Synthesis of Herbicidal 3-Substituted-4(3*H*)-Pyrimidinones under High Pressure

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The reaction of an *N*-monosubstituted amidine with a β-ketoester to afford a pyrimidinone is sluggish at best under normal conditions. We now report that this reaction can be effected in moderate yield under high pressure. Thus, 2,6-dichloro-4-pyridyl-(*N*-prop-2-ynyl)carboxamidine (**4b**) was reacted with three α-substituted-β-ketoesters (**2b-d**) at 10-16 kbar to afford herbicidal 2-(2,6-dichloro-4-pyridyl)-3-(prop-2-ynyl)-4(3*H*)-pyrimidinones **5b** and **5c** in 15 - 43% yield. This result expands the scope of reactions promoted by application of high pressure.

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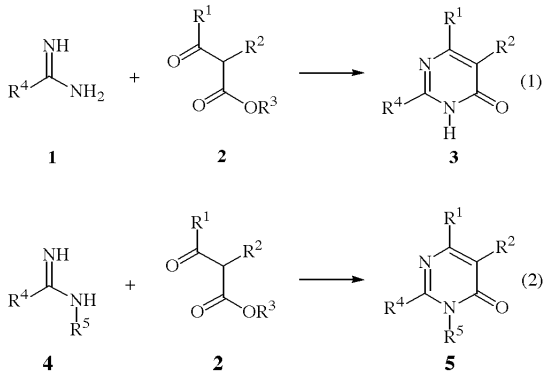
Introduction.

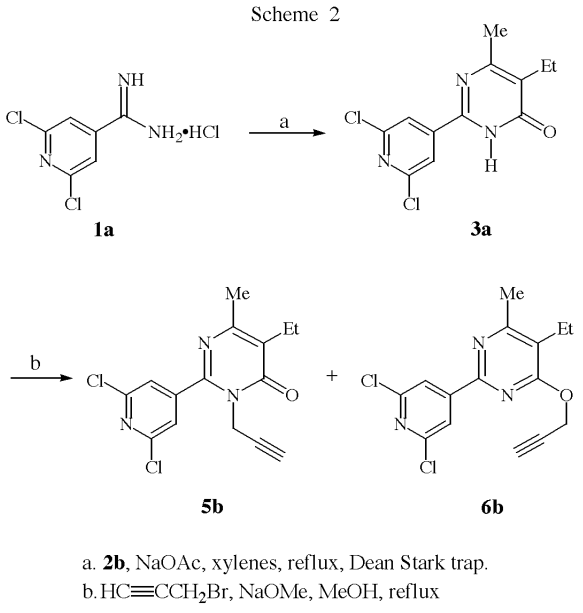
Since its discovery over a century ago by Pinner [1], the reaction of *N*-unsubstituted amidines **1** with β-ketoesters **2** to afford 3-unsubstituted-4(3*H*)-pyrimidinones **3** (Scheme 1, Reaction 1) has been widely used [2]. By contrast, the reaction of *N*-monosubstituted amidines **4** with β-ketoesters **2** to afford 3-susbstituted-4(3*H*)-pyrimidinones **5** (Scheme 1, Reaction 2) has seldom been reported [3-5]. In 1969, Sitte and Paul [3] reported prototypical examples of Reaction 2. The reaction between reaction of *N*-propylbenzamidine (**4a**, Figure 1) with methyl acetoacetate (**2a**) in a concentrated methanolic solution afforded a 64% yield of pyrimidinone **5a** (R^1 = Me, R^2 = H, R^4 = Ph, R^5 = *n*-Pr) after 2 weeks at room temperature in their hands. Heating the reaction led to inferior product yields. They also found that the reaction failed when **2a** was replaced with a β-ketoester bearing an alkyl substituent at the α-position (**2**, R^2 = alkyl). Our own exploratory experiments gave results consistent with those reported by Sitte and Paul.

Scheme 1



Reaction of amidines with β-Ketoesters.

