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SYNTHESIS OF MULTI-SUBSTITUTED PYRAZOLES UTILIZING THE *N*-ALKYLATED 3-HYDROXY-3-PROPARGYL- OR ALLENYLISOINDOLINES

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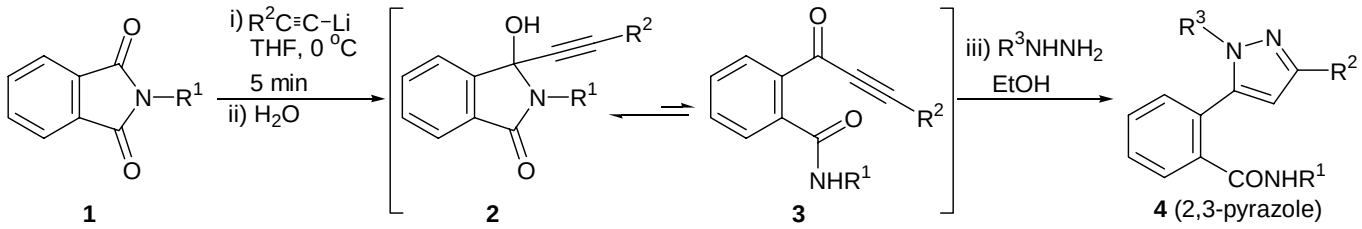
Abstract-*N*-Alkyl-substituted phthalimides (**1**) were easily converted to di-, tri-, and tetra-substituted pyrazoles (**10**) *via* a one-pot addition-decyclization-cyclocondensation process. Then, the structure and the position of N1-substitution of the 1,3-pyrazole ring were determined by X-Ray crystallographic analysis and ^{1}H-nOe experiments.

The synthetic development of heterocyclic compounds utilizing the allenic systems has been extensively studied.[1] However, their synthetic applications to pyrazoles which involve many possibilities of study have been briefly described by Tannefors,[2] Bertrand,[3] and Landor.[4] In fact, synthesis of the pyrazole ring is of considerable important due to its theoretical interest and biological activity.[5] In connection with our recent research program for the synthesis of the pyrazole derivatives, we reported that *N*-alkylated phthalimides

(**1**) were regioselectively transformed to mono-, di-, or tri-substituted 2,3-pyrazoles (**4**) *via* a one-pot addition-decyclization-cyclocondensation process.[6] Then, the key step involves the formation of the keto tautomers, ynone intermediates (**3**), of *N*-substituted 3-alkynyl-3-hydroxyisoindolines (**2**) by the nucleophilic addition of lithium acetylide onto the compounds (**1**) (Scheme 1). With regard to the cleavage of C3-N2 bond of **2**, Nagao and his co-workers[1g] also reported several 3-hydroxy-3-propargyl- or allenylisoindolines were converted to the corresponding ring-expanded benzazepines *via* a tandem decyclization-cyclization process. On the basis of viewpoints, these synthetic methods are found to be applicable for the synthesis of 1,3-pyrazole rings. In this paper, we describe a facial construction method of 1,3-pyrazole *via* a one-pot addition-decyclization-cyclocondensation process.



Scheme 1

Starting materials (**1a-c**) were prepared by a sequential reaction. Namely, phthalimides were converted to *N*-alkylated phthalimides (**1a-c**) by the Gabriel reaction.[7] Compound (**1d**) was prepared by the reaction of phthalic anhydride with *tert*-butylamine in the presence of *p*-toluenesulfonic acid (cat.) in xylene by azeotropic removal of the water formed. Subsequently, we investigated a one-pot addition-decyclization-cyclocondensation process. These results are summarized in Table 1. The typical procedure is as follow; to a solution of prop-2-ynylmagnesium bromide was added a solution of **1a** in THF at 0 °C. After disappearing of the starting materials **1a**, the reaction mixture was quenched by addition of H_2O and evaporated to give the residues, which were dissolved in EtOH and then the hydrazine monohydrate was added and the mixture was refluxed for 2 h to afford the 1,3-pyrazole (**10a**) in 42% yield. Subsequently, similar reactions of **1b** and **1c** with prop-2-ynylmagnesium bromide, H_2O, and hydrazine monohydrate under reflux conditions for 4 h gave the 1,3-pyrazoles (**10b**) (62%) and (**10c**) (87%), respectively. Interestingly, *N*-*tert*-butylphthalimide (**1d**) was converted easily to pyrazole (**10d-1**) at room temperature in 95% yield. Then, the reaction of **1d** with prop-2-ynylmagnesium bromide gave a mixture of the ring-

