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Vinylogous Blaise Reaction: Conceptually New Synthesis of Pyridin-2-ones

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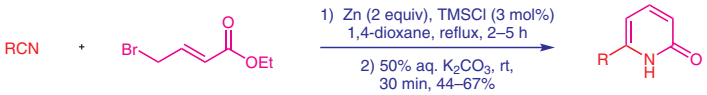

- R = Ar, benzyl, alkyl etc.
- Vinylogous Blaise reaction
- pyridine ring synthesis by [C4 + CN] assembly
- wide scope (12 examples) for C(6)-substituted pyridin-2-ones
- FAcile synthesis of agomelatine (antidepressant) analogue

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Abstract A conceptually new synthesis of pyridine rings by a [C_4 + CN] assembly has been developed by applying a vinylogous version of the classic Blaise reaction. The zinc-mediated reaction of (het)aryl or alkyl nitriles with ethyl-4-bromocrotonate provided a variety of C(6)-substituted pyridin-2-ones in a single-step.

Key words vinylogous Blaise reaction, pyridinones, pyridine ring synthesis, zinc catalysis, bromoalkenoates

The pyridine ring is a fundamental heterocycle[1] that has been known for over 170 years.[2] The pyridine structural element is present in many primary and secondary metabolites, and such natural products play extremely important roles in biological processes.[3] In the pyridine family, pyridin-2(1*H*)-one (**1**) (or its tautomer, pyridin-2-ol) (Figure 1) is a very important molecule, and its motif is well represented as a structural unit among alkaloids, many of which display useful biological activities.[4] For example, alkaloids with a pyridin-2-one motif (Figure 1) exhibit antibiotic or anticancer activities and can affect the central nervous system.[5] Camptothecin (**2**), an anticancer drug used extensively in cancer treatment, is notable among natural products having a pyridin-2-one motif (highlighted portion).[6] Some synthetic pyridin-2-ones, such as the antifungal agent ciclopirox (**3**)[7] and the vasodilator milrinone (**4**), are useful drugs .[8] Apart from their widespread use as drug candidates, pyridin-2-ones have found use in technology-driven applications in the fields of paints, pigments, fuels, lubricants, acid–base indicators, polymers, and others.[9] In addition, pyridin-2-one derivatives have been used as intermediates in the synthesis of six-membered nitrogen heterocycles such as pyridines, piperidines, quinolizidines, and indolizidines.[10] Although pyridin-2-ones are medicinally privileged,[11] there are surprisingly few methods for their direct synthesis.[12]

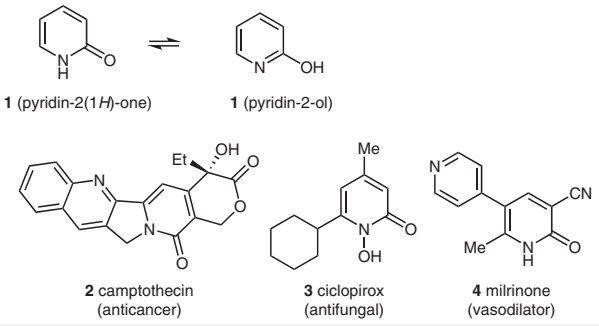
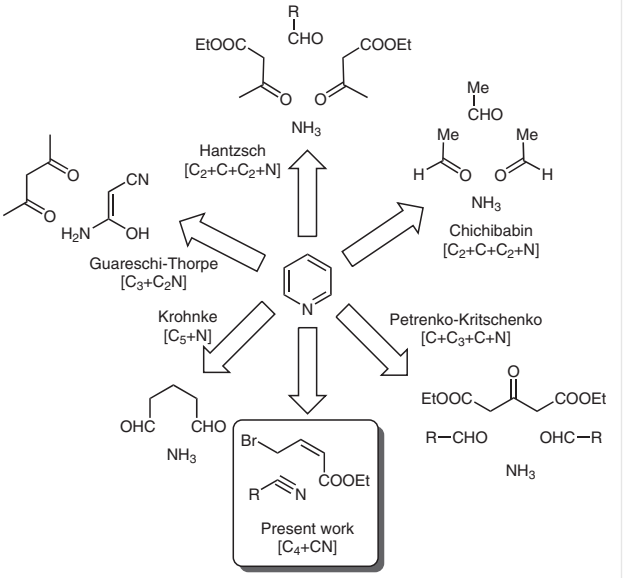


