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From dicarbonylallene to 1-aryl-3,6-dimethyl-4-aminoaryl-2-pyridones: a one-pot versatile and uncatalyzed synthesis

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Abstract—Reaction of amines with an allenic precursor leads to new 1-aryl-3,6-dimethyl-4-aminoaryl-2-pyridones in good yields. These syntheses can be performed in two distinct steps, allowing the possibility to introduce different substituents in the positions 1 and 4. By using *o*-aminopyridine, a new pyridopyrimidone is easily obtained.

1. Introduction

The 2-pyridone unit is a key structural feature in a number of biologically active compounds.[1–3] For instance, it can be found in the toxin ricinine,[4] the psychoactive huperzine A,[5] or in the lead anticancer alkaloid camptothecin (Fig. 1).[6] Other pyridones act as HIV-1 reverse transcriptase inhibitors,[7] or as herbicides,[8] pesticides,[9] and fungicides.[10–12]

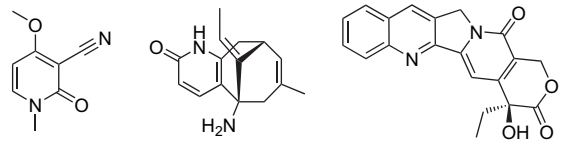

Figure 1.

In connection with ongoing projects in these fields,[13–17] we became interested in developing a versatile and efficient route to 1-aryl-3,6-dimethyl-4-aminoaryl-2-pyridones. Recent reviews describe the main strategies of preparation to the pyridone ring system.[18,19] Despite a large number of existing routes for their synthesis, new methods are still being developed.[20–26] A frequently encountered approach involves condensation of ammonia or amines with an unsaturated 1,5-dicarbonyl compound, with one of the carbonyl groups belonging to a carboxylic acid derivative.[27]

We have chosen to start our study with 3,6-dimethyl compounds. The strategy is based on the retrosynthetic analysis described in Figure 2, allene **3** being the precursor of the key dicarbonyl intermediate.[28] To the best of our knowledge, this type of allene has never been involved in 2-pyridone synthesis. In the same way as for acetylenic precursors,[29] the allene group should provide the unsaturation necessary for aromatization.

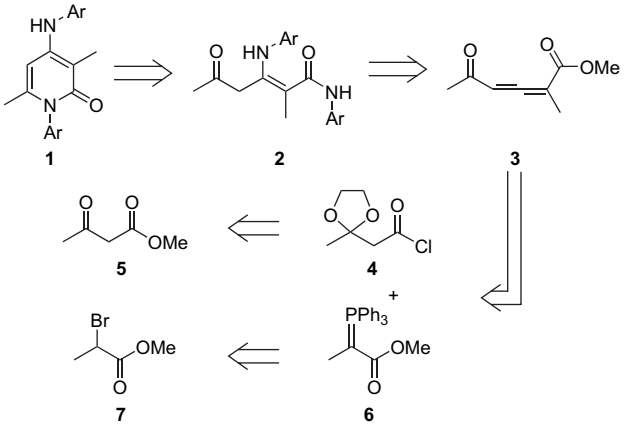

Figure 2. Retrosynthetic strategy for the synthesis of substituted 3,6-dimethylpyridones.

2. Results and discussion

2.1. Synthesis and reactivity of allene 3

Starting point of the synthesis was methyl acetoacetate **5**, whose protection of the ketone function has already been

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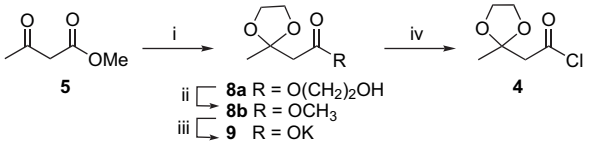
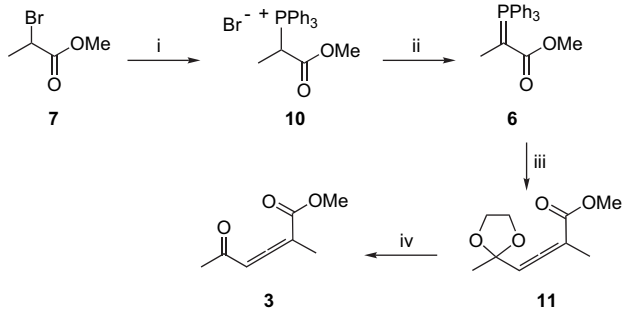
described.[30,31] In our hands, ketone protection was accompanied by a trans-esterification reaction, giving a mixture of both esters **8a** and **8b**. Thus, a back trans-esterification of glycol ester **8a** to methyl ester **8b** was realized by reacting the crude reaction medium with methanol in the presence of sodium methoxide (Scheme 1). Acid chloride **4** was a known compound,[32] whose reactivity with triphenylphosphoranes has already been reported.[33,34] We obtained this chloride by reacting potassium salt **9** with oxalyl chloride. Since some difficulties were experienced to obtain a perfectly dried salt **9**, ester **8b** was saponified with a solution of potassium silanolate[35–38] in tetrahydrofuran, dried with 3 Å molecular sieves (Scheme 1).



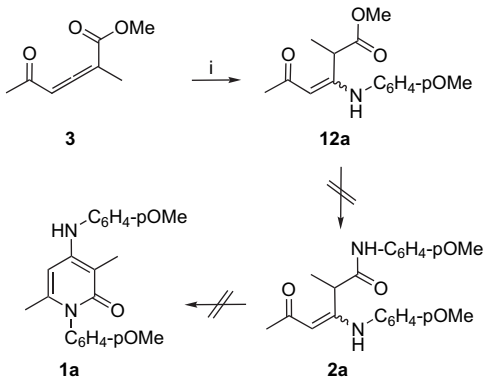
Scheme 1. Reagents and conditions: (i) $HOCH_2CH_2OH$, toluene, *p*TSA, reflux, Dean–Stark, 20 h; (ii) MeONa/MeOH, reflux, 24 h, 46% for two steps; (iii) TMSOK, THF, 3 Å MS, 20 °C, 12 h; (iv) $(ClCO)_2$, CH_2Cl_2, 0 °C, 12 h, 90% (crude yield).

Synthesis of allenes from an acid chloride and the appropriate phosphorane is a known method.[39–45] In this way, chloride **4** was reacted with the phosphorane **6**[46] obtained from salt **10**, again in the presence of 3 Å molecular sieves (Scheme 2). Allene **11** was prepared in an overall 55% yield from compounds **4** and **6** as a brown oil, which can be stocked at −40 °C for years, but slowly decomposes at room temperature. Deprotection of the acetal of an acetylenic aldehyde was described by Gorgues using formic acid at 40 °C.[47,48] This method has been adapted to the deprotection of allenic acetal **11**, by lowering temperature to 30 °C in order to avoid rapid decomposition of the product. Unprotected allene **3**, thus obtained with a 60% yield, readily decomposes at room temperature, but it can be stocked at −40 °C for months.