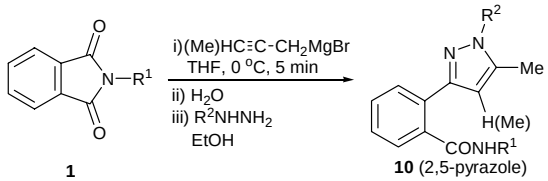
chain tautomers of the hydroxy lactam (**5d**) and keto amide (**6d**) with a 6 to 1 ratio, which was determined by the ^{1}H-NMR spectral analysis. As reported in previous results,[6] the size of *N*-substitution groups on **1** influences in the ring cleavage of C3-N2 bond of 3-hydroxy-3-propargylisoindoline. Similar treatment of **1d** with prop-2-ynylmagnesium bromide, H_2O, and two kinds of methyl- and *p*-nitrophenylhydrazines afforded the corresponding 1,3-pyrazoles (**10d-2**) (93%) and (**10d-4**) (61%), respectively. However, treatment of **1d** with phenylhydrazine gave **10d-3-1** (53%) and **10d-3-2** (36%), respectively (Table 1) (*vide infra*).

Subsequently, *N*-*tert*-butylphthalimide (**1d**) was reacted with 2-buynylmagnesium bromide, which was prepared according to Nagao's method[1g] to give multi-substituted pyrazoles. Namely, a solution of 1-bromo-2-butyne in THF was added very slowly to a mixture of *N*-*tert*-butylphthalimide (**1d**), magnesium flakes, and catalytic $HgCl_2$ in THF with vigorous stirring at 0 ºC under nitrogen atmosphere, and the whole was stirred for 2 h. The reaction mixture was then quenched by addition of H_2O and evaporated to give the crude residue, which was dissolved in EtOH and then hydrazine monohydrate was added at room temperature to give the desired 1,3-pyrazole (**10d-5**) in 95% yield. In order to confirm an allene intermediate (**8**) producing pyrazoles, we could also be achieved to isolate the conjugated allenyl ketone (**8**) in a quantitative yield. The structure of **8** was readily determined by their characteristic spectroscopic data; [IR (KBr) 1937 (allenyl) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.95 (t, *J* = 2.9 Hz, 3H, -Me) and 4.87 (q, *J* = 2.9 Hz, 2H, allenyl); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 197.9 (carbonyl) and 218.1 (allenyl)]. Similar treatment of **1d** with 2-butynylmagnesium bromide, H_2O, and two kinds of methyl- and *p*-nitro-phenylhydrazines afforded the corresponding 1,3-pyrazoles (**10d-6**) (93%) and (**10d-8**) (87%), respectively. Also, the reaction of **1d** with phenyl- and *p*-fluorophenylhydrazines gave (**10d-7-1**) (45%), (**10d-7-2**) (44%) and (**10d-9-1**) (48%), (**10d-9-2**) (18%), respectively (Table 1) (*vide infra*).

The structures of **10** were determined on the basis of their characteristic spectroscopic data. Especially, **10d-2** was illustrated by X-Ray crystallographic analysis (Figure 1).[8]