Scheme 2

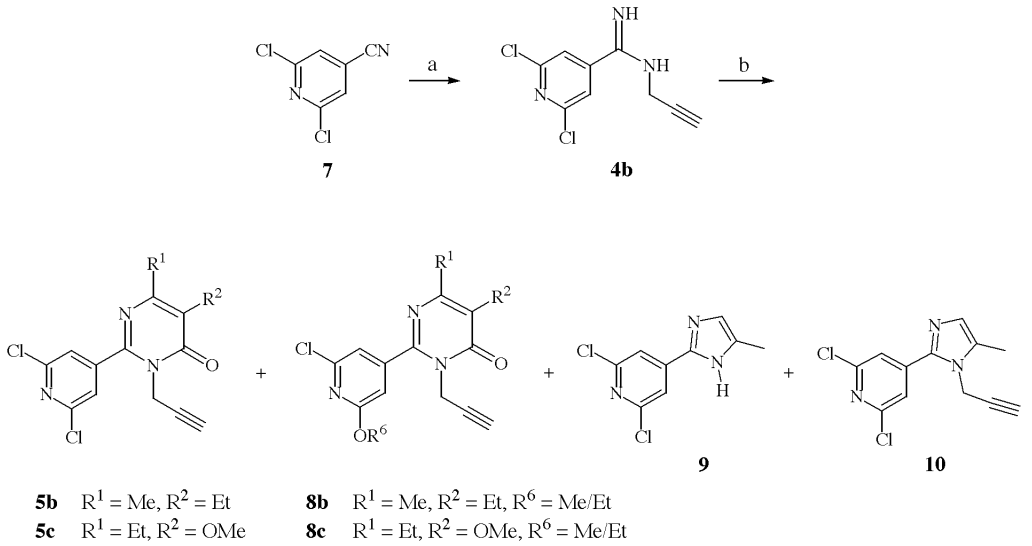


a. **2b**, NaOAc, xylenes, reflux, Dean Stark trap.
b. $HC{\equiv}CCH_2Br$, NaOMe, MeOH, reflux

Propargylation Route to 3-Substituted-4(3*H*)-Pyrimidinones.

We became interested in the herbicidal activity of 2-(2,6-dichloro-4-pyridyl)-3-(prop-2-ynyl)-4(3*H*)pyrimidinones **5b** and **5c** [6] and required 50 g quantities to test their efficacy in the field. Our original synthesis of these compounds is exemplified in Scheme 2 [6]. Reaction of amidine hydrochloride **1a** with β-ketoester **2b** proceeded smoothly to afford the 3-unsubstituted pyrimidinone **3a**. Propargylation of **3a** gave a mixture of N^3- and *O*-alkylated products, **5b** and **6b** [7]. Under the best conditions found (prop-2-ynyl bromide, NaOMe, MeOH, reflux) [8], the ratio of **5b**:**6b** formed was *ca*., 1:8 as determined by ^{1}H nmr and gc. Significant amounts of unreacted **3a** complicated product isolation. In an attempt to bypass the troublesome propargylation reaction, *N*-(prop-2-ynyl)amidine **4b** was prepared from commercially available 2,6-dichloropyridine-4-carbonitrile (**7**, Scheme 3) by treatment with

Scheme 3



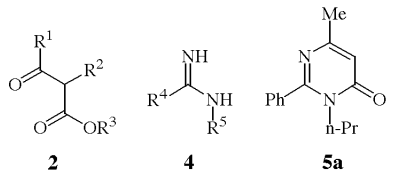
a. i. NaOMe (0.1 eq), MeOH. ii. $HC{\equiv}CCH_2NH_2{\bullet}HCl$. b. See Table 1

High Pressure Route to 3-Substituted-4-(3*H*)-Pyrimidinones.

catalytic sodium methoxide followed by addition of a slight excess of prop-2-ynylamine hydrochloride [9]. Amidine **4b** was then reacted with β-ketoester **2b** at room temperature for 5 days. As anticipated based on the work of Sitte and Paul [3], no significant amount of the desired pyrimidinone **5b** was formed. Heating the reaction did not afford **5b** but instead promoted decomposition of the starting materials to a mixture of products from which imidazoles **9** and **10** (Scheme 3) were isolated [10]. Similar results were obtained when amidine **4b** was reacted with ketoester **2d** in an attempt to produce **5c**. It occurred to us that application of high pressure to these reactions might effect the desired transformation [11].

