Ring-Opening/Recyclization Reactions of (Dimethylamino)propenoyl-Substituted Cyclopropanes: Facile Synthesis of Halogenated Pyridin-2(1*H*)-ones

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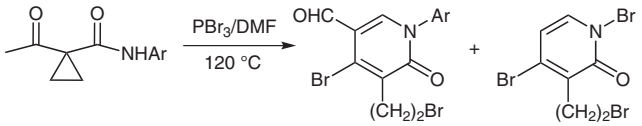
Abstract: A facile and efficient synthesis of substituted pyridin-2(1*H*)-ones has been developed by the reaction of readily available 1-carbamoyl-1-[3-(dimethylamino)propenoyl]cyclopropanes with phosphoryl chloride or phosphorus tribromide in dichloromethane at room temperature.

Key words: cyclization, cyclopropanes, enaminones, pyridin-2(1*H*)-ones, ring opening

The pyridin-2(1*H*)-one motif makes up the core structure of numerous biologically active natural products and synthetic compounds, such as elfamycin and ilicolicin, that find a wide range of application in the pharmaceutical and agrochemical industries.[1,2] Actually, functionalized pyridin-2(1*H*)-ones and their benzo-/hetero-fused analogues have become very important in the areas of natural product and pharmaceutical chemistry and are widely used as versatile intermediates in the synthesis of a variety of aza-heterocycles, such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[3,4] Extensive work has generated many synthetic approaches for pyridin-2(1*H*)-ones involving pyridinium salt chemistry,[5] Guareschi–Thorpe reaction,[6] hetero-Diels–Alder reaction,[7] Dieckmann-type condensation,[8] and metal-mediated cycloaddition.[9] Other notable methods starting from polarized ketene *S*,*S*- and *N*,*N*-acetals have been reported.[10]

Halogenated pyridin-2(1*H*)-ones represent an important subset of pyridin-2(1*H*)-ones, which have been utilized as useful intermediates for the synthesis of various aza-heterocycles and evaluated as a scaffold in natural product synthesis.[11] Unfortunately, the most available approaches for accessing pyridin-2(1*H*)-ones are not general for the preparation of halogenated pyridin-2(1*H*)-ones. During the course of our studies on Vilsmeier–Haack reactions, we developed an efficient synthesis of halogenated pyridin-2(1*H*)-ones from a range of β-oxo amide derivatives, such as α-unsubstituted/α-monosubstituted β-oxo amides,[12] 3-acetyl-2-(arylamino)-5,6-dihydro-4*H*-pyrans,[13] 1-acyl-1-carbamoylcyclopropanes,[14] and α-[(dimethylamino)methylene]-β-oxo amides[15] under Vilsmeier conditions. However, the reaction of 1-acyl-1-carbamoylcyclopropanes with the Vilsmeier reagent, phosphorus tribromide/*N*,*N*-dimethylformamide, produced an inseparable mixture even at 120 °C (Scheme 1).



Scheme 1 Reactions of cyclopropanes with the Vilsmeier reagent (PBr_3/DMF)

Very recently, we achieved divergent synthesis of fully substituted 1*H*-pyrazoles and isoxazoles from oximes of 1-acyl-1-carbamoylcyclopropanes in the presence of phosphoryl chloride/*N*,*N*-dimethylformamide and phosphoryl chloride/dichloromethane, respectively.[16] Similarly, substituted cyclophosphamidic chlorides and their analogues were obtained by subjecting 3-acetyl-2-(arylamino)-5,6-dihydro-4*H*-pyrans to phosphoryl chloride in dichloromethane.[17] These results suggest that phosphoryl chloride, as a reagent, showed different reaction behavior from the Vilsmeier reagent, phosphoryl chloride/*N*,*N*-dimethylformamide.

Inspired by these findings and in continuation with our research on the synthesis of functionalized heterocycles from β-oxo amide derivatives, we are interested in the synthetic potential of readily available 1-carbamoyl-1-[3-(dimethylamino)propenoyl]cyclopropanes **1**[18] and examined their reactivity toward phosphoryl chloride or phosphorus tribromide in dichloromethane. As a result of these studies, we provided an alternative one-pot synthesis of halogenated pyridin-2(1*H*)-ones **2** and **3** from cyclopropanes **1**. Herein, we report our experimental results and a proposed mechanism involved in the ring-opening/recyclization reactions.

