[M+H]^+$: 287, found: 287.

2,5-Bis(butylidene)cyclopentanone (3ba): Colorless oil. IR (KBr) υ 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.52 (2H, d, J = 9.7 Hz), 2.51-2.45 (4H, m), 2.13-2.05 (2H, m), 1.85-1.55 (14H, m), 1.24-1.09 (8H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 185.57, 144.25, 134.41, 40.20, 36.71, 31.73, 26.64, 23.72, 23.35; MS (ESI) calcd for $C_{13}H_{21}O$ $[M+H]^+$: 193, found: 193.

2,5-Bis(propylidene)cyclopentanone (3bd): Colorless oil. IR (KBr) υ 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.52 (2H, d, J = 9.7 Hz), 2.51-2.45 (4H, m), 2.13-2.05 (2H, m), 1.85-1.55 (14 H, m), 1.24-1.09 (8H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 185.57, 144.25, 134.41, 40.20, 36.71, 31.73, 26.64, 23.72, 23.35; MS (ESI) calcd for $C_{11}H_{17}O$ $[M+H]^+$: 165, found 165.

2,5-Bis(hexylidene)cyclopentanone (3be): Colorless oil. IR (KBr) υ 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.52 (2H, d, J = 9.7 Hz), 2.51-2.45 (4H, m), 2.13-2.05 (2H, m), 1.85-1.55 (14 H, m), 1.24-1.09 (8H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 185.57, 144.25, 134.41, 40.20, 36.71, 31.73, 26.64, 23.72, 23.35; MS (ESI) calcd for $C_{17}H_{29}O$ $[M+H]^+$: 249, found: 249.

General procedure for the preparation of 6-alkylidene-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones 12.

(*E*)-6-Butylidene-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (12a): A mixture of 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quina-zolin-11-one (**10**) (1.0 g, 5.0 mmol), *n*-butanal (0.72 g, 5.0 mol), and acetates or related compounds (0.5 mmol, 10% molar equiv) in 10 mL of glacial acetic acid was heated at 120 °C. The resulting mixture was poured to 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 hexanes:EtOAc (1:1).

The early fractions (R_f 0.75) afforded the desired product **12a** as an (*E*)-isomer as yellow needles (0.32 g, 25% yield): mp 87-88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (1H, d, J =

7.6 Hz), 7.70-7.61 (2H, m), 7.36 (1H, ddd, J = 7.9, 6.5, 1.8 Hz), 7.19 (1H, ddd, J = 8.0, 7.5, 1.2 Hz), 4.02 (2H, t, J = 5.7 Hz), 2.58 (2H, t, J = 5.3 Hz), 2.18 (2H, dt, J = 7.4, 6.3 Hz), 1.96 (2H, quintet, J = 6.3 Hz), 1.56 (2H, q, J = 7.5 Hz), 0.97 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 162.12, 151.70, 147.64, 139.12, 133.99, 128.82, 127.12, 126.56, 125.82, 119.95, 42.07, 30.83, 24.37, 24.03, 22.74, 21.93, 21.74, 14.10; MS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255, found: 255. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.72; H, 7.06; N, 11.08.

The latter fractions (R_f 0.40) afforded the compound **13a** (0.67 g, 46% yield): mp 107-108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (1H, dd, J = 8.0, 1.2 Hz), 7.65 (1H, td, J = 8.0, 0.8 Hz), 7.53 (1H, d, J = 8.0 Hz), 7.40 (1H, td, J = 8.0, 1.0 Hz), 6.51 (1H, t, J = 4.5 Hz), 4.26 (2H, t, J = 7.0 Hz), 3.61 (2H, s), 2.68 (2H, q, J = 7.3 Hz), 2.58 (2H, td, J = 7.0, 6.8 Hz), 1.10 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 208.9 ($C_{2'}$=O), 161.4 (C_{11}=O), 148.8 (C_{5a}), 147.2 (C_{4a}), 136.6 (C_7), 133.9 (C_3), 130.2 (C_6), 127.4 (C_4), 126.89 (C_1), 126.60 (C_2), 121.1 (C_{10a}), 44.8 ($C_{1'}$), 38.6 (C_9), 36.2 ($C_{3'}$), 23.0 (C_8), 7.93 ($C_{4'}$); MS (ESI) calcd for $C_{16}H_{17}N_2O_2$ $[M+H]^+$: 269, found: 269. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.85; H, 5.97; N, 10.61.