Results and Discussion.

To investigate this idea, a series of reactions of amidine **4b** with β-ketoester **2b** was performed. These experiments are summarized in Table 1, Entries 1-8. Crude product mixtures were analyzed by gc, gc-ms and ^{1}H nmr. Reactions were run in five solvents at temperatures ranging from 18-60 °C and at pressure ranging from 8 to 16 kbar. Triethylamine was added as base in all reactions. The best yield of **5b** (26%) was obtained at 16 kbar and 28 °C using anhydrous ethanol as solvent (Entry 8) and very similar results were obtained at slightly lower pressure and temperature using 96% ethanol as solvent (Entry 7). Analogous experiments in which dichloromethane (Entry 1) and toluene (Entry 2) were used gave no significant amounts of **5b**. An experiment using methyl ester **2c**, in place of ethyl ester **2b**, under the conditions of Entry 8 also gave promising results (Entry 9). In a number of cases (Entries 7, 10, 11) when methanol or ethanol was used as solvent, a second product with a similar gc retention time to **5b** was formed in addition to the desired product.. These byproducts were tentatively identified, based on gc-ms and ^{1}H nmr [12] of the crude products, as the 2-alkoxypyridyl pyrimidinones **8b** (R^6 = Me or Et, Scheme 3); however, these compounds could not be separated from **5b** for full characterization. When sodium methoxide was used as base, in place of



2a R^1 = Me, R^2 = H, R^3 = Me
2b R^1 = Me, R^2 = Et, R^3 = Et
2c R^1 = Me, R^2 = Et, R^3 = Me
2d R^1 = Et, R^2 = OMe, R^3 = Me

4a R^4 = Ph, R^5 = *n*-Pr
4b R^4 = 2,6-dichloro-4-pyridyl, $R^5 = CH_2C{\equiv}CH$

Figure 1. β–Ketoesters and Amidines.

Table 1

Entry	β-Ketoester 1.2 eq	P [kbar]	T [C°]	Solvent	t [h]	Additive 2.4 eq	Yield [%] **5b**/**5c**	**8b**/**8c** [a]	**9**
1	**2b**	16.0	28	CH_2Cl_2	20	Et_3N	trace	0	trace
2	**2b**	16.0	28	PhMe	20	Et_3N	trace	0	trace
3	**2b**	13.0	40	MeCN	50	Et_3N	0	0	trace
4	**2b**	12.5	60	99% MeOH	20	Et_3N	trace	0	trace
5	**2b**	8.0	60	96% EtOH	22	Et_3N	0	0	trace
6	**2b**	13.0	40	96% EtOH	50	Et_3N	6	0	trace
7	**2b**	14.5	18	96% EtOH	64	Et_3N	21	2	trace
8	**2b**	16.0	28	100% EtOH	20	Et_3N	26	trace	trace
9	**2c**	16.0	28	96% EtOH	20	Et_3N	15	0	trace
10	**2c**	18.0	40	99% MeOH	20	Et_3N	15	32	trace
11	**2c**	15.0	21	100% MeOH	65	Et_3N	31	47	trace
12	**2c**	15.0	18	100% MeOH	93	NaOMe	11	89	trace
13	**2d**	10.0	25	100% EtOH	65	Et_3N	43	0	5

[a]. R^6 = Me when the solvent was MeOH and R^6 = Et when the solvent was EtOH.

triethylamine, the compound tentatively identified as **8b** was the major product (Entry 12). The conversion of 2-chloropyridines to 2-methoxypyridines using sodium methoxide is well precedented [13].

