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Synthesis of 4-Alkyl-1(2*H*)-phthalazinones and 4-Alkyl-2,3-benzoxazin-1-ones via Ring Cleavage of 3-Substituted *N*-Alkylated-3-hydroxyisoindolin-1-ones

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ABSTRACT

N-Alkyl (Me, Et, *i*-Pr, *t*-Bu)-substituted phthalimdes **5a–d** were easily transformed to 1(2H)-phthalazinones **8d–i** and 2,3-benzoxazin-1-ones **9d**, **f**, and **j** via a one-pot addition–decyclization–cyclocondensation process.

Key Words: Heterocycles; *N*-alkyl; Hydrazine; Phthalimide.

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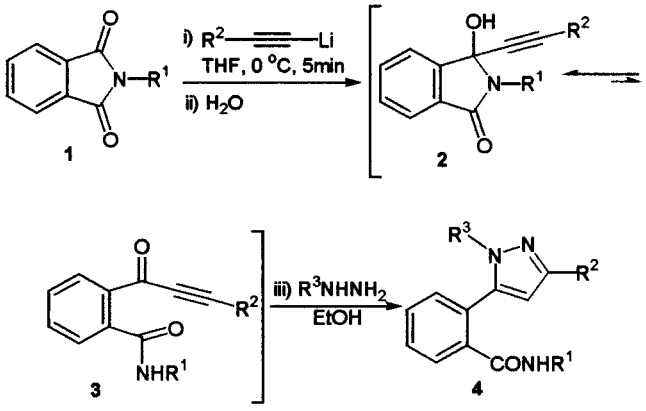
3-Substituted-3-hydroxyisoindolins are of considerable important building blocks for preparation of heterocycles because they behave in many reactions like ring-chain tautomers of the keto(aldehydo)-amide-hydroxylactam type.[1] Although numerous construction methods for the synthesis of 4-alkylated-1(*2H*)-phthalazin-1-ones have been developed,[2] the closest literature precedent using 3-substituted-3-hydroxyisoindolins has been independently studied by the groups of Ismail,[3] Brzeziński,[4] Kikugawa,[5] and Enders.[6] Ismail and Kikugawa groups reported that the reaction of *N*-amino (or -*N,N*-dimethyl-amino)phthalimide with arenes under Friedel–Crafts reaction conditions gave 2-aroylbenzoic acid hydrazide via an intermediate of 3-hydroxyisoindoline, which loose water to obtain 4-substituted-1(*2H*)-phthalazin-1-one. Also, Ismail et al.[3] described that *N*-aminophthalimide was reacted with Grignard reagents (e.g., *o*-methoxyphenyl-, *m*-tolyl-, or α-naphthylmagnesium bromides) to give the corresponding 4-arylphthalaz-1-ones in moderate yields. Brzeziński et al.[4] described that the reaction of *N*-phenyl-3-pyridyl-3-hydroxyisoindoline with hydrazine gave 4-pyridyl-1(*2H*)-phthalazin-1-one. Enders et al.[6] reported that the reaction of *N,N*-dimethylaminophthalimide with Grignard reagents (e.g., methyl- and phenylmagnesium bromides) gave the hydroxy-lactams in high yields. Recently, we have developed that *N*-alkyl (Me, Et, *i*-Pr, *t*-Bu)-substituted phthalimides **1** were transformed to multi-substituted pyrazoles **4** via a one-pot addition–decyclization–cyclocondensation process. The key step involves nucleophilic addition of lithium acetylide onto the *N*-substituted phthalimides **1** to give the keto tautomer **3** of alkynyl-3-hydroxyisoindolines **2**. Then, α-acetylenic ketones of type **3** was regioselectively reacted with a variety of hydrazines to produce the 2,3-pyrazoles **4** (Sch. 1).[7]



Scheme 1.

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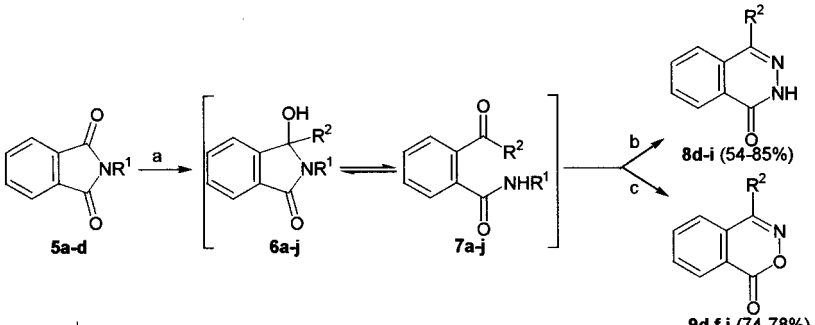
On the basis of viewpoints, these synthetic methods are found to be applicable for the synthesis of 4-alkyl-1(*2H*)-phthalazin-1-ones and 4-alkyl-2,3-benzoxazin-1-ones. Here, we describe a facial construction method of 1(*2H*)-phthalazinones and 2,3-benzoxazin-1-ones via a one-pot addition–decyclization–cyclocondensation process.