The substrates **1** were prepared from 1-acyl-1-carbamoylcyclopropanes and *N*,*N*-dimethylformamide dimethyl acetal in high yields (up to 91%) according to the procedure described in our previous work.[18] With a series of condensation adducts **1a–f** in hand, we selected 1-[3-(dimethylamino)propenoyl]-*N*-phenylcyclopropanecarboxamide (**1a**) as a model compound to examine its behavior under different conditions. Thus, the reaction of **1a** with phosphoryl chloride (5.0 equiv) in dichloromethane was first attempted at room temperature. As monitored by TLC, the reaction proceeded smoothly and furnished a white solid after workup and purification by column chro-

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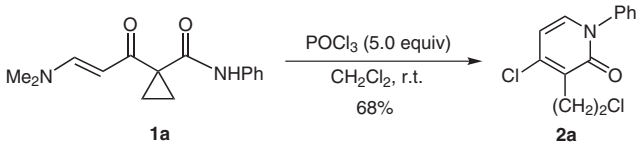
matography of the resulting mixture. The product was characterized as 4-chloro-3-(2-chloroethyl)-1-phenylpyridin-2(1*H*)-one (**2a**) (68% yield, Scheme 2) on the basis of its spectral and analytical data, which was in good agreement with that reported in our previous work.[14]



1a 2a

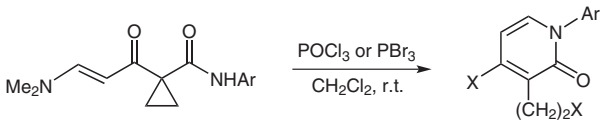
Scheme 2 Reaction of **1a** in the presence of phosphoryl chloride in dichloromethane

The optimization of the reaction conditions, including the ratio of phosphoryl chloride to **1a**, and reaction temperature, were then investigated. It seemed that the increase of temperature had no significant influence on the reaction rate and conversion. But too lower ratio of phosphoryl chloride to **1a**, 1.0:1.0 for example, resulted in prolonged reaction times and low yields. A series of experiments revealed that 1.5 equivalents of phosphoryl chloride was effective for the synthesis of halogenated pyridin-2(1*H*)-ones, and the optimal results were obtained when the reaction of **1a** was performed with 2.0 equivalents of phosphoryl chloride in dichloromethane at room temperature for ten hours, whereby the yield of **2a** reached 71% (Table 1, entry 1).

Under the optimized conditions as for the synthesis of **2a** (Table 1, entry 1), a range of reactions of 1-carbamoyl-1-[3-(dimethylamino)propenoyl]cyclopropanes **1b–f** was subjected to phosphoryl chloride in dichloromethane, and the results are summarized in Table 1. The efficiency of the cyclization proved to be suitable for **1b–f** affording the corresponding halogenated pyridin-2(1*H*)-ones **2b–f** in moderate to good yields (Table 1, entries 2–6). The versatility of this pyridin-2(1*H*)-one synthesis was further evaluated by performing the cyclopropanes **1a–f** with another halogenated reagent phosphorus tribromide under the otherwise identical conditions (Table 1, entries 7–12). The results demonstrated the efficiency and synthetic interest of the ring-opening/recyclization reactions of **1** bearing variable arylamide groups with respect to both phosphoryl chloride and phosphorus tribromide in dichloromethane. Therefore, we provided an alternative approach to halogenated pyridin-2(1*H*)-ones. In comparison to the synthetic approach to pyridin-2(1*H*)-ones of type **2** under Vilsmeier conditions,[14] the present protocol is associated with mild conditions and easy control of the reaction orientation.

On the basis of the obtained results and our previous studies,[15,17] a plausible mechanism for the synthesis of halogenated pyridin-2(1*H*)-ones **2** is presented in Scheme 3

Table 1 Reactions of 1-Carbamoyl-1-[3-(dimethylamino)propenoyl]cyclopropanes **1** with Phosphoryl Chloride or Phosphorus Tribromide in Dichloromethane[a]