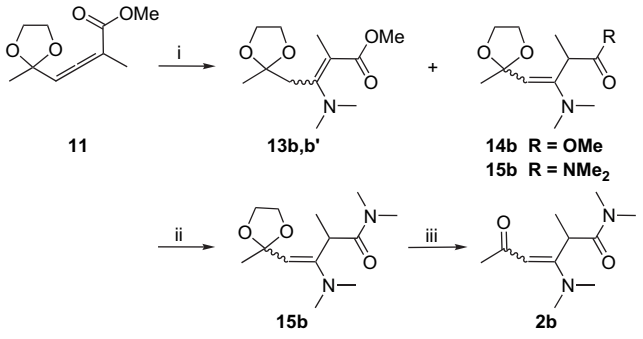
Scheme 2. Reagents and conditions: (i) PPh_3, EtOAc, reflux, 24 h, 80%; (ii) Et_3N, CH_2Cl_2, 3 Å MS, 20 °C, 30 min; (iii) **4**, 0 °C, 1 h, then 20 °C, 12 h, 55% for three steps; (iv) HCO_2H, 30 °C, 8 h, 60%.

Reactivity of unprotected allene **3** was then checked by treating it with *p*-anisidine (Scheme 3). Mainly mono-addition of the aromatic amine on the central carbon was observed, giving the enaminoester **12a** in unsatisfactory yield (20%, determined by NMR of the crude mixture).[49] A strong degradation of the reaction mixture occurred after prolonged reaction times, leading to only traces of the expected pyridone **1a**.



Scheme 3. Reagents and conditions: (i) *p*-$MeOC_6H_4NH_2$, 2 equiv, MeOH, reflux, 20 h, 20% NMR yield.

Because of the low stability of enaminoester **12a** (see later for the reactivity of compounds like **2a**), we focused our attention on the protected allene **11**. To estimate its reactivity, it was treated with to secondary aliphatic amines such as dimethylamine, piperidine, and *N*-methylpiperazine. In the former case (Scheme 4), using aqueous dimethylamine, three main products could be identified by NMR: enaminoester **13** as a couple of both *Z* and *E* stereoisomers **13b** and **13b′**, and only one isomer of the enamine **14b** (only traces of amidified **15b** can be detected).[50] These compounds could not be purified because ethylenedioxy protecting group was cleaved upon chromatography on silica gel, and separation of compounds could not be obtained. Nevertheless, the isomers were characterized by NMR according to their relative proportions in the reaction mixture (Table 1—entry 1). In other conditions, by bubbling dimethylamine in a solution of allene **11** in methanol, only amide **15b** was obtained. Purification of this compound by column chromatography on SiO_2 led again to cleavage of the protecting group, and enaminoketone **2b** was isolated in 40% yield (Table 1—entry 2).



Scheme 4. Reagents and conditions: (i) DMA 40%, 1.2 equiv, H_2O, rt, 10 h, 80%; (ii) DMA, excess MeOH, rt, 6 h; (iii) SiO_2, EtOAc, 40% for two steps.

Allene **11** was now reacted with piperidine (Scheme 5). Synthesis of amide **15c** was not observed; both couples of isomers **13c** and **13c′** and **14c** and **14c′** were formed at the beginning of the reaction. Then, enamines **14c** and **14c′** evolved during the heating of the mixture to give only enaminoesters **13c** and **13c′** (Table 1). The appearance of a vinylic hydrogen at 6.02 ppm indicated that the double bond slowly isomerized upon smooth treatment of the crude mixture by formic acid at room temperature. Surprisingly,

Table 1. Main chemical shifts for enamines **13b–d**, **14b** and **2b**

Entry	Mixture of compounds	Compound	Ratio (%)	a	b	c	d	e
1	**13b+13b′+14b**	**13b**	40	1.33, s, 3H	3.30, s, 2H	—	1.85, s, 3H	3.66, s, 3H
		13b′	27	1.38, s, 3H	2.80, s, 2H	—	1.92, s, 3H	3.68, s, 3H
		14b	33	1.41, s, 3H	6.05, dd, J=10.0, 2.1 Hz, 1H	3.75, q, J=6.1 Hz, 1H	2.12, d, J=6.1 Hz, 3H	3.82, s, 3H
2	**2b**	**2b**	100	2.31, s, 3H	6.04, dd, J=12.0, 2.4 Hz, 1H	3.69, q, J=6.0 Hz, 1H	2.13, d, J=6.0 Hz, 3H	2.73, d, J=2.1 Hz, 6H
3	**13c+13c′**	**13c**	75	1.34, s, 3H	3.23, s, 2H	—	1.87, s, 3H	3.68, s, 3H
		13c′	25	1.39, s, 3H	2.71, s, 2H	—	1.90, s, 3H	3.70, s, 3H
4	**13d+13d′**	**13d**	80	1.33, s, 3H	3.21, s, 2H	—	1.89, s, 3H	3.68, s, 3H
		13d′	20	1.38, s, 3H	2.71, s, 2H	—	1.91, s, 3H	3.71, s, 3H

Scheme 5. Reagents and conditions: (i) piperidine, 1 equiv, rt, 8 h, 90%; (ii) piperidine, 2 equiv, rt, 20 h.

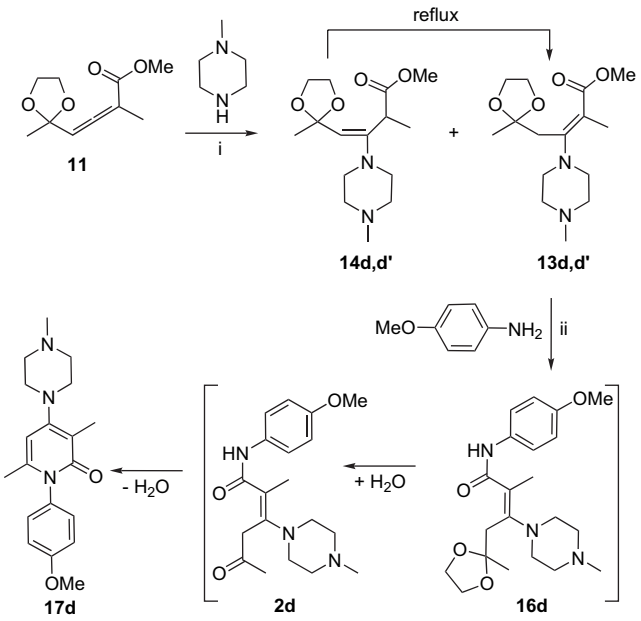
acetal function was rather stable under these conditions. Again, as for dimethylamine adducts, these compounds could not be purified because of their decomposition upon chromatography on silica gel, but each isomer was characterized by NMR (Table 1—entry 3).

