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PAPER

Synthesis of the pyridinyl analogues of dibenzylideneacetone (pyr-dba) *via* an improved Claisen–Schmidt condensation, displaying diverse biological activities as curcumin analogues†

Bin Cao,[a] Yong Wang,[a] Kan Ding,[a] Nouri Neamati[b] and Ya-Qiu Long*[a]

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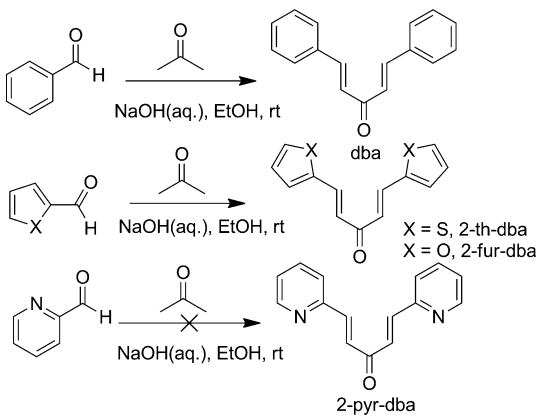
An efficient and easy procedure to synthesize the pyridinyl analogues of dibenzylideneacetone (pyr-dba) was developed by the condensation of substituted nicotinaldehyde and acetone in the presence of K_2CO_3 in toluene-EtOH-H_2O solvent system. Structurally diverse pyr-dba, including quinolinyl dba, can be prepared conveniently in moderate to excellent yields under mild conditions with this method. The resulting pyr-dba functioned as the enone analogs of curcumin and efficiently inhibited the activation of NF-κB and the growth of colorectal carcinoma HCT116 p53+/+ cells as well as the HIV-1 IN-LEDGF/p75 interaction.

Introduction

Dibenzylideneacetone (dba) is widely applied in Pd-catalyzed cross-coupling processes as a noninnocent ligand, for instance in form of $Pd_2(dba)_3$ used in combination with phosphine, amine and *N*-heterocyclic carbene ligands (L) to generate Pd^0L_n complexes *in situ*.[1] In recent years, substituted benzene dba (*e.g.* dba-*n*,*n*′-Z,Z′: n/n′ = 3, 4, or 5; Z/Z′ = OMe, *t*Bu, Br, H, F, CF_3, NO_2)[1–4] and heteroaromatic dba (het-dba)[5] have been explored as the noninnocent ligand by subtle electronic tuning of the aryl groups of dba. Some of them showed an improved catalytic activity compared with dba in different coupling reactions. Furthermore, the dba derivatives display a wide range of pharmacological activities such as anti-oxidant activities,[6] inhibition of the NF-κB (transcription factor NF-κB) activation in many cancer cells,[7] and excellent affinity for Aβ aggregates.[8] Among them, the pyridine-dba (pyr-dba) structure as the dienone analogues of curcumin exhibited promising inhibitory activity against NF-κB activation.[7] Therefore, a simple and efficient approach to synthesize variants of the "dba" structure especially pyr-dba is of particular interest.

The "dba" structures may be accessed synthetically using a number of methods. Arguably the most efficient and the earliest means is by Claisen–Schmidt condensation of an appropriate aldehyde and acetone in the presence of NaOH in aqueous EtOH (Scheme 1).[9] This procedure was improved by using partially dehydrated commercial barium hydroxide (C-200)[10] or indium trichloride[11] as the catalyst. Further improvement was reported by using titanium tetraalkoxide to induce the formation of α,β-unsaturated carbonyl compounds under neutral conditions.[12]



Scheme 1 The conventional synthetic routes toward dba, 2-th-dba and 2-fur-dba by using Claisen–Schmidt condensation.

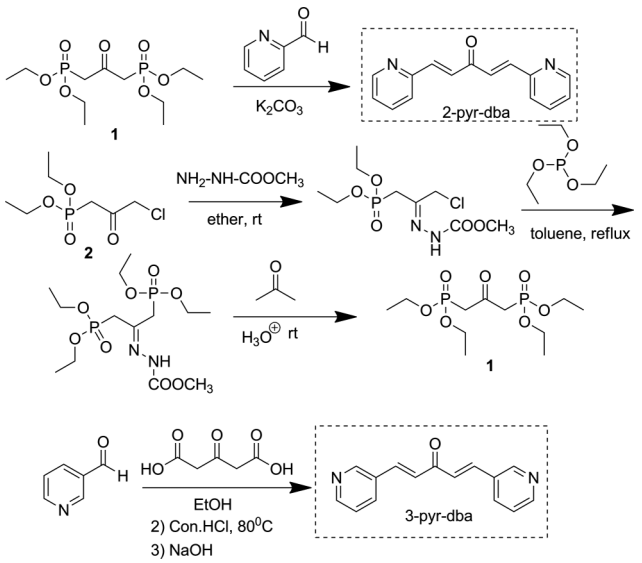
However, as far as the synthesis of 2-pyr-dba is concerned, the Claisen–Schmidt condensation failed to generate this het-dba structure starting from picolinaldehyde.[9,13] The mechanistic reason for this is postulated to be that H_2O elimination is hindered by the neighboring nitrogen atom through an inductive effect which results in electron withdrawal from the carbon atom bearing the hydroxyl group.[13] To confirm whether the Claisen–Schmidt condensation can be applied to picolinaldehyde, we tried classical reaction conditions of the Claisen–Schmidt condensation (1 eq acetone, 2 eq picolinaldehyde, 10% aqueous NaOH solution, EtOH, rt) in our lab, but only a complex reaction mixture resulted without any desired products.