Figure 1 Structures of pyridin-2(1*H*)-one and its tautomer (**1**) and of some natural (**2**) and synthetic drugs (**3** and **4**) containing a pyridin-2-one motif

There are many reports on pyridine ring synthesis in the literature.[13] Among them, some have become familiar named reactions, including the Kröhnke [C_5 + N],[14] Guareschi–Thorpe [C_3 + C_2 + N],[15] Hantzsch [C_3 + C_2 + N],[16] Chichibabin [C_3 + C_2 + N],[17] and Petrenko–Kritschenko [C_3 + C_2 + N][18] reactions (Scheme 1). We have designed a conceptually new method in which the C_5N unit of the pyridin-2-one ring is assembled through a [C_4 + CN] strategy (Scheme1; Present Work).

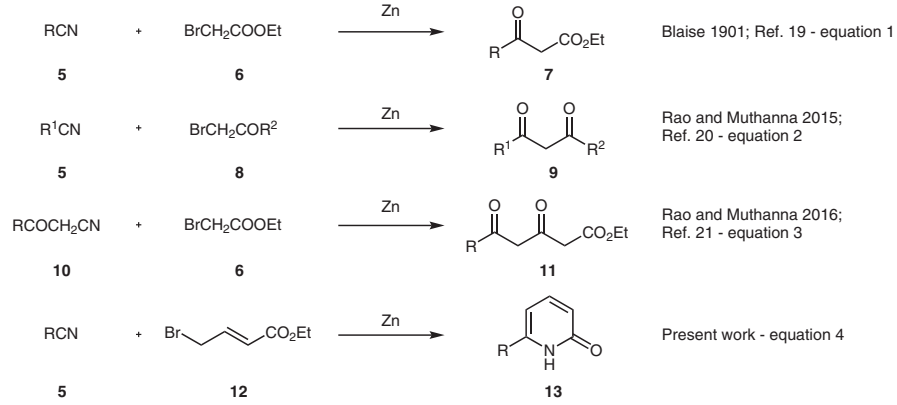
Recently, our group focused on the expansion of the scope of the classical Blaise reaction. Fundamentally, the Blaise reaction is a Zn-mediated transformation of alkyl or aryl nitriles **5** into β-keto esters **7** by reaction with ethyl bromoacetate (**6**) (Scheme 2; Equation 1).[19] Because β-keto esters provide an enormous range of opportunities for the synthesis of a wide variety of heterocyclic compounds, the



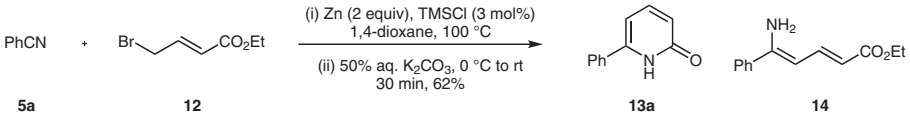
Scheme 1 Well-known methods and the present concept for the construction of pyridine rings

Blaise reaction has recently found its rightful place in mainstream synthetic organic chemistry. We found that by employing α-bromo ketones **8** instead of α-bromo esters, the reaction provides extremely useful 1,3-diketones **9** (Scheme 2; Equation 2).[20] In continuation of that work, we found that when acyl nitriles **10** are employed instead of alkyl or aryl nitriles, the reaction provides 3,5-diketo esters **11** (Scheme 2; Equation 3).[21] In the present work, we have further expanded the scope of the Blaise reaction by employing ethyl 4-bromocrotonate (**12**) instead of ethyl bromoacetate in the reaction with alkyl or aryl nitriles **5** to give pyridin-2-ones **13**. We refer to this variation as the vinylogous Blaise reaction. In our pyridine-ring synthesis, four carbon atoms originate from the 4-bromocrotonate **12** and one carbon atom and one nitrogen atom come from the nitrile. This is the first report of a one-step pyridine-ring synthesis in [C_4 + CN] fashion.