From these preliminary studies, it was learned that:

(i) in its protected dioxolanyl form, the allene is more stable than in its ketone counterpart;
(ii) amines react first at room temperature on the allenic central carbon and then eventually, more slowly, with the ester function;
(iii) after reaction with an amine, deprotection of the ketone group is an easy reaction;
(iv) there is a possibility of interconversion between the enamine and the enaminoester form of these compounds.

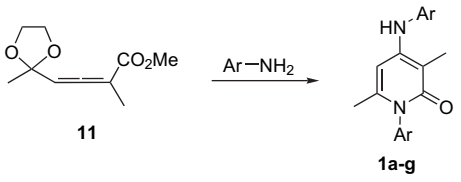
2.2. Synthesis of 1,4-disubstituted-2,5-dimethylpyridones

Taking these results into account, reaction of allene **11** with 1 equiv of *N*-methylpiperazine in methanol at room temperature for 5 h was carried out. As in the previous cases, a mixture of enamines **13d** and **13d′** and **14d** and **14d′** was obtained in a near quantitative yield, but now *p*-anisidine was added at the end of their formation. To our delight, after 18 h of reflux in methanol, pyridone **17** was obtained with a 90% reproducible yield. The initial reaction medium evolved to give only enamines **13d** and **13d′** after prolonged reaction times, allowing their unambiguous NMR description (Table 1—entry 4). Although compounds **16d** and **2d** were not characterized in the reaction media, we thought that a plausible mechanism involved amidification of the ester moiety of **13** and **14** by the aromatic amine to give amide **16d**. Then, a trace of water in the reaction mixture led to hydrolysis of the acetal group, and cyclization of ketone **2d** to pyridone **17** released the molecule of water needed for pursuing the reaction (Scheme 6). This two-step reaction sequence has then been generalized by using the primary and secondary amines described in Table 2.



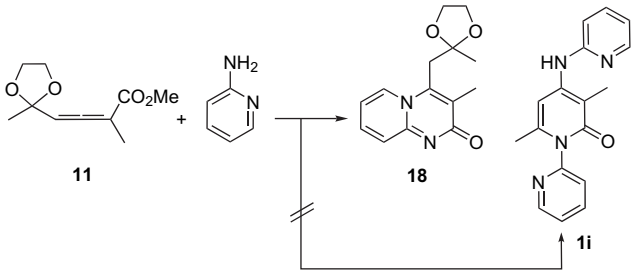
Scheme 6. Reagents and conditions: (i) dried MeOH, 20 °C, 5 h, or neat, 20 °C, 1 h; (ii) MeOH, reflux, 18 h, 90% for two steps.

Now, allene **11** was reacted with 2 equiv of substituted anilines in refluxing methanol for 3–48 h depending on the aniline, and pyridones **1a–g** were thus formed in 64–92% yield (Scheme 7). Reaction time decreases with the increase of electron-donating groups on the aromatic moiety (from 3 h for two to no reaction for a *para* nitro: Table 3—entries 4 and 8).



Scheme 7. Reagents and conditions: dried MeOH, reflux, 3–48 h, 64–92%.

In an attempt to introduce a nitrogen in the aromatic ring, allene **11** was reacted with 2-aminopyridine. Instead of a pyridone **1i**, pyridopyrimidone **18** was isolated in 65% yield (Scheme 8). Its structure was unambiguously determined by NOESY experiment to discriminate the other possible product **19** (Scheme 9—path B). Its formation involves first attack of the pyridine nitrogen on the allenic system, before cyclization on the ester moiety through the free amine group (path A).

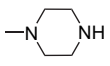
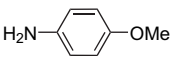
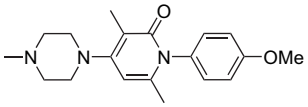
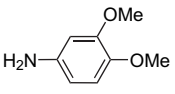
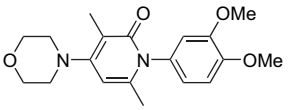
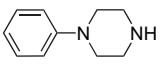
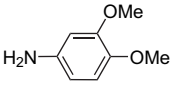
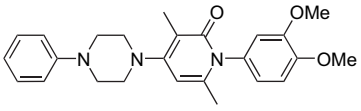
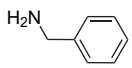
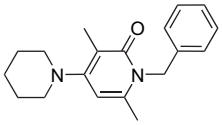


Scheme 8. Reagents and conditions: dried MeOH, reflux, 48 h, 65%.

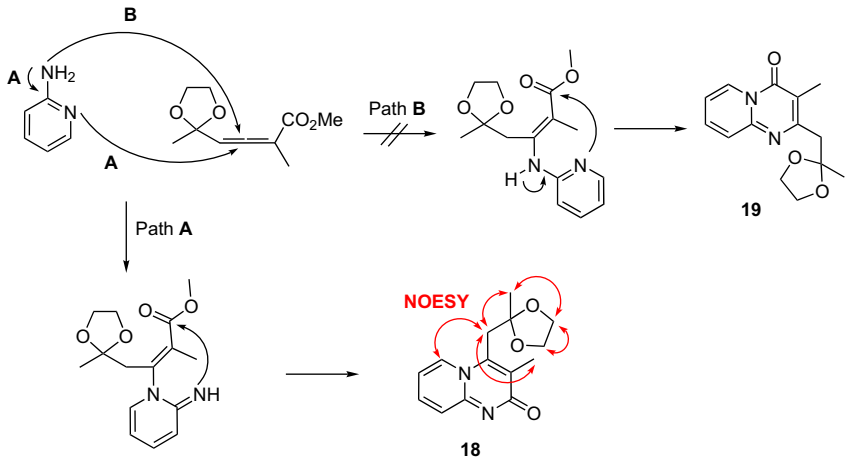
2.3. Important note

The first step of all the previous reaction sequences was realized either neat, or in dried methanol kept on 3 Å MS. While repeating some of these reactions by using methanol from an old bottle, the main (sometimes only) product obtained was a phenol, such as **22e** (Scheme 10). This type of reaction has been observed for piperidine and *N*-phenylpiperazine but only phenol **22e** has been isolated and fully characterized. The mechanism proposed for their formation involves addition of the amine on central allenic carbon of **13**, followed by deprotection of the acetal group, giving ketone **12**. In that case, where the water contents of methanol were higher than in the previous syntheses, hydrolysis of the acetal protection occurs before amidification of the ester function [as opposed to what was postulated for the synthesis of the previous pyridones **1a–g** (Scheme 6)]. This allows the amine catalyzed reaction of the methylketone group of **12** with the ester function leading to **20** by intramolecular