[a]*State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China. E-mail: yqlong@mail.shcnc.ac.cn; Fax: 86-21-50807088; Tel: 86-21-50806876*

[b]*Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, 1985 Zonal Avenue, Los Angeles, CA, 90089, USA*

† Electronic supplementary information (ESI) available: The ^{1}H NMR spectra of the starting material **6b–c**, **6e–j** and **6m–n**, the ^{1}H NMR and ^{13}C NMR spectra for the final products and the biological screening assays. See DOI: 10.1039/c1ob06773g

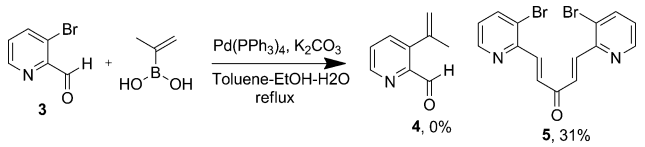
To the best of our knowledge, the synthesis of 2-pyr-dba available in the literature is by the Horner–Wadsworth–Emmons reaction of two equivalents of picolinaldehyde with one equivalent of bis(phosphonate) **1** in the presence of K_2CO_3 (Scheme 2).[5] However, the Wittig reagent **1** was rather troublesome to prepare from diethyl 3-chloro-2-oxopropylphosphonate **2** *via* a three-step reaction.[14] On the other hand, the literature-reported synthetic route toward 3-pyr-dba was by the reaction of nicotinaldehyde with 1,3-acetonedicarboxylic acid under strong acid and high temperature conditions (Scheme 2).[15] The harsh conditions greatly limit the further application of this method. Herein, we report our development of a simple and efficient approach to synthesize structurally diverse pyr-dba under mild conditions and the biological screening of these new pyr-dba derivatives.



Scheme 2 The literature-reported syntheses of 2-pyr-dba and 3-pyr-dba.

Results and discussion

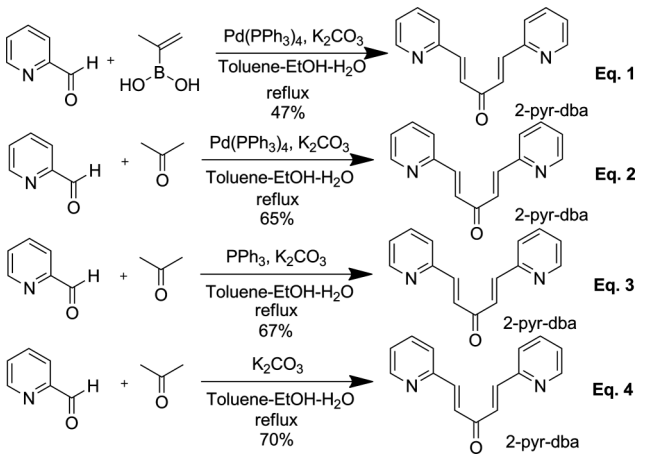
Our methodology program was initiated by an accidental discovery of pyr-dba as a major side-product of the coupling reaction of 3-bromo picolinaldehyde **3** with isopropenylboronic acid under Suzuki–Miyaura reaction conditions (1.5 eq isopropenylboronic acid, 0.1 eq $Pd(PPh_3)_4$, 4 eq K_2CO_3, Toluene-EtOH-H_2O = 5 : 2 : 1, reflux) (Scheme 3). This Suzuki–Miyaura type coupling reaction was supposed to yield product **4**, however, only compound **5** was obtained in 31% yield instead. The result implied that it might be the aldehyde instead of the bromide that was involved in the reaction, which might be an alternative approach to synthesize the pyr-dba derivatives. Therefore, based on the unexpected results, we



Scheme 3 The production of 2-pyr-dba **5** during the Suzuki–Miyaura reaction.

employed commercially available and cheap picolinaldehyde as the model substrate to investigate the reaction in detail.

Initially, we adopted the same reaction conditions to picolinaldehyde as compound **3** and got the desired product 2-pyr-dba in 47% yield (Scheme 4 Eq 1). Then, we replaced isopropenylboronic acid with acetone to determine whether the former was hydrolyzed into the latter during the reaction and the acetone might be the real reactive species instead (Scheme 4 Eq 2). Interestingly, 2-pyr-dba was indeed furnished in 65% yield, which confirmed our hypothesis for the reaction mechanism. So, we continued to examine the importance of $Pd(PPh_3)_4$ in this condensation reaction by designing two parallel reactions, one using PPh_3 instead of $Pd(PPh_3)_4$, the other omitting $Pd(PPh_3)_4$ (Scheme 4 Eq 3, 4). Surprisingly, they both afforded the products in higher yields, 67% and 70%, respectively. The results demonstrate that $Pd(PPh_3)_4$ is not necessary and the reaction is a K_2CO_3-promoted Claisen–Schmidt condensation.

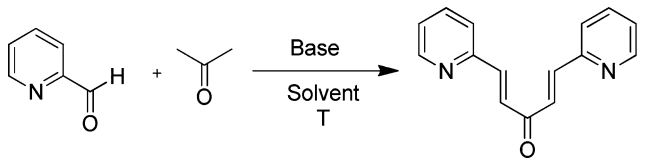


Scheme 4 Investigation on the reaction mechanism using picolinaldehyde as the model substrate.