To arrive at appropriate reaction conditions for effecting the vinylogous Blaise reaction of ethyl 4-bromocrotonate (**12**) with nitriles **5**, we selected benzonitrile (**5a**) as a model substrate (Scheme 3). Initially, we adopted the reaction conditions that we previously developed for the Blaise reaction between nitriles and ethyl bromoacetate.[22] The reaction between benzonitrile (**5a**; 1 mmol) and ethyl 4-bromocrotonate (**12**; 2 equiv) in the presence of a catalytic amount of trimethylsilyl chloride (TMSCl; 3 mol%) and two equivalents of Zn in 4 mL of THF at the reflux for ten hours, followed by hydrolysis with 3 N HCl gave 6-phenylpyridin-2(1*H*)-one (**13a**) in 30% yield. There was no trace of the initially formed open-chain Blaise product **14**. By changing solvent from THF (bp 67 °C) to higher-boiling 1,4-dioxane (bp 101 °C), the yield of the pyridin-2-one **13a** was increased to 52%.[23] Replacing the acidic hydrolysis with basic hydrolysis with 50% aq K_2CO_3 further increased the yield to 62%. Before, settling on 1,4-dioxane as the solvent, we screened a few ethereal solvents such as *tert*-butyl methyl ether (bp = 55 °C), dimethoxyethane (bp = 85 °C), and cyclopentyl methyl ether (bp = 106 °C), but in all the cases, for inexplicable reasons, the reaction did not proceed and



Scheme 2 The Blaise reaction and its variants

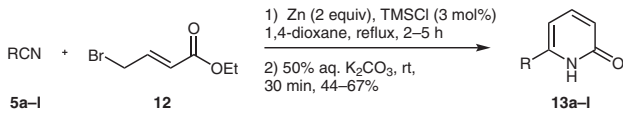


Scheme 3 Synthesis of 6-phenylpyridin-2(1*H*)-one (**13a**) from benzonitrile (**5a**) and ethyl 4-bromocrotonate (**12**)

benzonitrile remained unaltered even after 24 hours at the reflux. We conducted a reaction in a 9:1 mixture of 1,4-dioxane and DMF, reasoning that the DMF might provide a polar aprotic environment for the solvated zinc ions, but there was no improvement in the yield of the pyridine **13a**. Next, we varied the molar ratio of ethyl 4-bromocrotonate (**12**), Zn dust, and TMSCl to arrive at best reaction conditions. In summary, we found that for the conversion of 1 mmol of benzonitrile, the reaction required one equivalent of ethyl 4-bromocrotonate, two equivalents of Zn powder, 3 mol% of TMSCl (zinc activator), and 4 mL of dry 1,4-dioxane. The product, 6-phenylpyridin-2(1*H*)-one (**13a**) was isolated as a light-yellow solid (mp 194–195 °C)[24] and was characterized by means of IR and NMR spectroscopy.[25]

This simple, single-step, straightforward conversion of benzonitrile into 6-phenylpyridin-2(1*H*)-one proved to be general for a variety of nitriles. We employed a range of aromatic (**5a–e**), heteroaromatic (**5f–h**), benzylic (**5i–j**), aliphatic (**5k**), and sterically hindered (**5l**) nitriles (Table 1), which, on treatment with ethyl 4-bromocrotonate (**12**), were converted into the corresponding pyridin-2-ones **13a–l** in good yields (Table 1). The benzonitriles **5** included those with various substituents at the C(4) position, such as a strongly electron-withdrawing trifluoromethyl (**5b**; Table 1, entry 2), moderately electron-withdrawing but *ortho–para* directing chloro (**5c**; entry 3), electron-donating methyl (**5d**; entry 4), and strongly electron-donating methoxy (**5e**; entry 5) groups. Each of these benzonitriles, when treated with ethyl 4-bromocrotonate (**12**), provided the corresponding pyridine **13a–e** without much variation in the yield, indicating that the rate-determining step does not involve nucleophilic attack of the Reformatsky reagent on the nitrile. The transformation of 4-(trifluoromethyl)benzonitrile (**5b**) into the corresponding pyridin-2-one **13b**, however, gave the best yield (67%). The heteroaromatic nitriles 2-furonitrile (**5f**; entry 6), thiophene-2-carbonitrile (**5g**; entry 7), and *N*-tosyl-1*H*-indol-3-carbonitrile (**5h**; entry 8) underwent the one-step transformation to provide good yields of the corresponding pyridin-2-ones **13f–h**. Furthermore, phenylacetonitrile (**5i**; entry 9) and (4-fluorophenyl)acetonitrile (**5j**; entry 10) provided satisfactory yields of corresponding pyridines **13i** and 1**3j**, both of which incorporate a central-nervous-system-active arylethylamine motif. The aliphatic nitrile butyronitrile (**5k** entry 11) underwent the transformation to provide the pyridin-2-one **13k** indicating that large variations in the C(6)-substituted aliphatic chain are possible in the present method. The reaction of sterically hindered diphenylacetonitrile (**5l**) with **12** provided pyridine **13l**, albeit with a reduced yield (entry 12). Finally nitrile **5m**, which is a precursor to agomelatine **15** (a melatonergic antidepressant)[26] reacted with ethyl 4-bromocrotonate (**12**) and zinc to furnish the pyridin-2-one **13m** (entry 13); this product incorporates pharmacophore features of agomelatine (**15**) and might, therefore, emerge as a useful drug for the treatment of depression.