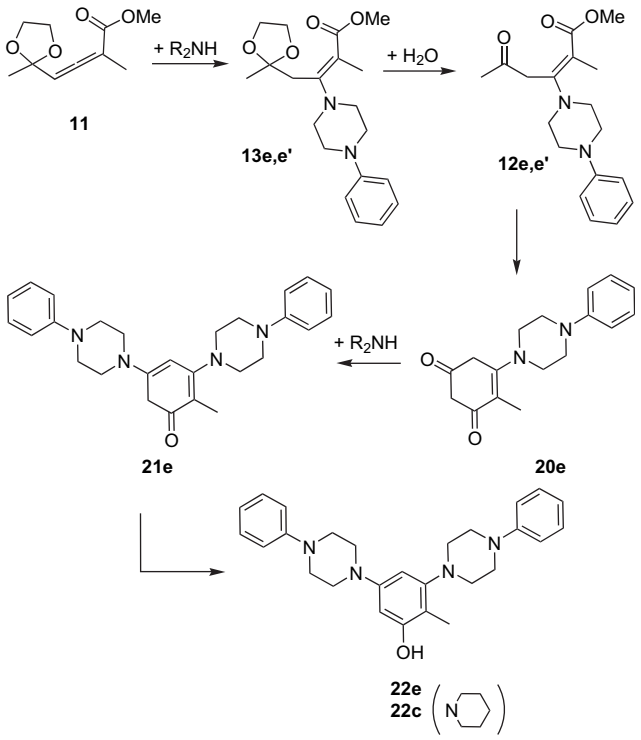
Table 2. Synthesis of unsymmetrically disubstituted pyridones

Entry	Secondary amine	Aniline		Product	Yield[a] (%)	Mp (solvent)
1			**17d**		86	170–dec (ether)
2			**17e**		68	202–dec (ether)
3			**17f**		73	196–198 (ether)
4			**17g**		83	130–132 (ether)

[a] Isolated yield.



Scheme 9. Plausible mechanism for the synthesis of compound **17**, and NOESY correlations.



Scheme 10. Synthesis and mechanism of formation of phenol **22**. Reagents and conditions: *N*-phenylpiperazine, MeOH, 20 °C, 6 h, 70%.

cyclization. A second molecule of amine finally adds to the unconjugated carbonyl group, giving **21** then **22**.[51]

3. Conclusion

In summary, we have achieved a one-pot simple and efficient synthesis of highly substituted 2-pyridones from a dicarbonylallene. Surprisingly, condensation occurred more readily while reacting the protecting form rather than the deprotected one. The yields are generally excellent and two different substitutions can be obtained using a two-step procedure. Especially, alkyl substituents can be introduced in the 4-position, widening its substitution pattern. Synthesis of a new pyridopyrimidone derivative has been achieved from 2-aminopyridine. Eventually, formation of substituted phenols under non-anhydrous conditions confirms functionalized allene **11** as a key building-block for a variety of structures of interest. Biological evaluation of compounds described herein is in progress and will be reported in due course.

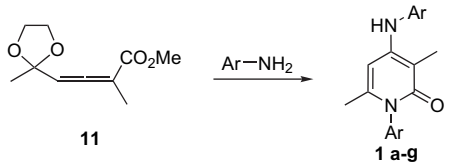
4. Experimental section

4.1. General

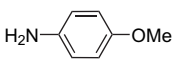
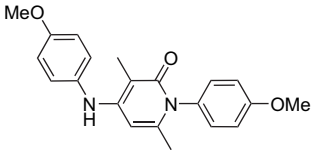
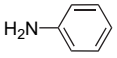
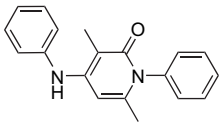
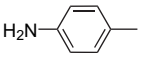
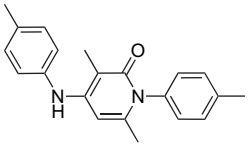
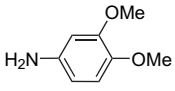
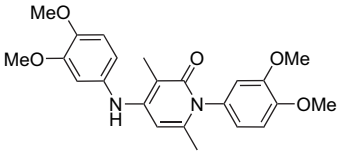
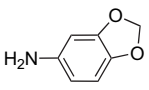
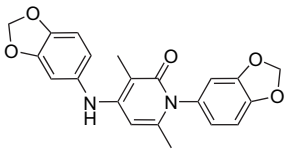
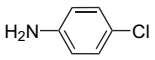
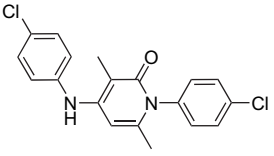
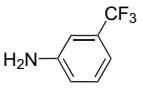
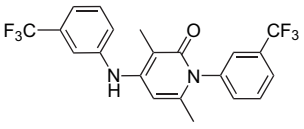
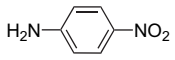
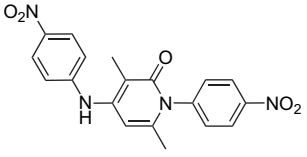
Melting points were determined using an Electrothermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. 2D NMR spectra were recorded on a Bruker DRX-300 spectrometer at 300 MHz. IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27. Thin layer chromatographies were performed on precoated Kieselgel 60F_{254} plates. APCI^{+} (atmospheric pressure chemical ionization) mass spectrum was obtained on an LC–MS system Thermo Electron Surveyor MSQ. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France.

4.1.1. Methyl (2-methyl-1,3-dioxolan-2-yl)acetate (8b). To a solution of methyl acetoacetate **5** (300 g, 2.58 mol) and ethylene glycol (208.5 g, 3.36 mol) in toluene (2.5 L) was added *p*-toluenesulfonic acid (0.22 g, 1.3 mmol). The reaction medium was equipped with a Dean–Stark apparatus and then refluxed until no more water was collected (20 h). The solvent was evaporated, the residue dissolved in dichloromethane (300 mL) and neutralized by an aqueous solution of potassium carbonate. The organic phase was then washed three times with water (100 mL), dried upon $MgSO_4$, and evaporated. The remaining solution was then back trans-esterified by adding methanol (1.5 L) and sodium methylate 40% in methanol (10 mL). The mixture was refluxed for 24 h, neutralized with citric acid, and evaporated. The resulting solution was distilled under reduced pressure to give pure **8b** (190.1 g, 46%) as a colorless liquid with the same properties as described in literature.[30] IR: ν cm^{-1} 1723, 1180, 1042; ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.49 (s, 3H, CH_3–C($OCH_2)_2$), 2.67 (s, 2H, CH_2–CO), 3.68

Table 3. Synthesis of 1,4-diaryl-3,5-dimethylpyrid-2-ones



11 **1 a-g**

Entry	No.	$ArNH_2$	Product	Reaction time (h)	Yield[a] (%)	Mp (solvent)
1	**1a**			6	95	158–160 (ether)
2	**1b**			24	80	159–161 (ether)
3	**1c**			19	88	206–208 (ether)
4	**1d**			3	92	133–135 (ether)
5	**1e**			12	92	134–136[b]
6	**1f**			48	64	190–192 (ether)
7	**1g**			20	92	82–84[b]
8	**1h**			96	NR[c]	—

[a] Isolated yield.
[b] Purified by preparative HPLC.
[c] No reaction.