Next, we focused our effort on the reaction optimization with respect to the solvent, base and temperature. The results were summarized in Table 1. Obviously, the solvent, base and temperature all had a remarkable effect on the reaction. 70 °C is the best temperature for the condensation. Increase or decrease of the temperature led to a reduced yield (Table 1, Entries 2, 3, 4). K_2CO_3 is the optimal base. Stronger bases such as NaOH and Cs_2CO_3 lowered the yields sharply (entries 5 and 7). Weaker bases such as Na_2CO_3 and $NaHCO_3$ were less effective (entries 8 and 9). Organic base such as Et_3N decreased the yield too (entry 10). Switching to phosphate or acetate resulted in poor yields (entries 11 and 12). No reaction occurred if no base was added (entry 6). The quantity of the base was an important factor as well. 4 equivalents of K_2CO_3 (based on acetone) turned out to be the best, while increase or reduction in the amount of the base gave a lower yield (entries 13 and 14). The combined solvent (Toluene-EtOH-H_2O) was the most optimal solvent system. Elimination of any solvent component caused a substantial drop of the yield (entries 15, 16, 17, 18). Utilizing acetone as the solvent proved unfavorable (entries 19 and 20). Consequently, the optimized reaction conditions are summarized in entry 2.

With the optimized conditions in hand, we further explored the generality of this protocol toward variously substituted

Table 1 Optimization of the reaction conditions[a]

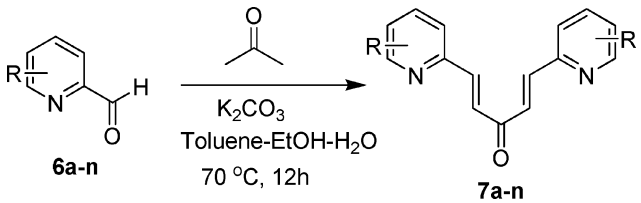


Entry	Solvent	Base	T/°C	Yield (%)[b]
1	Toluene-EtOH-H_2O	K_2CO_3	80	63
2	Toluene-EtOH-H_2O	K_2CO_3	70	80
3	Toluene-EtOH-H_2O	K_2CO_3	60	60
4	Toluene-EtOH-H_2O	K_2CO_3	rt	10
5	Toluene-EtOH-H_2O	NaOH	70	0[c]
6	Toluene-EtOH-H_2O	—[d]	70	nr[e]
7	Toluene-EtOH-H_2O	CS_2CO_3	70	34
8	Toluene-EtOH-H_2O	Na_2CO_3	70	70
9	Toluene-EtOH-H_2O	$NaHCO_3$	70	58
10	Toluene-EtOH-H_2O	Et_3N	70	48
11	Toluene-EtOH-H_2O	K_3PO_4	70	14
12	Toluene-EtOH-H_2O	NaOAc	70	0
13	Toluene-EtOH-H_2O	K_2CO_3[f]	70	62
14	Toluene-EtOH-H_2O	K_2CO_3[g]	70	51
15	EtOH-H_2O[h]	K_2CO_3	70	0[c]
16	Toluene[i]	K_2CO_3	70	0[c]
17	Toluene-H_2O[j]	K_2CO_3	70	11
18	Toluene-EtOH[k]	K_2CO_3	70	37
19	Acetone[l]	K_2CO_3	70	0[c]
20	Acetone[l]	—[d]	70	nr[e]

[a] Reaction conditions: picolinaldehyde (2 mmol), acetone (1.0 mmol), base (4 mmol), toluene-EtOH-H_2O (5.0 ml : 2.0 mL : 1.0 ml) at 70 °C for 12 h. [b] Isolated yield. [c] The reaction occurred, but no desired product was yielded. [d] No base. [e] No reaction took place. [f] K_2CO_3 (2.0 mmol). [g] K_2CO_3 (6.0 mmol). [h] EtOH-H_2O (4 ml : 2 ml). [i] Toluene (8 ml). [j] Toluene-H_2O (5 ml : 1 ml). [k] Toluene-EtOH (5 ml : 2 ml). [l] Acetone (8 ml).

pyridinylaldehydes. The results were summarized in Table 2. All the pyridine aldehydes underwent the Claisen–Schmidt condensation in the presence of K_2CO_3 smoothly and afforded the pyr-dba products **7a–n** in 40–98% isolated yields. Generally speaking, the electron donating groups on the pyridine ring (entries 10 and 11) conferred better yields than the electron withdrawing groups (entries 2, 3, 8 and 9). Furthermore, the halo substituent at the 3- or/and 4-position was well tolerated (entries 2, 3, 8 and 9) giving the corresponding pyr-dba products in yields of 40–78% (**7b–c**, **7h–i**), which can perform further cross-coupling reactions to introduce various groups. However, bulky aryl substituents, such as phenyl groups (entries 5, 12 and 13), adversely affected the reaction giving the desired pyr-dba products in yields of 43–64%, whereas the bulky heterocycle group such as morpholine potentiated the transformation in a yield of 98% (entry 10), partly due to its electron-donating property. Interestingly, under the optimized reaction conditions, vinyl substituted substrate (**6f**) was converted to the vinyl containing pyr-dba **7f** in excellent yield (entry 6). Potentially, the resulting **7f** can undertake olefin metathesis to build an 11-membered ring. Likewise, the alkynyl functionality was also well tolerated in the reaction affording the product **7g** in 67% yield which can be further functionalized *via* click chemistry (entry 7). Besides pyridine aldehydes, quinoline and isoquinoline aldehydes reacted with acetone affording the desired pyr-dba derivatives **7l** and **7m** in 43% and 60% yield, respectively. When nicotinaldehyde was employed as the substrate