Starting materials **5a–d** were prepared by a sequential reaction. phthalic anhydride and phthalimide were converted to *N*-alkylated phthalimides **5a–d** by the Gabriel reaction[8] with azeotropic removal of the water formed. Subsequently, we investigated a one-pot addition–decyclization–cyclocondensation process. These results are summarized in Sch. 2. The typical procedures are as follow; compounds **5a–d** was treated with benzylmagnesium bromide in THF to give the crude *N*-alkyl (Me, Et, *i*-Pr, *t*-Bu)-3-benzyl-3-hydroxyisoindoline intermediates **6a–d**. After disappearing of starting materials **5a–d**, the reactions were quenched by addition of H_2O and evaporated to afford the residues, which were dissolved in EtOH and then hydrazine monohydrate was treated to obtain the same 4-benzyl-1(*2H*)-phthalazin-1-one **8d** in 80% (R^1 = Me), 75% (R^1 = Et), 82% (R^1 = *i*-Pr), and 85% (R^1 = *t*-Bu) yields, respectively. In the case of **5d** *N*-substituted with *tert*-butyl group, a one to one ratio of the ring-chain tautomers of the hydroxylactam **6d** and the ketoamide **7d** were determined by the ^{1}H NMR analysis. Similar reaction of **5d** with various organometallic agents gave the mixture of hydroxylactams **6e–i** and keto tautomers **7e–i**, which were cyclized with hydrazine monohydrate to give **8e–i** in good yields, respectively (Sch. 2).



5-9	a	b	c	d	e	f	g	h	i	j
R^1	Me	Et	*i*-Pr	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu
R^2	Bn	Bn	Bn	Bn	Et	*i*-Pr	*n*-Bu	*n*-C_5H_{11}	Ph$(CH_2)_2$-	Biphenyl

Scheme 2. Reagents and conditions: (a) R^2MgBr, THF, 0°C, 5 min. (b) NH_2NH_2, EtOH, reflux, 12–36 hr. (c) NH_2OH, EtOH, reflux, 30–48 hr.

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On the other hand, treatment of **5d** with benzyl-, isopropyl- and biphenylmagnesium bromides gave the mixture of 3-hydroxylactams **6d**, **6f**, and **6j** and keto tautomers **7d**, **7f**, and **7j**, which were cyclized with hydroxylamine hydrochloride to afford the desired 4-benzyl-, isopropyl- and biphenyl-2,3-benzoxazin-1-ones **9d**, **9f**, and**9j** in 78%, 74%, and 74% yields, respectively (Sch. 2). Also, 4-isopropyl-2,3-benzoxazin-1-one **9f** was treated with hydrazine monohydrate in EtOH to give the 4-isopropyl-1(*2H*)-phthalazin-1-one **8f** in good yield, which was identical with **8f** that was obtained by the reaction of a mixture of intermediates of **6d** and **7d** with hydrazine monohydrate.

The structures of these 4-alkylated-1(*2H*)-phthalazin-1-ones **8d–i** were determined by their characteristic spectroscopic data; namely, **8d–i** show a strong band in a range of 1650–1670 cm^{-1} due to attributed to the carbonyl of amide moiety. Especially, **8d** was identical with authentic spectrum and showed IR absorption at 1660 cm^{-1} ($\nu_{C=O}$) (lit. 1660 cm^{-1}), 2904– 3163 cm^{-1} ($\nu_{NH, OH}$) (lit. 2900–3180 cm^{-1}), and m.p. 199–200°C (lit. 201°C).

4-Alkylated-2,3-benzoxazin-1-ones (**9d**, **9f**, and **9j**) also show a strong band in a range of 1722–1744 cm^{-1} due to attributed to the carbonyl of ester moiety.

In conclusion, we found that 3-substituted-3-hydroxyisoindolins were easily converted to 4-alkylated-1(*2H*)-phthalazin-1-ones **8d–i** and 4-alkylated-2,3-benzoxazin-1-ones **9d**, **9f**, and **9j** via a one-pot addition–decyclization–cyclocondensation process.

Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on Bruker AVANCE 300 and 400 spectrometers with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a EQUINOX55 spectrometer. Elemental analyses were performed with a Perkin Elmer 240C.