(*E*)-6-Isobutylidene-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]-quinazolin-11-one (12b): Pale yellow needles [R_f 0.80 hexanes:EtOAc (1:1)] (70% yield): mp 103 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.22 (1H, d, J = 7.8 Hz), 7.71-7.61 (2H, m), 8.36 (1H, ddd, J = 8.0, 7.5, 1.0 Hz), 7.07 (1H, dt, J = 10.0, 1.5 Hz, vinylic H), 4.09 (2H, dd, J = 6.8, 5.8 Hz), 2.72 (1H, heptet, J = 6.8 Hz), 2.63 (2H, td, J = 5.8 Hz), 1.97 (2H, quint, J = 5.8 Hz), 1.10 (6H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 162.15, 151.68, 147.52, 145.56, 133.93, 127.07, 126.64, 126.47, 125.78, 119.84, 42.18, 27.86, 23.72, 22.02, 21.71; MS (ESI) calcd for $C_{16}H_{18}N_2O$: 255 $[M+H]^+$, found: 255. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.62; H, 7.12; N, 11.04.

(*E*)-6-Propylidene-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]-quinazolin-11-one (12c): Pale yellow needles [R_f 0.80 hexanes: EtOAc (1:1)] (67%): mp 125-126 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.23 (1H, dd, J = 7.8, 0.8 Hz), 7.65 (2H, m), 7.38 (1H, td, J = 8.0, 0.8 Hz), 7.19 (1H, td, J = 8.0, 1.0 Hz), 4.11 (2H, t, J = 5.6 Hz), 2.61 (2H, t, J = 5.6 Hz), 2.26 (2H, quintet, J = 7.5 Hz), 2.02-1.89 (2H, m), 1.16 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 162.13, 151.75, 147.63, 140.72, 134.04, 128.29, 127.11, 126.70, 126.59, 126.01, 125.87, 119.95, 42.05, 23.90, 22.07, 21.72, 13.16; MS (ESI) calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241, found: 241. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.03; H, 6.68; N, 11.64.

(*E*)-4-Pentylidene-1,2,3,4-tetrahydro-11*H*-pyrido[2,1-*b*]-quinazolin-11-one (12d): Pale yellow needles [R_f 0.51 hexanes: EtOAc (2:1)] (83% yield): mp 86-87 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.21 (1H, dd, J = 7.8, 0.4 Hz), 7.70-7.61 (2H, m), 7.36 (1H, ddd, J = 8.0, 7.8, 0.8 Hz), 7.19 (1H, ddd, J = 8.0, 7.8, 1.0 Hz), 4.08 (2H, dd, J = 11.4, 5.7 Hz), 2.60 (2H, t, J = 6.3 Hz), 2.27 (2H, q, J = 7.5 Hz), 1.96 (2H, quintet, J = 7.5 Hz), 1.50 (2H, quintet, J = 7.5 Hz), 1.38 (2H, quintet, J = 7.5 Hz), 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 162.12, 151.75, 147.60, 140.40, 139.40, 134.00, 128.59, 127.06, 126.54, 125.81, 119.89, 42.06, 30.75, 28.49, 23.96, 22.58, 21.71, 13.92; MS (ESI) calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$: 269, found: 269. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.06; H, 7.52; N, 10.46.