Table 2 Substrate scope of various pyridine aldehydes[a]



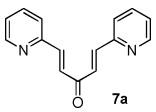
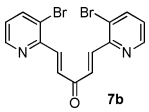
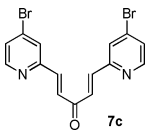
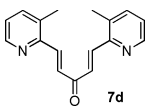
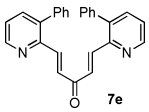
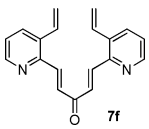
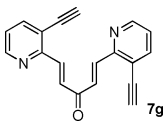
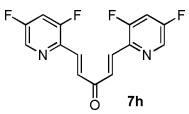
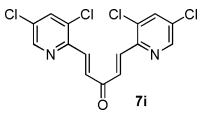
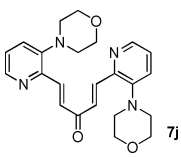
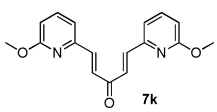
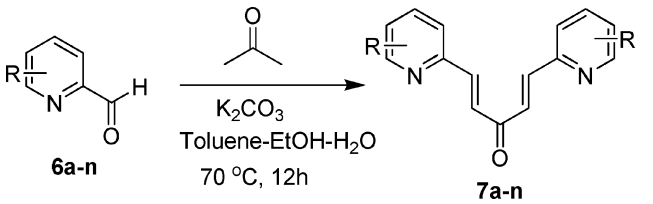
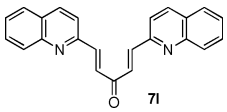
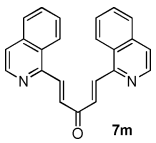
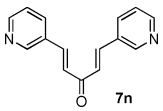
Entry	R	Product	Yield (%)[b]
1	H (**6a**)		80
2	3-Br (**6b**)		51
3	4-Br (**6c**)		40
4	3-Me (**6d**)		62
5	3-Ph (**6e**)		64
6	3-vinyl (**6f**)		85
7	3-acetylene (**6g**)		67
8	3,5-F, F (**6h**)		78
9	3,5-Cl, Cl (**6i**)		62
10	3-morpholino (**6j**)		98
11	6-OMe (**6k**)		91

Table 2 *(Contd.)*



Entry	R	Product	Yield (%)[b]
12	2-quinoline-carbaldehyde (**6l**)	 7l	43
13	Isoquinoline-1-carbaldehyde (**6m**)	 7m	60
14	Nicotinaldehyde (**6n**)	 7n	58

[a] Reaction conditions: aldehydes **6** (1 mmol), acetone (0.5 mmol), K_2CO_3 (2 mmol), toluene-EtOH-H_2O (2.5 ml : 1.0 ml : 0.5 ml) at 70 °C for 12 h. [b] Isolated yield.

we were pleased to find the condensation occurred smoothly yielding the 3-pyr-dba **7n** in 58% yield.

As a comparison, we tried our developed methodology on other aromatic substrates, *e.g.* benzaldehyde. However, when benzaldehyde was treated under the same reaction conditions as pyridinylaldehydes, only a small amount of starting material was transformed, resulting in a complex mixture without a major product. This observation is consistent with the Claisen–Schmidt condensation mechanism, which requires a strong base such as NaOH to facilitate the aldol formation by the nucleophilic addition of the enolate to the benzaldehyde followed by an elimination reaction. Because pyridinylaldehydes carry an electron-withdrawing N atom adjacent to the aldehyde functionality, the more electrophilic aldehyde is liable to the nucleophilic addition of the ketone enolate, even with the assistance of a weaker base. But for the following dehydration reaction, the presence of the neighboring electron-withdrawing N atom disfavors the water elimination of the pyridinyl aldol.[13] Therefore, an elevated temperature and toluene cosolvent secure the water elimination to generate the thermodynamically stable enones in our reaction system. On the other hand, the use of toluene as cosolvent affords a homogeneous reaction system which might be beneficial for advancing the Claisen–Schmidt condensation equilibrium to the elimination product.

Biological evaluation

Since the dba structure can be regarded as the aryl dienone analogs of the bioactive natural product curcumin, which contains ketene fragment in the solution (Scheme 5),[6–8] we were intrigued to screen

Table 3 Biological screening results of pyr-dba derivatives **7a–n**

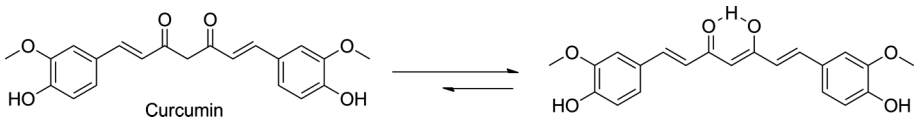
Entry	Compound	NF-κB IC_{50} (μM)	MTT IC_{50} HCT116 p53+/+ (μM)	LEDGF/p75 IC_{50} (μM)
1	**7a**	0.52	<1.1	1.6
2	**7b**	5.02	<1.1	2.0
3	**7c**	2.71	2.0	5.0
4	**7d**	1.06	<1.1	4.0
5	**7e**	0.94	2.5	5.2
6	**7f**	0.69	<1.1	7.9
7	**7g**	1.20	1.5	3.0
8	**7h**	0.78	1.5	12.0
9	**7i**	17.67	6.0	>20.0
10	**7j**	0.56	<1.1	>20.0
11	**7k**	4.68	1.8	>20.0
12	**7l**	3.95	6.0	1.2
13	**7m**	1.33	1.5	4.5
14	**7n**	2.42	<1.1	5.0
15	Curcumin	8.2[a]	—	—