At this point an alternative route to **5b** was reduced to practice [14] and our attention was redirected to synthesis of **5c** which proved not to be accessible by the other route. Thus, applying the best conditions developed for **5b**, amidine **4b** was reacted with β-ketoester **2d** [15] in ethanol at 28 °C under 10 kbar to afford **5c** in 43% yield (Entry 13).

In conclusion, we have demonstrated that the direct reaction between *N*-monosubstituted amidines **4** and α-substituted-β-ketoesters **2** to afford 3-substituted-4(3*H*)-pyrimidinones **5**, which does not occur under normal conditions, can be effected under high pressure. This methodology expands the scope of reactions effected by the application of high pressure and it was used for the preparation of a 50 g sample of **5c** for field testing as a herbicide [16].

EXPERIMENTAL

General.

All reagents were obtained commercially and used without further purification unless stated otherwise. Flash column chromatography was undertaken according to Still *et al* [17] on silica gel (Kieselgel-60, Merck, 200-400 mesh). Melting points were determined using a Koffler hot stage apparatus and are uncorrected. Infra red spectra were obtained with a Perkin Elmer 1640 FTIR or a Perkin Elmer Model BMC spectrophotometer. ^{1}H nmr spectra were recorded using a Varian Gemini (200 MHz) or a Bruker DPX300 (300 MHz) spectrometer. ^{13}C nmr spectra were recorded using a Varian Gemini (50 MHz) spectrometer or a Bruker DPX300 (75 MHz). All chemical shifts are quoted in parts per million downfield from tetramethylsilane (δ, 0.00 ppm) and coupling constants (J) are measured in Hertz. Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact technique. Elemental analyses were carried out by Robertson Microlit Laboratories. All high-pressure reactions were performed in a piston-cylinder apparatus (Unipress, Warsaw Poland) capable of pressures of about 18 kbar [11].

2,6-Dichloropyridine-4-(*N*-2-propynyl)carboxamidine (**4b**).

To a stirred suspension of 2,6-dichloropyridine-4-carbonitrile (**7**, 66.44 g, 0.38 mol) in methanol (800 mL) was added 25% by weight sodium methoxide in methanol (28.30 g, 38.4 mmol). The mixture was stirred at room temperature for 2 hours and solid (prop-2-ynyl)amine hydrochloride (42.28 g, 0.46 mol) was added. The mixture was stirred for 3 hours and evaporated to dryness under reduced pressure (bath temp < 40 °C). The solid residue was treated with cold 10% aqueous NaOH (1 L) and extracted with ethyl acetate (2 x 800 mL). The combined organic extracts were washed with 10% aqueous NaOH (200 mL), dried over $MgSO_4$ and evaporated to dryness under reduced pressure to afford crude **4b** (89.18 g, 103%) as a yellow solid. ^{1}H nmr (200 MHz; deuteriochloroform): δ 2.32 (1H, t, J = 2.5, C≡C*H*), 4.08 (2H, d, J = 2.5, CH_2C≡CH), 4.90-5.70 (2H, brs, N*H*'s), 7.57 (2H, s, pyridyl *H*'s). This material was used without further purification.

Typical Procedure for 2-(2,6-Dichloro-4-pyridyl)-5-ethyl-6-methyl-3-(prop-2-ynyl)-4(3*H*)-pyrimidinone (**5b**).

To solid **4b** as its hydrochloride (1.56 g, 5.8 mmol) at 0 °C under argon was added slowly by syringe a solution of triethylamine (1.48 g, 14.6 mmol) in absolute ethanol (*ca*. 7 mL). The mixture was stirred and allowed to warm to room temperature for 20 minutes. β-Ketoester **2b** (1.12 g, 7.1 mmol) was added by syringe. The reaction mixture was transferred to a TEFLON® ampoule, placed in a piston-cylinder high-pressure apparatus and compressed at a pressure of about 16 kbar for 20 hours at 28 °C. After decompression, the reaction mixture was evaporated and the residue was purified by flash chromatography (hexanes-ethyl acetate 9:1 to 6:4) to afford crystalline, analytically pure **5b** (0.49 g, 26%), mp 138-140 °C. ir (deuteriochloroform): 3310, 1665, 1595, 1530 cm^{-1}; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.16 (3H, t, J = 7.5, CH_2CH_3), 2.34 (3H, s, 6-pyrimidinyl CH_3), 2.44 (1H, t, J = 2.5, $CH_2C{\equiv}CH$), 2.62 (2H, q, J = 7.5, CH_2CH_3), 4.57 (2H, d, J = 2.5,