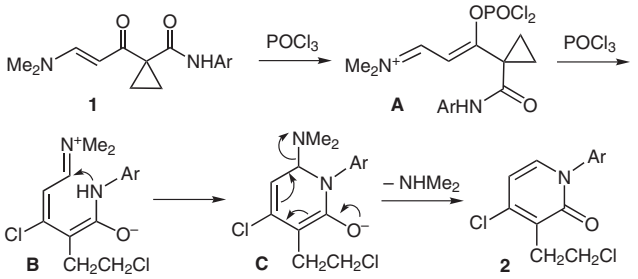


1 **2** X = Cl **3** X = Br

Entry	Substrate	Reagent	Ar	X	Product	Yield[b] (%)
1	**1a**	$POCl_3$	Ph	Cl	**2a**	71
2	**1b**	$POCl_3$	4-$MeOC_6H_4$	Cl	**2b**	70
3	**1c**	$POCl_3$	4-MeC_6H_4	Cl	**2c**	76
4	**1d**	$POCl_3$	4-ClC_6H_4	Cl	**2d**	63
5	**1e**	$POCl_3$	2,4-$Me_2C_6H_3$	Cl	**2e**	55
6	**1f**	$POCl_3$	5-Cl-2-$MeOC_6H_3$	Cl	**2f**	68
7	**1a**	PBr_3	Ph	Br	**3a**	65
8	**1b**	PBr_3	4-$MeOC_6H_4$	Br	**3b**	59
9	**1c**	PBr_3	4-MeC_6H_4	Br	**3c**	56
10	**1d**	PBr_3	4-ClC_6H_4	Br	**3d**	62
11	**1e**	PBr_3	2,4-$Me_2C_6H_3$	Br	**3e**	53
12	**1f**	PBr_3	5-Cl-2-$MeOC_6H_3$	Br	**3f**	69

[a] Reaction conditions: (i) for entries 1–6: $POCl_3$ (2.0 equiv), CH_2Cl_2, r.t., 8.0–12.0 h; (ii) for entries 7–12: PBr_3 (2.0 equiv), CH_2Cl_2, r.t., 7.0–10.0 h.
[b] Isolated yields.

(with $POCl_3$ as example). Iminium ion **A** is generated from the reaction of enaminone **1** with phosphoryl chloride, which then undergoes ring-opening and halogenation reactions to form intermediate **B**.[18,19] Intramolecular cyclization of **B** gives rise to intermediate **C**, followed by the elimination of dimethylamine to afford substituted pyridin-2(1*H*)-one **2**.



Scheme 3 Tentative mechanism of the reaction of 1-carbamoyl-1-[3-(dimethylamino)propenoyl]cyclopropanes **1** with phosphoryl chloride

In summary, we have described a facile and efficient synthesis of substituted pyridin-2(1*H*)-ones **2** from a series of 1-carbamoyl-1-[3-(dimethylamino)propenoyl]cyclopropanes **1** in the presence of phosphoryl chloride or phosphorus tribromide in dichloromethane. This protocol is associated with readily available starting materials, mild conditions, good yields, and wide range of synthetic potential of the product.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard at 25 °C on a Varian Inova-500 spectrometer. IR spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer in the range of 400–4000 cm^{-1}. Petroleum ether (PE) used was the fraction boiling in the range 30–60 °C.

4-Chloro-3-(2-chloroethyl)-1-phenylpyridin-2(1*H*)-one (2a); Typical Procedure

To a soln of **1a** (0.52 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was added $POCl_3$ (4.0 mmol) at r.t. with stirring. The mixture was stirred 10.0 h and then the reaction was quenched with sat. aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with sat. aq NaCl (3 × 20 mL), dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. Purification was carried out by flash chromatography (silica gel, PE–EtOAc, 8:1) to give **2a** (0.38 g, 71%).

Pyridin-2(1*H*)-ones **2a–e** are known compounds, their analytical data are in good agreement with those reported in our previous work.[14]

4-Chloro-3-(2-chloroethyl)-1-(5-chloro-2-methoxyphenyl)pyridin-2(1*H*)-one (2f)

White solid: mp 95–97 °C.

IR (KBr): 3073, 2945, 1653, 1605, 1545, 905, 787, 707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.23 (t, *J* = 7.5 Hz, 2 H), 3.78 (t, *J* = 7.5 Hz, 2 H), 3.80 (s, 3 H), 6.30 (d, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 9.0 Hz, 1 H), 7.06 (d, *J* = 7.0 Hz, 1 H), 7.26 (s, 1 H), 7.38 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.8, 41.4, 56.2, 108.0, 113.4, 125.6, 127.4, 128.6, 130.3, 136.1, 145.6, 153.0, 160.8.

Anal. Calcd for $C_{14}H_{12}Cl_3NO_2$: C, 50.55; H, 3.64; N, 4.21. Found: C, 50.23; H, 3.79; N, 4.27.

4-Bromo-3-(2-bromoethyl)-1-phenylpyridin-2(1*H*)-one (3a)

White solid: mp 108–110 °C.