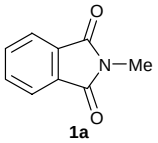
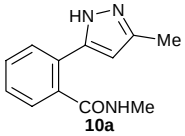
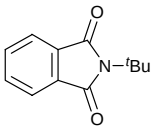
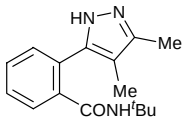
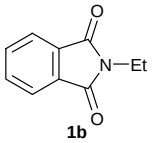
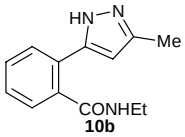
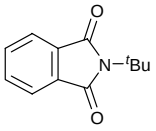
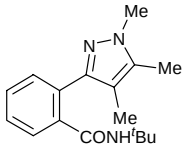
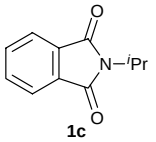
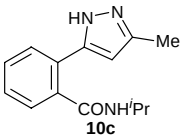
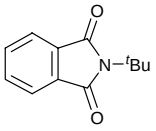
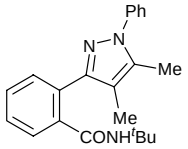
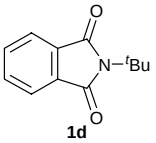
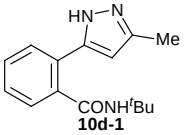
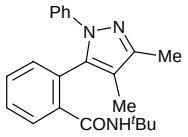
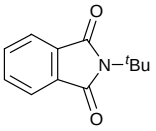
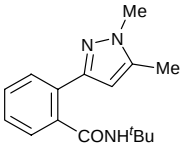
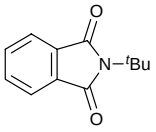
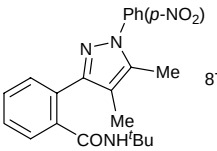
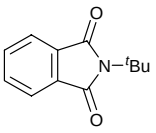
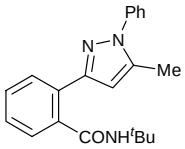
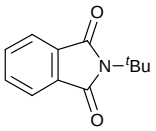
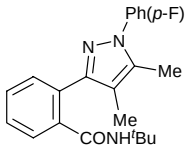
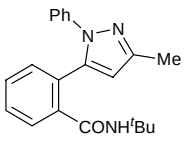
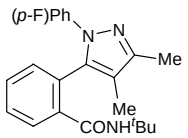
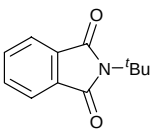
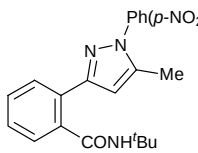
Also, the position of the N1-*p*-fluorophenyl group of **10d-9-1** was determined by the ^{1}H-nOe experiments. Namely, irradiation of methyl protons at C5 of **10d-9-1** resulted in 3.39 % and 3.92 % nuclear overhauser

enhancement of the N1-*p*-fluorophenyl protons and C4-methyl protons, respectively.



1 **10** (2,5-pyrazole)

Table 1. Regioselective synthesis of pyrazoles (**10**) *via* ring cleavage of **1** by one-pot decyclisation-cyclocondensation process[a]

Substrates **1**	Conditions[b]	Products[c] **10**	Yield (%)	Substrates **1**	Conditions[b]	Products[c] **10**	Yield (%)
 **1a**	i) HC≡C-CH2MgBr ii) H2O iii) NH2NH2 reflux, 2 h	 **10a**	42	 **1d**	i) MeC≡C-CH2MgBr ii) H2O iii) NH2NH2 rt, 5 min	 **10d-5**	95
 **1b**	i) HC≡C-CH2MgBr ii) H2O iii) NH2NH2 reflux, 4 h	 **10b**	62	 **1d**	i) MeC≡C-CH2MgBr ii) H2O iii) MeNHNH2 rt, 5 min	 **10d-6**	93
 **1c**	i) HC≡C-CH2MgBr ii) H2O iii) NH2NH2 reflux, 4 h	 **10c**	87	 **1d**	i) MeC≡C-CH2MgBr ii) H2O iii) PhNHNH2 rt, 1 h	 **10d-7-1**	45
 **1d**	i) HC≡C-CH2MgBr ii) H2O iii) NH2NH2 rt, 5 min	 **10d-1**	95			 **10d-7-2**	44
 **1d**	i) HC≡C-CH2MgBr ii) H2O iii) MeNHNH2 rt, 5 min	 **10d-2**	93	 **1d**	i) MeC≡C-CH2MgBr ii) 5% HCl iii) (*p*-NO2)PhNHNH2 reflux, 5 h	 **10d-8**	87
 **1d**	i) HC≡C-CH2MgBr ii) H2O iii) PhNHNH2 rt, 10 min	 **10d-3-1**	53	 **1d**	i) MeC≡C-CH2MgBr ii) H2O iii) (*p*-F)PhNHNH2 rt, 5 h	 **10d-9-1**	48
		 **10d-3-2**	36			 **10d-9-2**	18
 **1d**	i) HC≡C-CH2MgBr ii) H2O iii) (*p*-NO2)PhNHNH2 reflux, 2 h	 **10d-4**	61				

a) 3.0 equiv. of hydrazine hydrate and 2.0 equiv. of methyl-, phenyl-, *p*-nitro-, *p*-fluorophenylhydrazines were used. b) Reaction time with hydrazine derivatives. c) The structure and position of substitution were determined by their characteristic data, nOe experiments, and X-Ray analysis.