(s, 3H, CO_2CH_3), 3.94–3.98 (m, 4H, O–CH_2–CH_2–O); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 23.4 (CH_3), 40.1 (CH_2), 52.4 (CH_3), 64.7 ($2CH_2$), 113.3 (C), 171.4 (C).

4.1.2. (1-Methoxycarbonyl-ethyl)-triphenyl-phosphonium bromide (10). To a solution of methyl 2-bromopropanoate **7** (50 g, 0.3 mol) in EtOAc (200 mL) was added triphenylphosphine (94.2 g, 0.4 mol). The mixture was then heated under reflux for 24 h with vigorous stirring. After cooling to room temperature, the resulting precipitate was filtered and rinsed twice with EtOAc (40 mL) to give **10** as a white salt (103.5 g, 80%), which was not analyzed. Mp (EtOAc) 131–133 °C. IR: ν cm^{-1} 2767, 1745, 1439, 1110; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.70 (dd, J=18.4, 7.3 Hz, 3H, CH_3–CH), 3.58 (s, 3H, CO_2CH_3), 6.97 (sext, J=7.3 Hz, 1H, CH_3–C*H*), 7.63–7.86 (m, 9H,

Ar*H*), 7.93–8.08 (m, 6H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 12.9 (d, J=3.1 Hz, CH_3), 36.6 (d, J=51.7 Hz, CH), 53.3 (CH_3), 117.7 (d, J=87.0 Hz, 3C), 130.2 (d, J=12.7 Hz, 6CH), 134.2 (d, J=9.7 Hz, 6CH), 134.9 (d, J=3.3 Hz, 3CH), 168.7 (d, J=2.0 Hz, C).

4.1.3. Methyl 2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)-buta-2,3-dienoate (11). A stirred solution of potassium trimethylsilanolate (11 g, 0.085 mol) in THF (100 mL) was dried over 3 Å molecular sieves (15 g) overnight then filtered under nitrogen. To this solution compound **8b** (12.5 g, 0.078 mol) was added. The resulting mixture was stirred under inert atmosphere for 4 h, and the resulting white salt was filtered under nitrogen and rinsed with CH_2Cl_2. Potassium salt **9** was then introduced in a flask containing CH_2Cl_2 (70 mL) and then cooled to 0 °C. Oxalyl chloride (6.5 mL, 0.074 mol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction medium over a period of 30 min at 0 °C, and stirring was continued for 12 h to obtain a solution of acyl chloride **4** in CH_2Cl_2. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.49 (s, 3H, C*H*$_3$–C(OCH$_2$)$_2$), 3.26 (s, 2H, C*H*$_2$–CO), 4.01 (s, 4H, O–C*H*$_2$–C*H*$_2$–O); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 24.3 (CH_3), 53.3 ($2CH_2$), 55.5 (CH_2), 106.6 (C), 159.0 (C).

Meanwhile, to a stirred solution of phosphonium bromide **10** (33.5 g, 0.078 mol) in CH_2Cl_2 (200 mL) was added 3 Å molecular sieves (30 g) and dropwise triethylamine (21.7 mL, 0.156 mol). The yellow solution was allowed to stir at room temperature for 30 min to give phosphorane **6**. The spectroscopic data were in agreement with those described in the literature.[52]

To this suspension was added at 0 °C the acyl chloride **4** solution prepared previously. The resulting mixture was allowed to warm to room temperature and stirred for 12 h. The solvent was then partially evaporated, and heptane was added to obtain two phases. The suspension was kept cold overnight to precipitate the triphenylphosphine oxide and filtered. Solvents were evaporated to give protected allene **11** as a brown oil (9.3 g, 55%), which was used directly in the next step. IR: ν cm^{-1} 1963, 1714, 1276, 1177, 1120, 1102, 1034, 868; ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.58 (s, 3H, C*H*$_3$–C(OCH$_2$)$_2$), 1.91 (d, J=2.9 Hz, 3H, C*H*$_3$–C=C), 3.75 (s, 3H, CO$_2$C*H*$_3$), 3.98–4.02 (m, 4H, O–C*H*$_2$–C*H*$_2$–O), 5.49 (q, J=2.9 Hz, 1H, C=C*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 14.8 (CH_3), 25.1 (CH_3), 52.0 (CH_3), 64.4 (CH_2), 64.7 (CH_2), 97.4 (CH), 98.2 (C), 106.4 (C), 167.3 (C), 208.6 (C).

4.1.4. Methyl 2-methyl-5-oxohexa-2,3-dienoate (3). A solution of compound **11** (2 g, 0.011 mol) in formic acid (2.5 g, 0.055 mol) was stirred at 30 °C for 8 h, and then partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The organic phase was washed two times with water (5 mL), once with a saturated solution of sodium hydrogenocarbonate, then with water. The resulting solution was dried over magnesium sulfate, filtered, and evaporated to give **3** as a light brown oil (1.36 g, 80%). This unstable product was not analyzed. IR: ν cm^{-1} 1948, 1722, 1686, 1276, 1220, 1160, 1119; ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 2.05 (s, 3H, C*H*$_3$–CO), 2.30 (d, J=3.1 Hz, 3H, C*H*$_3$–C=C), 3.81 (s, 3H, CO$_2$C*H*$_3$), 6.10 (q, J=3.1 Hz, 1H, C=C*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 14.4 (CH_3), 27.4 (CH_3), 52.7 (CH_3), 99.5 (CH), 99.6 (C), 165.6 (C), 196.3 (C), 219.9 (C).

4.2. General procedure for the synthesis of unsymmetrically 1,4-disubstituted 3,6-dimethyl-pyridones 17d–g

A mixture of allene **11** (0.25 g, 2.7 mmol) and 1 equiv of secondary amine (2.7 mmol) was stirred at room temperature under nitrogen for 1 h. Aniline of 1 equiv in dried methanol (5 mL) was then added and the solution was refluxed for 6 h. Solvent was evaporated under reduced pressure, and the dark residue was purified by column chromatography on SiO_2 eluted by a gradient of ethyl acetate in heptane to give unsymmetrically disubstituted pyridones **17d–g**.

4.2.1. 1-(4-Methoxyphenyl)-3,6-dimethyl-4-(4-methylpiperazin-1-yl)pyridin-2(1*H*)-one (17d). Gray powder (86%); mp (ether) 170 °C (dec); TLC R_f (EtOAc): 0.8; IR: ν cm^{-1} 1638, 1611, 1589, 1539, 1511, 1250, 1022, 1003, 807; ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.95 (s, 3H, CO–C–C*H*$_3$), 2.05 (s, 3H, N–C–C*H*$_3$), 2.39 (s, 3H, N–C*H*$_3$), 2.60 (br s, 4H, CH$_3$N–C*H*$_2$CH$_2$), 3.10 (br s, 4H, CH$_3$N–CH$_2$C*H*$_2$), 3.85 (s, 3H, OC*H*$_3$), 5.94 (d, J=0.8 Hz, 1H, C*H*), 6.98 (td, J=9.4, 2.6 Hz, 2H, Ar*H*), 7.08 (td, J=9.4, 2.6 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 13.0 (CH_3), 21.7 (CH_3), 46.1 (CH_3), 50.0 ($2CH_2$), 55.2 ($2CH_2$), 55.5 (CH_3), 100.0 (CH), 113.1 (C), 114.8 (2CH), 129.0 (2CH), 132.9 (C), 143.0 (C), 157.8 (C), 159.3 (C), 165.4 (C). Anal. Calcd for $C_{19}H_{25}N_3O_2\cdot 4/3H_2O$: C 64.93, H 7.93, N 11.96. Found: C 65.00, H 7.55, N 12.05.