CH_2C≡CH), 7.60 (2H, s, pyridyl *H*'s); ^{13}C nmr (75 MHz, deuteriochloroform): δ 12.3 (CH_2CH_3), 19.8 (CH_2CH_3), 21.0 (6-pyrimidinyl CH_3), 36.0 (CH_2C≡CH), 74.0 (CH_2C≡CH), 77.2 (CH_2C≡CH), 121.9 (3-pyridyl *C*, 5-pyridyl *C*), 126.7 , 146.3, 151.3, 151.4, 157.5 (*C*=O), 160.7 (2-pyrimidinyl *C*); ms (EI): m/z 321 (M^+, 65%), 320 (M-H$^+$, 85), 306 (15), 282 (M-$C_3H_3^+$, 100), 268 (4), 211 (15), 173 (5), 137 (9), 108 (9), 39 (50); hrms: Calcd for $C_{15}H_{13}N_3OCl_2$ $(M)^+$ 321.04357. Found: 321.04363.

Anal. Calcd for $C_{15}H_{13}N_3OCl_2$: C, 55.92; H, 4.07; N, 13.04; Cl, 22.00. Found: C, 55.72; H, 4.09; N, 12.75; Cl, 21.83.

2-(2,6-Dichloro-4-pyridyl)-6-ethyl-5-methoxy-3-(prop-2-ynyl)-4(3*H*)-pyrimidinone (**5c**).

Preparation of **5c** was carried out following the procedure described above for **5b**. Thus, the high-pressure apparatus (initial working volume of 150 mL) was charged with a mixture of amidine **4b** as its hydrochloride (21.82 g, 82.0 mmol), triethylamine (20.74 g, 205.0 mmol), β-ketoester **2d** (15.76 g, 98.4 mmol) and absolute ethanol (100 mL). The mixture was pressurised at 10 kbar at 25 °C for 65 hours. After decompression, the reaction mixture was evaporated and pyrimidinone **5c** was purified by recrystallization. Flash chromatography of the mother liquors (hexanes-ethyl acetate 9:1 to 6:4) afforded additional **5c** and imidazole **9** (0.9 g, 5%). The batches of **5c** from recrystallization and chromatography were combined (12.0 g, 43%), mp 118-120 °C (hexane/ethyl acetate). ir (KBr): 3261.9, 2974.1, 1680.7, 1584.7, 1519.0, 1449.7; 1385.3; 1369.9, 1285.6; 1266.0, 1217.4, 1172.9, 1114.0, 1049.0, 886.9, 824.0, 796.1, 737.2, 682.2, 561.3 cm^{-1}; ^{1}H nmr (200 MHz , deuteriochloroform): δ 1.22 (3H, t, J = 7.6, CH_2CH_3), 2.53 (1H, t, J = 2.5, CH_2C≡C*H*), 2.67 (2H, q, J = 7.6, CH_2CH_3), 3.98 (3H, s, OCH_3), 4.61 (2H, d, J = 2.5, CH_2C≡CH), 7.65 (2H, s, pyridylC*H*s); ^{13}C nmr (50 MHz, deuteriochloroform): δ 12.2 (CH_2CH_3), 24.4 (CH_2CH_3), 35.9 (CH_2C≡CH), 59.8 (OCH_3), 74.2 (CH_2C≡CH), 77.0 (CH_2C≡CH), 121.9 (3-pyridyl *C*, 5-pyridyl *C*), 141.8, 146.1, 148.7, 151.0 (2-pyridyl *C*, 6-pyridyl *C*), 155.4 (*C*=O), 157.4 (2-pyrimidinyl *C*); ms (EI): m/z 339 (52%), 337 (M^+, 80), 324 (12), 322 (21), 300 (62), 298 (M-$C_3H_3^+$, 100), 268 (6), 211 (11), 173 (7), 137 (11), 109 (10), 39 (65); hrms: Calcd for $C_{15}H_{13}N_3O_2Cl_2$ $(M)^+$ 337.03848. Found: 337.0381.