The latter fractions [R_f 0.32 hexanes:EtOAc (2:1)] afforded **13d** as a pale yellow oil (8% yield). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.22 (1H, d, J = 8.0 Hz), 7.64 (1H, td, J = 8.0, 0.8 Hz), 7.52 (1H, d, J = 8.0 Hz), 7.38 (1H, td, J = 8.0, 1.0 Hz), 6.50 (1H, t, J = 4.8 Hz), 4.27 (2H, t, J = 7.0 Hz), 3.61 (2H, s), 2.63 (2H, q, J = 7.3 Hz), 2.55 (2H, td, J = 7.0, 6.8 Hz), 1.61 (2H, quintet, J = 7.5 Hz), 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 208.0 ($C_{2'}$=O), 161.0 (C_{11}=O), 148.7 (C_{5a}), 147.2 (C_{4a}), 136.6 (C_7), 133.9 (C_3), 130.2 (C_6), 127.4 (C_4), 126.77 (C_1), 126.56 (C_2), 121.1 (C_{10a}), 44.8 ($C_{1'}$), 42.6 (C_9), 38.0 ($C_{3'}$), 25.7 (C_8), 23.0 ($C_{4'}$), 14.9 ($C_{5'}$); MS (ESI) calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$: 283, found: 283. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.89; H, 6.82; N, 9.51.

(*E*)-6-Hexylidene-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]-quinazolin-11-one (12e): Semisolid [R_f 0.42 hexanes:EtOAc (2:1)] (23% yield). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.26 (1H, d, J = 7.8 Hz), 7.73-7.66 (2H, m), 7.42 (1H, td, J = 8.0, 0.8 Hz), 7.18 (1H, t, J = 8.0 Hz), 4.13 (2H, dd, J = 11.0, 5.8 Hz), 2.74 (2H, m), 2.12-1.83 (4H, m), 1.22-1.13 (6H, m), 0.84 (3H, t, J = 7.5 Hz); MS (ESI) calcd for $C_{18}H_{23}N_2O$ $[M+H]^+$: 283, found: 283. Anal. Cald for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 86.55; H, 7.84; N, 9.94.

The latter fractions [R_f 0.28 hexanes:EtOAc (2:1)] afforded **13e** as a pale yellow needles (47% yield): mp 98-99 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.24 (1H, d, J = 8.0 Hz), 7.65 (1H, td, J = 8.0, 0.8 Hz), 7.52 (1H, d, J = 8.0 Hz), 7.40 (1H, td, J = 8.0, 1.0 Hz), 6.50 (1H, t, J = 4.8 Hz), 4.27 (2H, t, J = 7.0 Hz), 3.61 (2H, s), 2.64 (2H, q, J = 7.3 Hz), 2.56 (2H, td, J = 7.0, 6.8 Hz), 1.61 (2H, quintet, J = 7.5 Hz), 1.27 (2H, quintet, J = 7.5 Hz), 0.90 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 208.5 ($C_{2'}$=O), 161.4 (C_{11}=O), 148.8 (C_{5a}), 147.2 (C_{4a}), 136.6 (C_7), 133.9 (C_3), 130.2 (C_6), 127.4 (C_4), 126.77 (C_1), 126.56 (C_2), 121.1 (C_{10a}), 45.1 ($C_{1'}$), 42.7 (C_9), 38.6 ($C_{3'}$), 25.9 (C_8), 23.0 ($C_{4'}$), 22.3 ($C_{5'}$), 13.9 ($C_{6'}$); MS (ESI) calcd for $C_{18}H_{21}N_2O_2$ $[M+H]^+$: 297, found: 297. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.92; H, 6.82; N, 9.48.

(*E*)-6-Cyclohexylmethylidene-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (12f): Pale yellow needles (96% yield): mp 169-170 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.22 (1H, d, J = 7.6 Hz), 7.71-7.61 (2H, m), 7.36 (1H, ddd, J = 7.5, 6.8, 1.8 Hz), 7.08 (1H, dt, J = 9.8, 1.8 Hz), 4.10 (2H, t, J = 5.8 Hz), 2.65 (2H, td, J = 7.9, 1.7 Hz), 2.38-2.34 (1H, br m), 1.97 (2H, quintet, J = 6.9 Hz), 1.76-1.69 (5H, m), 1.40-1.18 (5H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 162.25, 151.77, 147.62, 144.07, 133.95, 127.17, 127.04, 126.52, 125.78, 119.92, 42.29, 37.87, 31.99, 25.89, 25.77, 23.88, 21.82; MS (ESI) calcd for $C_{19}H_{23}N_2O$ $[M+H]^+$: 295, found: 295. Anal. Cald for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.55; H, 7.49; N, 9.49.

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