Table 1 Vinylogous Blaise Method for the Synthesis of C(6)-Substituted Pyridin-2-ones **13a–i**



5a–l 12 13a–l

Entry	Nitrile	R	Time (h)	Product	Yield (%)
1	**5a**	Ph	4	**13a**	62
2	**5b**	4-$F_3CC_6H_4$	4	**13b**	67
3	**5c**	4-ClC_6H_4	5	**13c**	58
4	**5d**	4-Tol	5	**13d**	61
5	**5e**	4-$MeOC_6H_4$	5	**13e**	60
6	**5f**	2-furyl	2	**13f**	54
7	**5g**	2-thienyl	2	**13g**	64
8	**5h**	*N*-tosylindol-3-yl	5	**13h**	60
9	**5i**	Bn	5	**13i**	57
10	**5j**	CH_2-4-FC_6H_4	4	**13j**	64
11	**5k**	Pr	5	**13k**	54
12	**5l**	$CHPh_2$	5	**13l**	44
13	**5m**	(7-methoxy-2-naphthyl)methyl	5	**13m**	47

The structures of the C(6)-substituted pyridin-2-ones **13a–m** prepared in this study and that of agomelatine {*N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide} (**15**) are given in Table 1 of the Supplementary Information.

To explain the formation of the pyridin-2-ones **13**, we propose the mechanism shown in Scheme 4. Initially, Zn inserts into the C–Br bond of **12** to form an organozinc intermediate **18**. This intermediate is in equilibrium with the zinc enolate **19**. Intermediates **18** and **19** possess nucleophilic C(2) and C(4) carbons. In the cases of nitriles **5**, the reaction takes place at the C(4) position to provide the push–pull diene **14** (γ-addition). Further cyclization of **14** via the intermediate **20** with concomitant loss of ethanol provided the C(6)-substituted pyridin-2-one **13**. On the other hand, the reaction of **19** with highly reactive 4-cyanopyridine **5p** takes place at C(2) to provide **17** (α-addition). In a related vinylogous Reformatsky reaction, Hudlicky and co-workers isolated diene products similar to **17**, and proposed a similar mechanism.[27]

Although, the vinylogous Blaise reaction was successful in many cases, there were a few failures, as noted below. Attempts at the conversion of pyridine-2-, -3-, or -4-carbonitriles (**5n–p**) into corresponding pyridin-2-ones were unsuccessful (Scheme 5). The zinc-mediated reaction of ethyl 4-bromocrotonate (**12**) with pyridine-2-carbonitrile (**5n**) gave pyridine-2-carbamide (**16**) as the sole product, generated by partial hydrolysis of the nitrile functional group. The reaction of pyridine-3-carbonitrile (**5o**) did not

proceed, even after 12 hours at the reflux. With pyridine-4-carbonitrile (**5p**) the reaction provided the diene **17** as the sole product. We reason that in the reaction of **5p**, condensation of the organozinc intermediate is thermodynamically controlled and proceeds through reaction at the α-carbon of the zinc alkoxide instead of the γ-carbon, as seen in other cases.

In conclusion, we have discovered and elaborated a new method for the synthesis of pyridin-2-ones by employing the vinylogous Blaise reaction.[28] The method constitutes a new pyridine-ring synthesis through a [C_4 + CN] assembly. The vinylogous Blaise reaction with ethyl bromobut-2-enoate on a variety of nitriles furnished C(6)-substituted pyridin-2-ones. We expect to be able to expand the scope of this reaction by using various substituted 4-bromocrotonates for the syntheses of polysubstituted pyridin-2-ones.

Funding Information

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Supporting Information

Detailed experimental procedures and spectra of the pyridin-2-ones **13a-m** made in this study are given in the supplementary material available online at https://doi.org/10.1055/s-0037-1610171.