4.2.2. 1-(3,4-Dimethoxyphenyl)-3,6-dimethyl-4-(morpholin-4-yl)pyridin-2(1*H*)-one (17e). Light gray powder (73%); mp (ether) 202 °C (dec); TLC R_f (EtOAc/MeOH 80:20): 0.65; IR: ν cm^{-1} 1654, 1590, 1547, 1514, 1206, 1141, 1021; ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.99 (s, 3H, CO–C–C*H*$_3$), 2.08 (s, 3H, N–C–C*H*$_3$), 3.02–3.09 (m, 4H, N–C*H*$_2$CH$_2$–O), 3.80–3.89 (m, 4H, N–CH$_2$C*H*$_2$–O), 3.86 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 5.94 (s, 1H, C*H*), 6.68 (d, J=2.3 Hz, 1H, Ar*H*), 6.73 (dd, J=8.3, 2.3 Hz, 1H, Ar*H*), 6.95 (d, J=8.3 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 12.9 (CH_3), 21.4 (CH_3), 50.6 ($2CH_3$), 56.0 ($2CH_2$), 67.0 ($2CH_2$), 99.6 (CH), 111.1 (CH), 111.4 (CH), 113.4 (C), 120.0 (CH), 132.1 (C), 143.2 (C), 148.9 (C), 149.6 (C), 157.6 (C), 165.7 (C). Anal. Calcd for $C_{19}H_{25}N_3O_2\cdot H_2O$: C 62.97, H 7.23, N 7.73. Found: C 63.12, H 7.31, N 7.69.

4.2.3. 1-(3,4-Dimethoxyphenyl)-3,6-dimethyl-4-(4-phenylpiperazin-1-yl)pyridin-2(1*H*)-one (17f). Gray powder (68%); mp (ether) 196–198 °C; TLC R_f (EtOAc/MeOH): 0.76; IR: ν cm^{-1} 1649, 1597, 1546, 1514, 1496, 1220, 1141, 1023, 771; ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 2.00 (s, 3H, CO–C–C*H*$_3$), 2.11 (s, 3H, N–C–C*H*$_3$), 3.18–3.27 (m, 4H, N–C*H*$_2$CH$_2$–NPh), 3.30–3.38 (m, 4H, N–CH$_2$C*H*$_2$–NPh), 3.86 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 6.02 (s, 1H, C*H*), 6.69 (d, J=2.3 Hz, 1H, Ar*H*), 6.74 (dd, J=8.3, 2.3 Hz, 1H, Ar*H*), 6.95 (d, J=8.3 Hz, 1H, Ar*H*), 6.86–7.03 (m, 3H, Ar*H*), 7.26–7.36 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 13.0 (CH_3), 21.4 (CH_3), 46.2 ($2CH_2$), 50.4 ($2CH_3$), 56.0 ($2CH_2$), 100.4 (CH), 111.2 (CH), 111.4 (CH), 113.1 (C), 116.3 (2CH), 120.0 (CH), 120.2 (CH), 129.2 (2CH),

132.0 (C), 143.3 (C), 148.9 (C), 149.6 (C), 151.1 (C), 158.1 (C), 164.5 (C). Anal. Calcd for $C_{19}H_{25}N_3O_2 \cdot 1/2H_2O$: C 70.07, H 7.06, N 9.81. Found: C 69.87, H 7.02, N 9.45.

4.2.4. 1-Benzyl-3,6-dimethyl-4-piperidin-1-ylpyridin-2(1*H*)-one (17g). White crystals (83%); mp (ether) 130–132 °C; TLC R_f (EtOAc): 0.68; IR: ν cm^{-1} 2935, 1635, 1589, 1546, 1220, 1108, 1012; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.54–1.75 (m, 6H, $N(CH_2CH_2)_2CH_2$), 2.10 (s, 3H, CO–C–CH_3), 2.21 (s, 3H, N–C–CH_3), 2.89–3.04 (m, 4H, $N(CH_2CH_2)_2CH_2$), 5.33 (s, 2H, NCH_2Ph), 5.88 (s, 1H, C*H*), 7.10–7.17 (m, 2H, Ar*H*), 7.19–7.33 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 13.4 (CH_3), 20.5 (CH_3), 24.2 (CH_2), 26.0 ($2CH_2$), 47.1 (CH_2), 51.5 ($2CH_2$), 101.1 (CH), 112.1 (C), 126.3 (2CH), 126.8 (CH), 128.5 (2CH), 137.2 (C), 142.3 (C), 158.6 (C), 164.8 (C). Anal. Calcd for $C_{19}H_{25}N_3O_2 \cdot 1/3H_2O$: C 69.59, H 7.97, N 7.73. Found: C 69.52, H 7.93, N 7.56.

4.3. General procedure for the synthesis of 3,6-dimethyl-1,4-diarylpyridones 1a–g

To a solution of allene **11** (0.6 g, 3 mmol) in dried methanol (5 mL) was added 6 mmol of substituted aniline. The mixture was then refluxed under nitrogen for the time mentioned in Table 3, then partitioned between CH_2Cl_2 (20 mL) and water (10 mL). The organic phase was washed once with a 5% aqueous solution of HCl, twice with water, dried over $MgSO_4$, and evaporated. Crude product was purified either by recrystallization in ether or by preparative HPLC eluted by EtOAc.

4.3.1. 1-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)amino]-3,6-dimethylpyridin-2(1*H*)-one (1a). Gray powder; mp (ether) 158–160 °C; TLC R_f (EtOAc/MeOH 9:1): 0.65; IR: ν cm^{-1} 3250, 1634, 1613, 1577, 1562, 1507, 1459, 1248, 1034, 830; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.83 (s, 3H, CO–C–CH_3), 2.09 (s, 3H, N–C–CH_3), 3.84 (s, 6H, OCH_3), 5.70 (br s, 1H, N*H*), 5.81 (s, 1H, C*H*), 6.95 (td, J=8.8, 2.8 Hz, 4H, Ar*H*), 7.11 (td, J=8.8, 2.8 Hz, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.4 (CH_3), 21.5 (CH_3), 55.3 ($2CH_3$), 96.3 (CH), 101.0 (C), 114.5 (4CH), 126.2 (4CH), 132.2 (C), 132.5 (C), 143.1 (C), 150.4 (C), 157.0 (C), 159.0 (C), 164.3 (C). Anal. Calcd for $C_{21}H_{22}N_2O_3 \cdot 1/2H_2O$: C 70.18, H 6.45, N 7.79. Found: C 69.88, H 6.26, N 8.04.