4-Benzyl-*2H*-phthalazin-1-one (8a): Typical Procedure

To a solution of benzylmagnesium bromide, which was prepared by treatment of benzyl bromide (3.24 mL, 4.65 mmol) with magnesium flakes (113.04 mg, 4.65 mmol) in tetrahydrofuran (10 mL), was added a solution of **5a** (500 mg, 3.10 mmol) in tetrahydrofuran (10 mL) at 0°C. After 5 min, the reaction mixture was quenched by addition of water (5 mL) and evaporated to give the residue, which was dissolved in ethanol (10 mL) and then a solution of hydrazine monohydrate (465.56 μL, 9.3 mmol, 80% in water) was added at rt. After being refluxed for 36 hr, the reaction mixture was cooled to rt and evaporated under reduced pressure to give the residue, which was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to give the crude

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product, which was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **8a** (587.5 mg, 80%) as colorless prisms (CH_2Cl_2/hexane), m.p. 199–200°C (lit. m.p. 201°C); IR (KBr): 3163, 3012, 2904, 1660, 1493, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.34 (s, 2H), 7.20–7.31 (m, 5H), 7.69–7.75 (m, 3H), 8.46 (dd, 1H, $J = 2.7$ and 0.8 Hz), 10.97 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.9, 125.4, 126.8, 127.0, 128.3, 128.5, 128.7, 129.8, 131.3, 133.4, 137.6, 146.4, 160.6. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found C, 76.47; H, 5.30; N, 11.69.

According to the typical procedure, treatment of **5b–d** with benzylmagnesium bromide, water, and hydrazine monohydrate gave the pure **8a** in 75% (**5b**: R^1 = Et, R^2 = Bn, 36 hr), 82% (**5c**: R^1 = *i*-Pr, R^2 = Bn, 36 hr) and 85% (**5d**: R^1 = *t*-Bu, R^2 = Bn, 34 hr) yields, respectively.

4-Ethyl-*2H*-phthalazin-1-one (8e). Compound **8e** was obtained accordingly, starting from **5d** (300 mg, 1.48 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **8e** (141.70 mg, 55%) as colorless prisms (CH_2Cl_2/hexane), m.p. 156–157°C; IR (KBr) 3170, 3015, 2975, 1670, 1348, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, 3H, $J = 7.4$), 2.97 (q, 2H, $J = 7.4$), 7.72–7.82 (m, 3H), 8.47 (d, 1H, $J = 7.9$), 11.15 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 25.3, 124.5, 127.0, 128.0, 129.8, 131.1, 133.3, 148.5, 160.8. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found C, 69.12; H, 5.97; N, 16.25.

4-Isopropyl-*2H*-phthalazin-1-one (8f). Compound **8f** was obtained accordingly, starting from **5d** (300 mg, 1.48 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **8f** (317.13 mg, 78%) as colorless prisms (CH_2Cl_2/hexane), m.p. 155–156°C; IR (KBr): 3168, 3068, 2964, 1650, 1474, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, 6H, $J = 6.8$), 3.47 (m, 1H), 7.69–7.87 (m, 3H), 8.49 (dd, 1H, $J = 1.5$ and 0.8), 11.69 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 29.5, 124.2, 127.1, 128.1, 129.4, 130.9, 133.2, 151.5, 160.8. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found C, 70.38; H, 6.27; N, 14.72.

The reaction of **9f** with hydrazine monohydrate. To a solution of **9f** (500 mg, 2.65 mmol) in EtOH (25 mL) was added hydrazine monohydrate (321.35 μL, 5.3 mmol, 80% in water) at rt. After being refluxed for 10 hr, the reaction mixture was cooled to rt and evaporated to give residue, which was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **8f** (408.72 mg, 82%).

4-*n*-Butyl-*2H*-phthalazin-1-one (8g). Compound **8g** was obtained accordingly, starting from **5d** (300 mg, 1.48 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to

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give the pure **8g** (239.30 mg, 80%,) as colorless prisms (CH_2Cl_2/hexane), m.p. 152°C; IR (KBr) 3164, 3008, 2952, 1650, 1358 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H, $J = 7.3$), 1.45 (m, 2H), 1.74 (m, 2H), 2.93 (t, 2H, $J = 7.5$), 7.77 (m, 3H), 8.47 (d, 1H, $J = 7.7$), 10.80 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 22.6, 30.0, 31.8, 124.7, 127.0, 128.1, 130.0, 131.2, 133.3, 147.9, 160.6. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found C, 71.50; H, 6.81; N, 13.62.