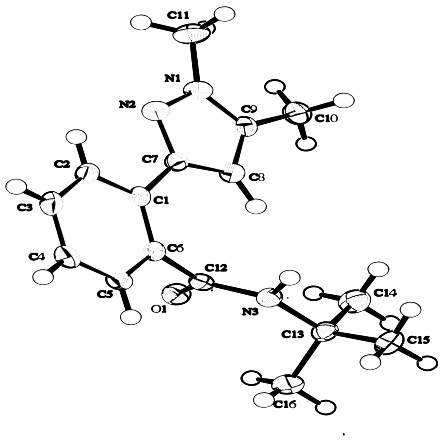
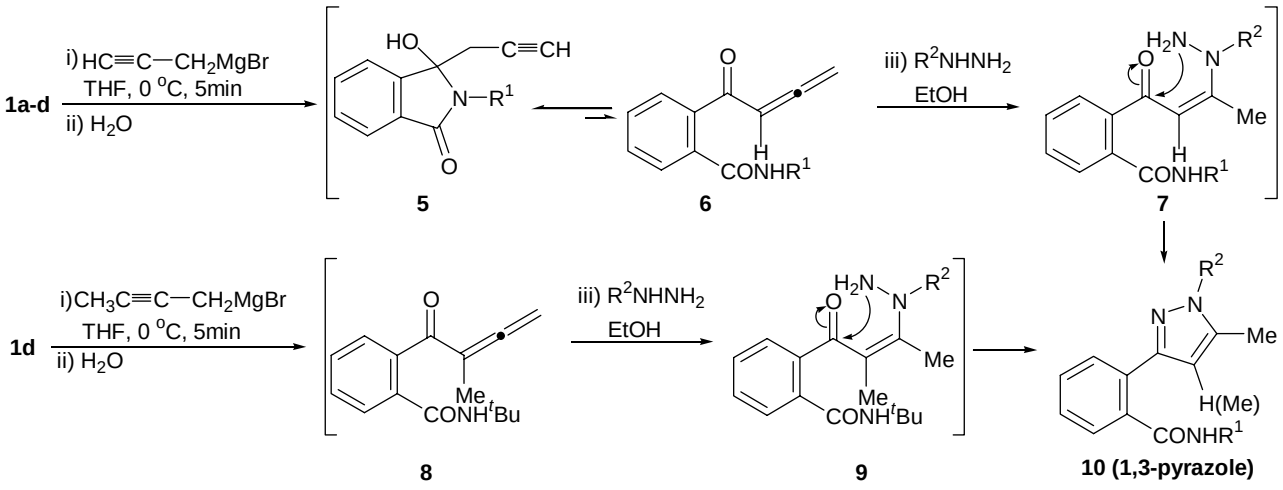


Figure 1 X-Ray crystal structure of **10d-2**.

In contrast to our previous results using an α-acetylenic ketone giving the 2,3-pyrazoles,[6] the conjugated allenyl ketone intermediates could be converted regioselectively to the corresponding 1,3-pyrazoles, except for the use of pheny- and *p*-fluorophenylhydrazines. The reaction mechanism for pyrazoles (**10**) may be rationalized as shown in Scheme 2. Namely, the more electron-rich nitrogen of methylhydrazine attacks the β-position of the allenyl ketone intermediates (**6**) and (**8**) to give β-hydrazine-substituted alkenones (**7**) and (**9**), in which the unsubstituted nitrogen is brought into close proximity to the carbonyl carbon allowing rapid completion of the cyclization with expulsion of water to give predominantly the 1,3-pyrazoles. However, the use of phenyl- and *p*-fluorophenylhydrazines was not shown the selectivity. As a result, the regiochemical preference in this addition depends on steric, electronic, and mechanistic factors.



Scheme 2

In conclusion, we found that *N*-alkylated 3-hydroxy-3-propargyl- or allenylisoindolines were easily converted to the 1,3-pyrazoles. Among the *N*-substitution groups of compounds (**1**), *N-tert*-butyl group has proven to be the most effective giving the pyrazole derivatives.