4.3.2. 4-Anilino-3,6-dimethyl-1-phenylpyridin-2(1*H*)-one (1b). Light brown powder; mp (ether) 159–161 °C; TLC R_f (EtOAc): 0.37; IR: ν cm^{-1} 3242, 1641, 1595, 1555, 1495, 1396, 756, 700; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.85 (s, 3H, CO–C–CH_3), 2.10 (s, 3H, N–C–CH_3), 5.94 (br s, 1H, N*H*), 6.07 (s, 1H, C*H*), 7.10–7.22 (m, 5H, Ar*H*), 7.32–7.53 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.6 (CH_3), 21.5 (CH_3), 97.0 (CH), 103.1 (C), 122.8 (2CH), 124.0 (CH), 128.1 (CH), 128.2 (2CH), 129.3 (4CH), 139.4 (C), 139.8 (C), 142.7 (C), 149.3 (C), 164.2 (C). Anal. Calcd for $C_{19}H_{18}N_2O \cdot 1/4H_2O$: C 77.39, H 6.32, N 9.50. Found: C 77.45, H 6.30, N 9.60.

4.3.3. 3,6-Dimethyl-1-(4-methylphenyl)-4-[(4-methylphenyl)amino]pyridin-2(1*H*)-one (1c). Light brown powder; mp (ether) 206–208 °C; TLC R_f (EtOAc/MeOH 9:1): 0.72; IR: ν cm^{-1} 3250, 1635, 1611, 1577, 1562, 1511, 1463, 1392, 1307, 817, 725; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.84 (s, 3H, CO–C–CH_3), 2.07 (s, 3H, N–C–CH_3), 2.36 (s, 3H, ArCH_3), 2.39 (s, 3H, ArCH_3), 5.84 (br s, 1H, N*H*), 5.97 (d, J=0.8 Hz, 1H, C*H*), 7.06 (dq, J=8.6, 2.6 Hz, 4H, Ar*H*), 7.18 (dtd, J=8.6, 2.3, 0.6 Hz, 2H, Ar*H*), 7.26 (dtd, J=8.6, 2.2, 0.6 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.7 (CH_3), 20.9 (CH_3), 21.2 (CH_3), 21.6 (CH_3), 96.8 (CH), 102.2 (C), 123.7 (2CH), 128.0 (2CH), 130.0 (2CH), 130.1 (2CH), 134.2 (C), 136.9 (C), 137.2 (C), 138.0 (C), 143.0 (C), 149.9 (C), 164.4 (C). Anal. Calcd for $C_{21}H_{22}N_2O \cdot 2/3H_2O$: C 76.33, H 7.12, N 8.48. Found: C 76.25, H 6.90, N 8.59.

4.3.4. 1-(3,4-Dimethoxyphenyl)-4-[(3,4-dimethoxyphenyl)amino]-3,6-dimethylpyridin-2(1*H*)-one (1d). Light brown powder; mp (ether) 133–135 °C; TLC R_f (EtOAc/MeOH 9:1): 0.42; IR: ν cm^{-1} 3246, 1638, 1600, 1557, 1509, 1234, 1022, 799, 766; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.87 (s, 3H, CO–C–CH_3), 2.11 (s, 3H, N–C–CH_3), 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 6H, OCH_3), 5.73 (br s, 1H, N*H*), 5.86 (s, 1H, C*H*), 6.68–6.80 (m, 4H, Ar*H*), 6.88 (dd, J=7.7, 1.0 Hz, 1H, Ar*H*), 6.93 (d, J=8.4 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.6 (CH_3), 21.5 (CH_3), 56.0 (CH_3), 56.1 ($2CH_3$), 56.2 (CH_3), 96.5 (CH), 101.3 (C), 109.2 (CH), 111.3 (CH), 111.5 (CH), 111.6 (CH), 117.1 (CH), 120.4 (CH), 132.5 (C), 132.8 (C), 143.4 (C), 146.8 (2 C), 149.5 (C), 149.6 (C), 150.5 (C), 164.4 (C). Anal. Calcd for $C_{23}H_{26}N_2O_5 \cdot 5/4H_2O$: C 63.80, H 6.63, N 6.47. Found: C 63.99, H 6.43, N 6.37.

4.3.5. 1-(1,3-Benzodioxol-5-yl)-4-(1,3-benzodioxol-5-ylamino)-3,6-dimethylpyridin-2(1*H*)-one (1e). Brown powder; mp 134–136 °C; TLC R_f (EtOAc/MeOH 9:1): 0.70; IR: ν cm^{-1} 3246, 1640, 1559, 1502, 1483, 1460, 1396, 1212, 1190, 1035, 790, 761; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.89 (s, 3H, CO–C–CH_3), 2.06 (s, 3H, N–C–CH_3), 5.76 (br s, 1H, N*H*), 5.85 (d, J=1 Hz, 1H, C*H*), 6.00 (d, J=1.4 Hz, 2H, OCH_2O), 6.01 (d, J=1.4 Hz, 2H, OCH_2O), 6.59–6.66 (m, 3H, Ar*H*), 6.71 (d, J=2.1 Hz, 1H, Ar*H*), 6.80 (d, J=8.1 Hz, 1H, Ar*H*), 6.86 (dd, J=7.7, 0.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.5 (CH_3), 21.5 (CH_3), 96.5 (CH), 101.3 (CH), 101.4 (C), 101.6 (CH), 106.4 (CH), 108.3 ($2CH_2$), 109.2 (CH), 117.8 (CH), 121.5 (CH), 133.1 (C), 133.6 (C), 145.0 (C), 147.3 (C), 148.1 (C), 148.2 (C), 150.2 (C), 164.2 (C). Anal. Calcd for $C_{21}H_{18}N_2O_5 \cdot 1/2H_2O$: C 65.11, H 4.94, N 7.23. Found: C 64.72, H 4.97, N 7.03.