IR (KBr): 3082, 2969, 1635, 1580, 1535, 959, 759, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.36 (t, *J* = 8.0 Hz, 2 H), 3.64 (t, *J* = 8.0 Hz, 2 H), 6.48 (d, *J* = 8.0 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.34–7.36 (m, 2 H), 7.41–7.44 (m, 1 H), 7.45–7.51 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.0, 34.7, 110.8, 126.3, 128.7, 129.0, 129.3, 135.4, 136.1, 140.1, 160.3.

Anal. Calcd for $C_{13}H_{11}Br_2NO$: C, 43.73; H, 3.11; N, 3.92. Found: C, 44.15; H, 2.92; N, 3.68.

4-Bromo-3-(2-bromoethyl)-1-(4-methoxyphenyl)pyridin-2(1*H*)-one (3b)

White solid: mp 115–116 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.35 (t, *J* = 7.5 Hz, 2 H), 3.63 (t, *J* = 7.5 Hz, 2 H), 3.84 (s, 3 H), 6.45 (d, *J* = 7.5 Hz, 1 H), 6.98–7.00 (m, 2 H), 7.14 (d, *J* = 7.0 Hz, 1 H), 7.25–7.27 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.4, 35.1, 55.8, 111.0, 114.8, 127.7, 130.7, 133.3, 136.1, 136.3, 159.8, 160.9.

Anal. Calcd for $C_{14}H_{13}Br_2NO_2$: C, 43.44; H, 3.39; N, 3.62. Found: C, 43.18; H, 3.53; N, 3.58.

4-Bromo-3-(2-bromoethyl)-1-(4-methylphenyl)pyridin-2(1*H*)-one (3c)

White solid: mp 87–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.35 (t, *J* = 8.0 Hz, 2 H), 3.63 (t, *J* = 7.5 Hz, 2 H), 6.46 (d, *J* = 7.5 Hz, 1 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.29 (t, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 29.1, 34.8, 110.8, 126.1, 130.0, 130.6, 135.6, 136.2, 137.7, 138.8, 160.5.

Anal. Calcd for $C_{14}H_{13}Br_2NO$: C, 45.32; H, 3.53; N, 3.77. Found: C, 45.43; H, 3.57; N, 3.69.

4-Bromo-3-(2-bromoethyl)-1-(4-chlorophenyl)pyridin-2(1*H*)-one (3d)

White solid: mp 82–84 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.35 (t, *J* = 7.5 Hz, 2 H), 3.63 (t, *J* = 8.0 Hz, 2 H), 6.49 (d, *J* = 7.0 Hz, 1 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.9, 34.6, 111.2, 127.6, 129.5, 130.8, 134.6, 134.9, 136.3, 138.5, 160.1.

Anal. Calcd for $C_{13}H_{10}Br_2ClNO$: C, 39.88; H, 2.57; N, 3.58. Found: C, 39.52; H, 2.46; N, 3.72.

4-Bromo-3-(2-bromoethyl)-1-(2,4-dimethylphenyl)pyridin-2(1*H*)-one (3e)

White solid: mp 81–84 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.37 (s, 3 H), 3.37 (t, *J* = 7.5 Hz, 2 H), 3.61–3.71 (m, 2 H), 6.47 (d, *J* = 7.5 Hz, 1 H), 7.01–7.06 (m, 2 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 7.15 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 21.0, 29.2, 34.6, 110.8, 126.6, 127.8, 130.6, 131.8, 134.4, 135.7, 136.2, 136.9, 139.3, 160.2.

Anal. Calcd for $C_{15}H_{15}Br_2NO$: C, 46.78; H, 3.93; N, 3.64. Found: C, 47.29; H, 4.11; N, 3.43.

4-Bromo-3-(2-bromoethyl)-1-(5-chloro-2-methoxyphenyl)pyridin-2(1*H*)-one (3f)

White solid: mp 103–104 °C.

IR (KBr): 3071, 2942, 1650, 1601, 1542, 1495, 1273, 1018, 750, 711 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.35 (t, *J* = 7.5 Hz, 2 H), 3.61–3.64 (m, 2 H), 3.80 (s, 3 H), 6.45 (dd, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 1 H), 6.97–6.99 (m, 2 H), 7.26 (d, *J* = 2.0 Hz, 1 H), 7.38 (dd, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2, 35.0, 56.5, 111.0, 113.7, 125.8, 128.8, 129.8, 130.6, 131.0, 136.2, 136.7, 153.2, 160.3.

Anal. Calcd for $C_{14}H_{12}Br_2ClNO_2$: C, 39.89; H, 2.87; N, 3.32. Found: C, 40.37; H, 2.98; N, 3.35.

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