[a] The IC_{50} value for inhibition by curcumin of the TNFα-induced activation of NF-κB was cited from reference 7c.

the biological activities of our new structure pyr-dba series. When tested on the LPS-induced activation of NF-κB, these compounds all displayed marked inhibitory activity. As shown in Table 3, most of the compounds showed better inhibitory activity than curcumin and the reported related enones.[7c] A cytotoxicity assay by MTT showed that these pyr-dba derivatives were active in inhibiting the cell growth of colorectal carcinoma HCT116 p53+/+ cells with low to sub-micromolar IC_{50} values as well (Table 3). Surprisingly, our pyr-dba derivatives were found to be novel inhibitors of the interaction between enzyme HIV-1 integrase (IN) and the nuclear protein lens epithelium growth factor LEDGF/p75 (Table 3), and the most potent compound **7l** inhibited the IN-LEDGF/p75 interaction with an IC_{50} of 1.2 μM. LEDGF/p75 is a new promising target for anti-HIV chemotherapy and only a few inhibitors have been reported so far.[16] Therefore, this new class of pyr-dba compounds may provide new scaffold for the discovery and development of novel HIV-1 integrase inhibitors targeting the IN-LEDGF/p75 interaction.

Conclusions

In summary, we have developed a useful and efficient protocol to synthesize pyr-dba in moderate to excellent yields through the condensation of substituted nicotinaldehyde and acetone using K_2CO_3 as base and Toluene-EtOH-H_2O as solvent. The reaction features simple and readily available starting materials, wide substrate scope, high functional group tolerance, mild conditions, high efficiency, and easy-handling. These features constitute a considerable improvement over the existing methods and will likely render it a useful tool in the synthesis of pyr-dba which is widely used in organic chemistry and medicinal chemistry. In addition, preliminary biological screening revealed that this class of pyr-dba compounds displayed diverse biological activities, *e.g.* inhibitory activities against the activation of NF-κB, the growth of colon tumor HCT116 p53+/+ cells as well as the HIV-1 IN-LEDGF/p75 interaction. Further SAR study for improving the activity and selectivity and further application of the pyr-dba in organic chemisty like the Nazarov reaction and six-membered



Scheme 5 Curcumin exists in solution as an equilibrium mixture of the symmetrical dienone and the keto-enol tautomer stabilized by intramolecular H-bonding.[7]

cyclization to extend the scope of synthetic utility of the reaction are under progress in our group.

Experimental section

All ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hz. High resolution mass spectra were recorded on a Finnigan MAT 95 mass spectrometer (EI). Column chromatography was performed with 200–300 mesh silica gel using flash column techniques. Melting points are uncorrected. Starting materials **6a**, **6d**, **6k**, **6l**, **6n** were obtained from commercial sources, and were used without further purification.

Preparation of the starting material

3-bromopicolinaldehyde (6b)[17]. The mixture of SeO_2 (666 mg, 6 mmol) and 1,4-dioxane (5 mL) was heated over 80 °C, then was added 3-bromo-2-methylpyridine (172 uL, 1.5 mmol) in 1,4-dioxane (5 mL). After stirring at 80 °C for 18 h, the reaction mixture was cooled and filtered. The filtrate was concentrated, the residue was purified by column chromatography to yield **6b** as a pale yellow solid (175 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.22 (s, 1H), 8.74 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.2 Hz), 8.03 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.38–7.34 (m, 1H).

4-bromopicolinaldehyde (6c)[18]. A mixture of SeO_2 (244 mg, 2.2 mmol) and 4-bromo-2-methylpyridine (237 ul, 2 mmol) in dioxane (10 ml) was heated to reflux under N_2 for 12 h. After cooling, the solvent was evaporated and the residue was partitioned between DCM and H_2O. The aqueous layer was further extracted with DCM twice and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuum and the residue was purified by flash column chromatography to give **6c** as a yellow oil (70 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.04 (s, 1H), 8.60 (d, 1H, *J* = 5.4 Hz), 8.11 (s, 1H), 7.69 (d, 1H, *J* = 5.4 Hz).

2-methyl-3-phenylpyridine (8)[19]. A solution of phenylboronic acid (268 mg, 2.20 mmol) in EtOH (1.46 ml), aqueous Na_2CO_3 (2.93 ml, 2 M), and $Pd[P(Ph)_3]_4$ (110 mg, 0.09 mmol) were added to a solution of 3-bromo-2-methylpyridine (84 ul, 0.73 mmol), in toluene (1 ml) with stirring. The heterogeneous mixture obtained was purged with nitrogen and refluxed for 24 h. After cooling to 25 °C, the organic layer was separated and the aqueous solution was extracted with ether. The combined organic phases were dried over Na_2SO_4, the solvent was removed *in vacuo*, and the residue was purified by column chromatography to yield the title compound as a yellow oil (105 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.48 (d, 1H, *J* = 5.1 Hz), 7.49 (d, 1H, *J* = 7.8 Hz), 7.44–7.35 (m, 3H), 7.29 (d, 2H, *J* = 6.9 Hz), 7.17–7.13 (m, 1H), 2.50 (s, 3H).