4.3.6. 1-(4-Chlorophenyl)-4-[(4-chlorophenyl)amino]-3,6-dimethylpyridin-2(1*H*)-one (1f). White powder; mp (ether) 190–192 °C; TLC R_f (EtOAc/MeOH 9:1): 0.74; IR: ν cm^{-1} 3288, 1648, 1597, 1558, 1490, 1463, 1090, 822, 738; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.87 (s, 3H, CO–C–CH_3), 2.09 (s, 3H, N–C–CH_3), 5.81 (br s, 1H, N*H*), 5.98 (s, 1H, C*H*), 7.1 (td, J=8.7, 2.1 Hz, 2H, Ar*H*), 7.13 (td, J=8.6, 2.1 Hz, 2H, Ar*H*), 7.34 (td, J=8.7, 2.1 Hz, 2H, Ar*H*), 7.45 (td, J=8.6, 2.1 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.7 (CH_3), 21.6 (CH_3), 97.2 (CH), 103.6 (C), 124.2 (2CH), 129.5 (2CH), 129.5 (C), 129.8 (4CH), 134.3 (C), 137.9 (C), 138.5 (C), 142.7 (C), 149.1 (C), 164.2 (C). Anal. Calcd for $C_{19}H_{16}Cl_2N_2O \cdot 3/4H_2O$: C 61.22, H 4.73, N 7.51. Found: C 61.32, H 4.42, N 7.77.

4.3.7. 3,6-Dimethyl-1-[3-(trifluoromethyl)phenyl]-4-{[3-(trifluoromethyl)phenyl]amino}pyridin-2(1*H*)-one (1g). Yellowish powder; mp 82–84 °C; TLC R_f (EtOA/MeOH 9:1): 0.77; IR: ν cm^{-1} 3261, 1644, 1598, 1560, 1328, 1118, 698; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.88 (s, 3H, CO–C–CH_3), 2.09 (s, 3H, N–C–CH_3), 6.05 (s, 1H, C*H*), 6.17 (br s, 1H, N*H*), 7.28–7.53 (m, 6H, Ar*H*), 7.56–7.72 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.9 (CH_3), 21.7 (CH_3), 97.0 (CH), 105.0 (C), 118.8 (q, J=4 Hz, CH), 120.3 (q, J=4 Hz, CH), 123.6 (q, J=272 Hz, CF_3), 123.8 (q, J=272 Hz, CF_3), 125.3 (q, J=2 Hz, CH), 125.4 (q, J=4 Hz, CH), 125.6 (q, J=4 Hz, CH), 130.0 (CH), 130.2 (CH), 131.9 (q, J=33 Hz, C), 132.1 (q, J=33 Hz, C), 132.1 (q, J=2 Hz, CH), 139.9 (C), 140.7 (C), 142.5 (C), 148.7 (C), 164.4 (C). Anal. Calcd for $C_{21}H_{16}F_6N_2O$: C 59.16, H 3.78, N 6.57. Found: C 59.48, H 4.17, N 6.40.

4.4. 3-Methyl-4-[(2-methyl-1,3-dioxolan-2-yl)methyl]-1,8-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (18)

To a solution of allene **11** (0.6 g, 3 mmol) in methanol (5 mL) was added 2-aminopyridine (0.28 g, 3 mmol). The mixture was refluxed under nitrogen for 20 h, then partitioned between CH_2Cl_2 (20 mL) and water (10 mL). The organic phase was washed once with a 5% aqueous solution of HCl, twice with water, dried over $MgSO_4$, and evaporated. Crude product was recrystallized in ether to afford pure **18** as a white powder (0.45 g, 65%). Mp (ether) 214–216; TLC R_f (EtOAc): 0.23; IR: ν cm^{-1} 1686, 1625, 1591, 1550, 1475, 1450, 1038, 1028, 1129, 771, 763; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.53 (s, 3H, $(CH_2O)_2$–C–CH_3), 2.33 (s, 3H, ArCH_3), 3.46 (br s, 2H, OC$H_2$$CH_2$O), 3.59 (br s, 2H, OCH_2CH_2O), 3.87 (br s, 2H, CH_2–C–$(CH_2O)_2$), 6.77 (ddd, J=7.8, 6.5, 1.7 Hz, 1H, Ar*H*), 7.32 (ddd, J=9.0, 1.7, 0.8 Hz, 1H, Ar*H*), 7.49 (ddd, J=9.0, 6.5, 1.4 Hz, 1H, Ar*H*), 8.28 (ddd, J=7.8, 1.4, 0.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 14.1 (CH_3), 25.8 (CH_3), 37.7 (CH_2), 64.8 ($2CH_2$), 109.7 (C), 111.9 (CH), 124.9 (CH), 127.3 (C), 130.2 (CH), 134.5 (CH), 139.8 (C), 151.6 (C), 168.3 (C). Anal. Calcd for $C_{14}H_{16}N_2O_3\cdot 1/3H_2O$: C 63.15, H 6.31, N 10.52. Found: C 63.27, H 6.23, N 10.82.

4.5. 2-Methyl-3,5-bis(4-phenylpiperazin-1-yl)phenol (22e)

To a solution of allene **11** (0.5 g, 2.5 mmol) in methanol taken from an opened bottle (5 mL) was added *N*-phenylpiperazine (0.4 g, 2.5 mmol), and the solution was stirred at room temperature for 6 h. Solvent was evaporated under reduced pressure, and the resulting oil was purified by chromatography on SiO_2 eluted by EtOAc to afford phenol **22e** as colorless needles (370 mg, 70%). Mp (ether) 165–167 °C; TLC R_f (EtOAc): 0.81; IR: ν cm^{-1} 2835, 1599, 1583, 1504, 1450, 1271, 1240, 1119, 993, 761, 688; ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 2.16 (s, 3H, CH_3), 3.03–3.10 (m, 4H, N–CH_2CH_2–N), 3.22–3.38 (m, 12H, N–CH_2CH_2–N), 4.95 (br s exch., 1H, O*H*), 6.22 (d, J=2.5 Hz, 1H, C*H*), 6.36 (d, J=2.5 Hz, 1H, C*H*), 6.84–6.95 (m, 2H, Ar*H*), 6.95–7.03 (m, 4H, Ar*H*), 7.25–7.35 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ ppm 9.9 (CH_3), 49.3 ($2CH_2$), 49.6 ($4CH_2$), 52.0 ($2CH_2$), 99.9 (CH), 100.6 (CH), 109.6 (C), 116.1 (2CH), 116.3 (2CH), 119.7 (2CH), 129.0 (2CH), 129.1 (2CH), 150.5 (C), 151.1 (C), 151.3 (C), 153.1 (C), 155.2 (C); LC–MS ($APCI^+$) m/z 429 (MH^+). Anal. Calcd for $C_{19}H_{25}N_3O_2\cdot 1/4H_2O$: C 74.88, H 7.56, N 12.94. Found: C 74.81, H 7.52, N 12.86.

4.6. 2-Methyl-3,5-dipiperidin-1-ylphenol (22c)

Formed by the same procedure as **22e** (not isolated). ^1H NMR ($CDCl_3$, 200 MHz): δ ppm 1.63–1.77 (m, 12H, $N(CH_2C\mathit{H}_2)_2C\mathit{H}_2$), 2.10 (s, 3H, C$H_3$), 2.98–3.12 (m, 8H, $N(C\mathit{H}_2CH_2)_2CH_2$), 6.16 (d, J=2.4 Hz, 1H, C*H*), 6.27 (d, J=2.4 Hz, 1H, C*H*).

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