2-(2,6-Dichloro-4-pyridyl)-4-methylimidazole (**9**) and 2-(2,6-Dichloro-4-pyridyl)-4-methyl-3-(prop-2-ynyl)imidazole (**10**).

A stirred mixture of **4b** (8.01 g, 35.1 mmol), **2c** (9.20 g, 63.9 mmol) and THF (6 mL) was heated at 75 °C for 40 hours. The mixture was diluted with ether (100 mL) and 5% aqueous HCl (100 mL), stirred for a few minutes and filtered. Both the solid collected and the filtrate were retained. The solid was stirred with 5% aqueous NaOH (50 mL) for 0.5 hour and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated to leave an orange oil which solidified on standing (1.67 g). This material was triturated with 1:1 ether:hexanes (40 mL) and recrystallized from ethyl acetate (5 mL) to afford **9** (1.42 g, 18%) as a yellow solid, mp 196-200 °C; ^{1}H nmr (300 MHz; deuteriochloroform): δ 2.35 (3H, s, CH_3), 6.98 (1H, s, imidazole C*H*), 7.63 (2H, s, pyridyl C*H*s).

Anal. Calcd for $C_9H_7Cl_2N_3$: C, 47.40; H, 3.09; N, 18.42; Cl, 31.09. Found: C, 47.23; H, 2.96; N, 18.14; Cl, 31.30

The aqueous layer of the filtrate was separated, carefully basified with 50% aq NaOH and extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated to leave an orange oil (3.29 g) which was subjected to flash chromatography on silica gel (45 g) eluting with 0, 20, 40, 60, 80 and 100% ether in hexanes (150 mL of each). The crude product was triturated twice with 1:1 ether:hexanes (40 mL) to afford **10** (0.61 g, 7%) as a pale yellow solid, mp 158-161 °C; ir (deuteriochloroform): 3310, 1600 cm^{-1}; ^{1}H nmr (300 MHz; deuteriochloroform): δ 2.39 (3H, s, CH_3), 2.59 (1H, t, J = 2.4, CH_2C≡C*H*), 4.70 (2H, d, J = 2.4, CH_2C≡CH), 6.98 (1H, s, imidazole C*H*), 7.68 (2H, s, pyridyl C*H*s); ^{13}C nmr (75 MHz, deuteriochloroform): δ 9.7 (CH_3), 34.7 (CH_2C≡CH), 75.2 (CH_2C≡CH), 77.2 (CH_2C≡CH), 121.0 (3-pyridyl *C*, 5-pyridyl *C*), 128.4 (5-imidazole *C*), 131.7, 142.2, 142.7, 151.2 (2-pyridyl *C*, 6-pyridyl *C*).

Anal. Calcd for $C_{12}H_9Cl_2N_3$: C, 54.16; H, 3.41; N, 15.79; Cl, 26.64. Found: C, 54.07; H, 3.21; N, 15.51, Cl, 26.34.

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[12] Samples containing significant quantities of **8b** (R^6 = Me) exhibited the folowing peaks in their ^{1}H nmr spectra: δ 3.99 (s) assigned to be the 2-CH_3O pyridyl, 6.95 (d, J = 1.1 Hz) assigned to be the proton at the 3-pyridyl position and 7.16 (d, J = 1.1 Hz) assigned to be the proton at the 5-pyridyl position.

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