3-phenylpicolinaldehyde (6e)[20]. **6e** was prepared in a similar fashion as described for **6c**, red oil, yield 61%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.09 (s, 1H), 8.79 (d, 1H, *J* = 4.5 Hz), 7.79 (d, 1H, *J* = 7.8 Hz), 7.54–7.49 (m, 1H), 7.44–7.35 (m, 3H), 7.29 (d, 2H, *J* = 6.9 Hz).

3-((trimethylsilyl)ethynyl)picolinaldehyde (9)[21]. A 50-mL round-bottomed flask was charged with 3-bromopicolinaldehyde (**6b**, 558 mg, 3 mmol), dichlorobis(triphenylphosphine)palladium(II) (105 mg, 0.15 mmol), copper(I) iodide (29 mg, 0.15 mmol) and DMF (3 mL). The resulting suspension was treated with triethylamine (418 uL, 3 mmol), followed by (trimethylsilyl)acetylene (768 uL, 5.4 mmol). The reaction mixture was stirred at room temperature for 1.5 h and diluted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography to give the title compound (560 mg, 93%) as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.42 (s, 1H), 8.73 (d, 1H, *J* = 4.8 Hz), 7.92 (d, 1H, *J* = 7.8 Hz), 7.46–7.42 (m, 1H), 0.30 (s, 9H).

3-ethynylpicolinaldehyde (6g). (CAS number 1211578-06-1). 3-((trimethylsilyl)ethynyl)picolinaldehyde (518 mg, 2.55 mmol) was treated with potassium fluoride dihydrate (480 mg, 5.10 mmol) in DMF (3 ml) under nitrogen at rt for 3 h. It was then poured into water and extracted with DCM dried over Na_2SO_4 and concentrated to yield title compound **6g** (247 mg, 74%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.26 (s, 1H), 8.71 (d, 1H, *J* = 4.5 Hz), 7.91 (d, 1H, *J* = 8.1 Hz), 7.46–7.42 (m, 1H), 3.58 (s, 1H).

3-vinylpicolinaldehyde (6f)[22]. To a solution of **6g** (74 mg, 0.56 mmol) in 5 ml EtOAc was added Lindlar catalyst (8 mg), the mixture was stirred at rt under H_2 for 2 h. The catalyst was filtered out, and the filtrate was concentrated, the residue was purified by flash chromatography to provide the title compound (60 mg, 81%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.14 (s, 1H), 8.65 (d, 1H, *J* = 4.2 Hz), 7.93 (d, 1H, *J* = 8.1 Hz), 7.72–7.63 (m, 1H), 7.45–7.40 (m, 1H), 5.76 (d, 1H, *J* = 17.7 Hz), 5.49 (d, 1H, *J* = 11.4 Hz).

3,5-difluoropicolinaldehyde (6h)[23]. To a solution of 3,5-difluoropicolinonitrile (350 mg, 2.5 mmol) in THF (30 mL) at –20 °C under N_2, was added a solution of DIBAL-H (1.0 M) in toluene (2.5 mL, 2.5 mmol). The mixture was stirred at –20 °C for 4 h. Methanol was added to the reaction mixture to quench the reaction and 1.0 N HCl was used to adjust the solution to pH 4–5. The mixture was diluted with ethyl acetate and washed with H_2O twice. Organic layer was separated and dried over Na_2SO_4. Solvent was removed under reduced pressure. The resulting residue was purified by column chromatography to afford the title compound as a white solid (153 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.13 (s, 1H), 8.51 (s, 1H), 7.35 (t, 1H, *J* = 9.0 Hz).

3,5-dichloropicolinaldehyde (6i)[24]. **6i** was prepared in a similar fashion as described for **6h**, yellow solid, yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.24 (s, 1H), 8.66 (d, 1H, J = 1.8 Hz), 7.87 (d, 1H, J = 2.1 Hz).

4-(2-methylpyridin-3-yl)morpholine (10). 3-Bromo-2-methylpyridine (206 mg, 1.2 mmol), morpholine(125 mg, 1.44 mmol), $Pd_2(dba)_3$ (22 mg, 0.024 mmol), (±) BINAP (30 mg, 0.048 mmol) NaOtBu (161 mg, 1.68 mmol) and toluene (4 mL) were added to an oven-dried flask which was purged with argon for approximately 5 min. The reaction mixture was heated to 70° under argon until the 3-bromopyridine was consumed. The reaction was then cooled to room temperature, and taken up in 10 mL diethyl ether, washed 3 times with 10 mL saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography afforded **10** (212 mg, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.16 (d, 1H, J = 4.8 Hz), 7.22 (d, 1H, J = 8.1 Hz), 7.06–7.02 (m, 1H), 3.80 (t, 4H, J = 4.5 Hz), 2.84 (t, 4H, J = 4.5 Hz), 2.48 (s, 3H).

3-morpholinopicolinaldehyde (6j)[25]. **6j** was prepared in a similar fashion as described for **6b**, yellow oil, yield 20%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.16 (s, 1H), 8.42 (t, 1H, J = 3.0 Hz), 7.42 (d, 1H, J = 3.0 Hz), 3.95–3.92 (m, 4H), 3.15–3.12 (m, 4H).