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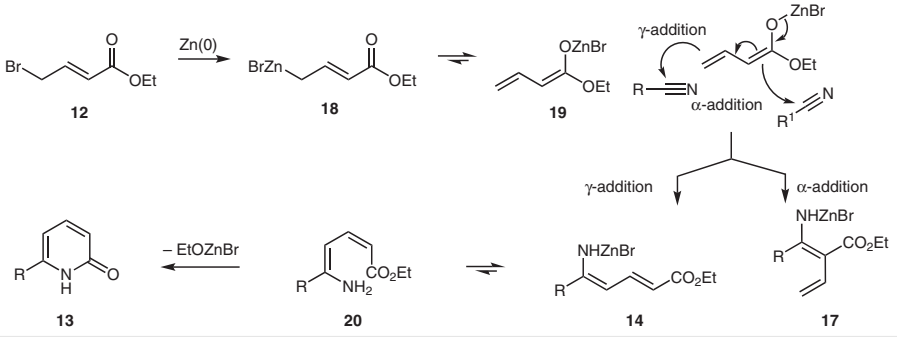
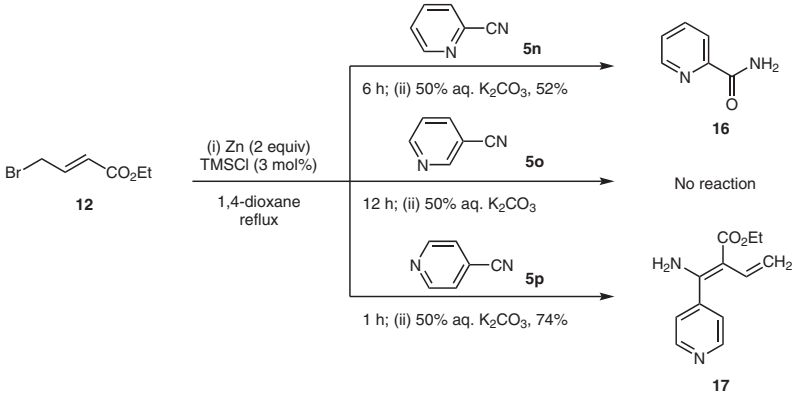


Scheme 4 Plausible mechanism for the formation of pyridin-2-ones and highly substituted 1,3-dienes



Scheme 5 Reactions of pyridine nitriles with ethyl 4-bromocrotonate

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(28) **Pyridin-2-ones 13a–m; General Procedure**

A solution of TMSCl (3 mol%) in anhyd 1,4-dioxane (1 mL) was added to a suspension of Zn dust (2 equiv) in anhyd 1,4-dioxane (3 mL), and the resulting suspension was refluxed with vigorous stirring for 25 min. The appropriate nitrile (2 mmol) in dry 1,4-dioxane (1 mL) and ethyl (*E*)-4-bromobut-2-enoate (**12**; 2 equiv) in dry 1,4-dioxane (1 mL) were simultaneously added dropwise to the refluxing suspension during 10 min by using two syringes. The resulting light-green mixture was refluxed until all the starting material was consumed and the color changed to brown (TLC; 3–6 h). The mixture was cooled to r.t. then centrifuged (700 rpm). The upper solution was decanted and the remaining solid was washed with 1,4-dioxane (4 × 1 mL). The 1,4-dioxane solutions were combined and concentrated to about 1 mL under reduced pressure in a rotatory evaporator. The residue was treated with 50% aq K_2CO_3 until the pH reached 13 (~5 mL). The resulting mixture was stirred for 30 min at r.t. (30 °C) then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was separated, washed sequentially with H_2O (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a crude product that was purified by column chromatography [silica gel (100–200 mesh); 15–60% EtOAc–hexane].

6-Phenylpyridin-2(1*H*)-one (13a)

By following the general procedure, the reaction of PhCN (**5a**; 201 mg, 1.94 mmol) with crotonate **12** (374 mg, 1.94 mmol) in the presence of Zn (252 mg, 3.88 mmol) and TMSCl (7 mg, 3 mol %) in 1,4-dioxane (6 mL) for 4 h, followed by hydrolysis with 50% aq K_2CO_3 (5 mL) gave a light-yellow solid; yield: 205 mg (62%); mp 194–195 °C; R_f = 0.5 (hexanes–EtOAc, 2:1).

IR (KBr): 2904, 1643, 1612, 1550, 1493, 990, 921, 795, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.49 (br s, 1 H), 7.72 (d, *J* = 6.9 Hz, 2 H), 7.59–7.40 (m, 4 H), 6.55–6.47 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 147.1, 141.5, 133.6, 130.1, 129.2, 126.8, 118.7, 105.0. HRMS (ESI): *m/z* [M + H] calcd for $C_{11}H_9NO$: 172.0762; found: 172.0750.