4-*n*-Pentyl-*2H*-phthalazin-1-one (8h). Compound **8h** was obtained accordingly, starting from **5d** (300 mg, 1.48 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : chexane = 1 : 2) to give the pure **8h** (172.73 mg, 54%) as colorless prisms (CH_2Cl_2/hexane), m.p. 129–130°C; IR (KBr) 3163, 3012, 2937, 1652, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.9 (t, 3H, $J = 7.0$), 1.36–1.76 (m, 6H), 2.91 (t, 2H, $J = 7.7$), 7.72–7.83 (m, 3H), 8.46 (dd, 1H, $J = 2.1$ and 0.8), 10.04 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.5, 27.6, 31.7, 32.1, 124.7, 127.0, 128.1, 129.9, 131.2, 133.4, 148.0, 160.6. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found C, 71.98; H, 7.52; N, 12.72.

4-Phenethyl-*2H*-phthalazin-1-one (8i). Compound **8i** was obtained under refluxing condition, starting from **5d** (300 mg, 1.48 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **8i** (281.32 mg, 76%) as colorless prisms (CH_2Cl_2/hexane), m.p. 146–147°C; IR (KBr) 3180, 3053, 1651, 1452, 1354 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.10 (m, 2H), 3.25 (dt, 2H, $J = 1.5$ and 7.4), 7.20–7.30 (m, 6H), 7.80 (m, 3H), 8.49 (dd, 1H, $J = 1.0$ and 8.6), 10.99 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.6, 33.8, 124.4, 126.2, 127.1, 128.0, 128.4, 128.5, 129.8, 131.3, 133.4, 141.1, 146.7, 160.6. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found C, 76.95; H, 5.82; N, 11.30.

4-Benzyl-2,3-benzoxazin-1-one (9d): Typical Procedure

To a solution of benzylmagnesium bromide, which was prepared by treatment of benzyl bromide (3.24 mL, 4.65 mmol) with magnesium flakes (113.04 mg, 4.65 mmol) in tetrahydrofuran (10 mL), was added a solution of **5d** (629.58 mg, 3.10 mmol) in tetrahydrofuran (10 mL) at 0°C. After 5 min, the reaction mixture was quenched by addition of water (10 mL) and added the solution of hydroxylamine hydrochloride (646.26 mg, 9.3 mmol) in 10 mL of ethanol was refluxed for 48 hr. After cooling to rt, the reaction mixture was evaporated under reduced pressure to give the residue, which was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to give the crude

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product. Purification by flash column chromatography on silica gel (EtOAc : hexane = 1 : 1) gave the pure **9d** (573.26 mg, 78%) as colorless prisms (CH_2Cl_2/hexane), m.p. 128–129°C; IR (KBr) 3035, 2923, 1744, 1452, 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.28 (s, 2H), 7.23–7.32 (m, 5H), 7.61 (m, 1H), 7.76 (m, 2H), 8.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0, 123.0, 125.8, 126.8, 127.4, 128.4, 128.9, 129.0, 133.5, 135.3, 135.6, 154.7, 163.6. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found C, 76.12; H, 4.85; N, 5.68.

4-Isopropyl-2,3-benzoxazin-1-one (9f). Compound **9f** was obtained under refluxing condition, starting from **5d** (300 mg, 1.48 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **9f** (207.08 mg, 74%) as colorless prisms (CH_2Cl_2/hexane), m.p. 79–80°C; IR (KBr) 2975, 1722, 1595, 1456, 1289, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (d, 6H, $J = 6.8$), 3.42 (m, 1H), 7.76 (dd, 1H, $J = 0.5$ and 7.8), 7.82 (dd, 1H, $J = 1.1$ and 7.7), 7.90 (dd, 1H, $J = 1.4$ and 7.6), 8.38 (dd, 1H, $J = 0.9$ and 7.7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 29.9, 122.8, 124.5, 126.5, 129.0, 133.2, 135.3, 159.2, 163.7. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found C, 69.61; H, 5.99; N, 7.19.

4-Biphenyl-2,3-benzoxazin-1-one (9j). Compound **9j** was obtained under refluxing condition, starting from **5d** (300 mg, 1.48 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **9j** (327.56 mg, 74%) as colorless prisms (CH_2Cl_2/hexane), m.p. 142–143°C; IR (KBr) 1738, 1488,1285 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.3 (s, 2H), 7.31–7.80 (m, 12H), 8.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.6, 122.9, 125.8, 126.8, 126.9, 127.1, 127.3, 127.4, 127.7, 127.78, 128.8, 133.6, 134.6, 135.4, 140.3, 154.7, 163.6. Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found C, 80.37; H, 4.40; N, 4.75.

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