Isoquinoline-1-carbaldehyde (6m)[26]. **6m** was prepared in a similar fashion as described for **6b**, white solid, yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.29 (s, 1H), 9.18 (d, 1H, J = 8.7 Hz), 8.63 (d, 1H, J = 5.1 Hz), 7.78–7.74 (m, 2H), 7.66–7.59 (m, 2H).

General procedure for the synthesis of compounds 7a–7n. The reaction mixture of aldehyde **6a–n** (1 mmol), acetone (37 ul, 0.5 mmol) and K_2CO_3 (276 mg, 2 mmol) in the solvent of toluene-EtOH-H_2O (2.5 ml + 1.0 mL + 0.5 ml) was stirred at 70 °C for 12 h. After cooling to rt, the solvent was evaporated *in vacuo*. The resulting residue was partitioned between DCM and H_2O. The aqueous phase was further extracted with DCM twice. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, then filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to afford the desired product.

(1*E*,4*E*)-1,5-di(pyridin-2-yl)penta-1,4-dien-3-one (7a)[5]. Pale yellow solid (80%). Mp 111–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, 2H, J = 4.2 Hz), 7.79–7.74 (m, 4H), 7.62 (d, 2H, J = 15.9 Hz), 7.50 (d, 2H, J = 7.8 Hz), 7.32–7.27(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.4, 153.0, 150.0, 142.0, 136.9, 128.8, 124.9, 124.4; EI-MS: 236 (M^+); HRMS (EI): calcd for $C_{15}H_{12}N_2O$ 236.0950; found 236.0941.

(1*E*,4*E*)-1,5-bis(3-bromopyridin-2-yl)penta-1,4-dien-3-one (7b). Pale yellow solid (51%). Mp 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, 2H, J = 4.5 Hz), 8.17 (d, 2H, J = 15 Hz), 7.92 (d, 2H, J = 7.8 Hz), 7.74 (d, 2H, J = 15 Hz), 7.18 (dd, 2H, J_1 = 8.1 Hz, J_2 = 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.2, 151.2, 148.4, 141.1, 139.0, 131.4, 125.4, 123.5; EI-MS: 392 (M^+); HRMS (EI): calcd for $C_{15}H_{10}Br_2N_2O$ 391.9160; found 391.9181.

(1*E*,4*E*)-1,5-bis(4-bromopyridin-2-yl)penta-1,4-dien-3-one (7c). Yellow solid (40%). Mp 138–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, 2H, J = 5.1 Hz), 7.69–7.56 (m, 6H), 7.47 (dd, 2H, J_1 = 5.1 Hz, J_2 = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 188.8, 154.3, 150.6, 140.7, 133.7, 130.0, 128.1, 127.5; EI-MS: 392 (M^+); HRMS (EI) calcd for $C_{15}H_{10}Br_2N_2O$ 391.9160; found 391.9169.

(1*E*,4*E*)-1,5-bis(3-methylpyridin-2-yl)penta-1,4-dien-3-one (7d). Yellow solid (62%). Mp 120–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, 2H, J = 4.2 Hz), 7.99 (d, 2H, J = 15 Hz), 7.72 (d, 2H, J = 15.3 Hz), 7.50 (d, 2H, J = 7.8 Hz), 7.18 (dd, 2H, J_1 = 7.8 Hz, J_2 = 4.5 Hz), 2.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.6, 151.0, 147.3, 138.7, 138.1, 133.9, 129.8, 124.4, 18.7; EI-MS: 264 (M^+); HRMS (EI) calcd for $C_{17}H_{16}N_2O$ 264.1263; found 264.1260.

(1*E*,4*E*)-1,5-bis(3-phenylpyridin-2-yl)penta-1,4-dien-3-one (7e). Yellow solid (64%). Mp 153–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, 2H, J = 4.8 Hz), 7.77 (d, 2H, J = 15.3 Hz), 7.70–7.65 (m, 4H), 7.48–7.36 (m, 6H), 7.34–7.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.4, 150.1, 148.6, 139.6, 139.0, 138.2, 137.8, 130.1, 129.6, 128.6, 128.1, 124.0; EI-MS: 388 (M^+); HRMS (EI): calcd for $C_{27}H_{20}N_2O$ 388.1576; found 388.1575.

(1*E*,4*E*)-1,5-bis(3-vinylpyridin-2-yl)penta-1,4-dien-3-one (7f). Yellow-green solid (85%). Mp 138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 2H), 8.08 (d, 2H, J = 14.7 Hz), 7.82 (d, 2H, J = 7.2 Hz), 7.73 (d, 2H, J = 15.0 Hz), 7.31–7.12 (m, 4H), 5.72 (d, 2H, J = 16.5 Hz), 5.55 (d, 2H, J = 10.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.3, 149.6, 148.6, 138.0, 134.9, 134.4, 132.2, 130.7, 124.5, 120.0; EI-MS: 288 (M^+); HRMS (EI): calcd for $C_{19}H_{16}N_2O$ 288.1263; found 288.1252.

(1*E*,4*E*)-1,5-bis(3-ethynylpyridin-2-yl)penta-1,4-dien-3-one (7g). Yellow-green solid (67%). Mp 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, 2H, J = 4.5 Hz), 8.24 (d, 2H, J = 15.3 Hz), 7.83 (d, 2H, J = 6.0 Hz), 7.79 (d, 2H, J = 14.7 Hz), 7.29–7.25 (m, 2H), 3.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.5, 154.2, 149.1, 140.9, 138.6, 130.7, 123.6, 120.1, 85.9, 79.0; EI-MS: 284 (M^+); HRMS (EI): calcd for $C_{19}H_{12}N_2O$ 284.0950; found 284.0943.

(1*E*,4*E*)-1,5-bis(3,5-difluoropyridin-2-yl)penta-1,4-dien-3-one (7h). Yellow-green solid (78%). Mp 117–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, 2H, J = 2.1 Hz), 7.90 (d, 2H, J = 15.6 Hz), 7.62 (d, 2H, J = 15.6 Hz), 7.29–7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 188.7, 159.5(d, $^1J_{CF}$ = 270.1 Hz), 158.0(d, $^1J_{CF}$ = 268.3 Hz), 138.2(d, $^2J_{CF}$ = 10.4 Hz), 134.8(dd, $^2J_{CF}$ = 23.7 Hz, $^4J_{CF}$ = 4.6 Hz), 133.2, 129.6, 111.8(t, $^2J_{CF}$ = 21.5 Hz); EI-MS: 308 (M^+); HRMS (EI): calcd for $C_{15}H_8F_4N_2O$ 308.0573; found 308.0563.

(1*E*,4*E*)-1,5-bis(3,5-dichloropyridin-2-yl)penta-1,4-dien-3-one (7i). Yellow-green solid (62%). Mp 167–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, 2H, J = 2.1 Hz), 8.08 (d, 2H, J = 15.6 Hz), 7.76 (d, 2H, J = 2.4 Hz), 7.71 (d, 2H, J = 15.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 188.8, 148.2, 147.0, 137.0, 135.8, 132.9, 132.6, 131.3; EI-MS: 372 (M^+); HRMS (EI): calcd for $C_{15}H_8Cl_4N_2O$ 371.9391; found 371.9390.

(1*E*,4*E*)-1,5-bis(3-morpholinopyridin-2-yl)penta-1,4-dien-3-one (7j). Reddish brown solid (98%). Mp 91–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, 2H, J = 3.9 Hz), 8.14 (d, 2H, J = 15.6 Hz), 7.71 (d, 2H, J = 15.9 Hz), 7.40 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 4.8 Hz), 3.93(s, 4H), 3.00(s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.8, 148.9, 147.4, 144.0, 137.7, 129.2,

126.7, 124.9, 66.9, 52.9; EI-MS: 406 (M^+); HRMS (EI): calcd for $C_{23}H_{26}N_4O_3$ 406.2005; found 406.2005.

(1*E*,4*E*)-1,5-bis(6-methoxypyridin-2-yl)penta-1,4-dien-3-one (7k). Yellow-green solid (91%). Mp 113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.56 (m, 6H), 7.03 (d, 2H, J = 7.2 Hz), 6.75(d, 2H, J = 8.7 Hz), 4.00(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.9, 163.6, 150.4, 141.6, 139.0, 128.4, 119.2, 112.8, 53.3; EI-MS: 296 (M^+); HRMS (EI): calcd for $C_{17}H_{16}N_2O_3$ 296.1161; found 296.1157.

(1*E*,4*E*)-1,5-di(quinolin-2-yl)penta-1,4-dien-3-one (7l). Yellowish brown solid (43%). Mp 188–189 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.24–8.15 (m, 4H), 8.00 (d, 2H, J = 16.2 Hz), 7.86–7.70 (m, 8H), 7.59 (t, 2H, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 189.4, 153.1, 147.6, 142.3, 137.5, 130.6, 130.5, 129.3, 128.2, 127.7, 127.6, 121.0; EI-MS: 336 (M+); HRMS (EI): calcd for $C_{23}H_{16}N_2O$ 336.1263; found 336.1259.

(1*E*,4*E*)-1-(isoquinolin-1-yl)-5-(isoquinolin-3-yl)penta-1,4-dien-3-one (7m). Yellowish brown solid (60%). Mp 155–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72–8.64 (m, 4H), 8.47 (d, 2H, J = 7.8 Hz), 8.02 (d, 2H, J = 15 Hz), 7.89 (d, 2H, J = 7.5 Hz), 7.77–7.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 189.3, 152.0, 142.3, 137.0, 136.7, 131.7, 130.5, 128.1, 127.7, 127.4, 124.3, 122.4; EI-MS: 336 (M^+); HRMS (EI): calcd for $C_{23}H_{16}N_2O$ 336.1263; found 336.1264.

(1*E*,4*E*)-1,5-di(pyridin-3-yl)penta-1,4-dien-3-one (7n)[7]. Yellow solid (58%). Mp 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 2H), 8.62 (dd, 2H, J_1 = 4.8 Hz, J_2 = 1.5 Hz), 7.91 (dd, 2H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.72 (d, 2H, J = 16.2 Hz), 7.35 (dd, 2H, J_1 = 7.8 Hz, J_2 = 4.8 Hz), 7.13 (d, 2H, J = 15.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD, ppm): δ 187.9, 150.6, 149.3, 139.9, 135.0, 130.6, 126.9, 124.0; EI-MS: 236 (M^+); HRMS (EI): calcd for $C_{15}H_{12}N_2O$ 236.0950; found 236.0948.

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