EXPERIMENTAL

Melting points were measured on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra were measured downfield relative to tetramethyl silane in $CDCl_3$ unless otherwise noted (value in ppm); coupling constants *J* are reported in hertz; ^{1}H-NMR, ^{13}C-NMR spectrum and ^{1}H-nOe experiments were conducted on Bruker AVANCE 300 and 400 spectrometers. IR spectral data were obtained on a EQUINOX55 spectrometer. Elemental analyses were performed with a Perkin Elmer 240C. X-Ray diffraction data were obtained with a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation.

Preparation of an ethereal solution of the Grignard reagent (1M solution) from 1-bromopropyne and magnesium flakes

A mixture of magnesium flakes (0.24 g, 10.10 mmol) and mercury(II) chloride (0.14 g, 0.52 mmol) was placed in a two-necked flask (30 mL) equipped with a cooling condenser and then Et_2O (5 mL) was added under N_2 atmosphere. After 3-bromo-1-propyne (1.20 g, 10.10 mmol) was added, the mixture was stirred at rt for 5 min. Finally, the reaction mixture was diluted with Et_2O (5 mL).

N-Methyl-2-(5-methyl-*2H*-pyrazol-3-yl)benzamide (10a); Typical procedure

To a solution of **1a** (100 mg, 0.62 mmol) in THF (5 mL) was added prop-2-ynylmagnesium bromide (0.93 mL, 0.93 mmol, 1M solution in Et_2O) at 0 ^{o}C. After 5 min, the reaction mixture was quenched by addition of H_2O (0.1 mL) and evaporated to give the residue, which was dissolved in EtOH (5 mL) and then a solution of hydrazine hydrate (90.2 μL, 1.86 mmol, 80% in H_2O) in EtOH (3 mL) added at rt. After being refluxed for 2 h, the reaction mixture was cooled to rt, evaporated under reduced pressure, and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to give the crude product. Purification by column chromatography on silica gel (EtOAc : hexane = 1 : 2) gave the pure **10a** (56 mg, 42%) as colorless prisms, mp 178-180 ^{o}C (CH_2Cl_2/hexane); IR (KBr) 3407, 3105, 2933, 1647 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3H),

2.81 (d, *J* = 4.9 Hz, 3H), 6.19 (br, 2H), 7.29-7.53 (m, 4H). Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.88; H, 6.13; N, 19.70.

***N*-Ethyl-2-(5-methyl-*2H*-pyrazol-3-yl)benzamide (10b)**

Compound (**10b**) was obtained accordingly, starting from **1b** (200 mg, 1.14 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10b** (162 mg, 62%) as colorless prisms, mp 150-152 ^oC (CH_2Cl_2/hexane); IR (KBr) 3188, 3142, 2984, 1650 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.10 (t, *J* = 7.3 Hz, 3H), 2.23 (s, 3H), 3.27 (m, 2H), 6.16 (s, 1H), 6.24 (t, *J* = 7.2 Hz, 1H), 7.26-7.48 (m, 4H). Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.28; H, 6.70; N, 18.17.

***N*-Isopropyl-2-(5-methyl-*2H*-pyrazol-3-yl)benzamide (10c)**

Compound (**10c**) was obtained accordingly, starting from **1c** (200 mg, 1.06 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10c** (224 mg, 87%) as colorless prisms, mp 176-178 ^oC (CH_2Cl_2/hexane); IR (KBr) 3217, 3143, 1969, 1635 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3H), 1.06 (s, 3H), 2.28 (s, 3H), 4.12 (m, 1H), 5.83 (d, *J* = 7.7 Hz, 1H), 6.21 (s, 1H), 7.30-7.50 (m, 4H). Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.01; H, 7.18; N, 17.09.

***N*-*tert*-Butyl-2-(5-methyl-*2H*-pyrazol-3-yl)benzamide (10d-1)**

Compound (**10d-1**) was obtained accordingly, starting from **1d** (100 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (EtOAc) to give the pure **10d-1** (120 mg, 95%) as colorless prisms, mp 119-120 ^oC (CH_2Cl_2/hexane); IR (KBr) 3198, 3042, 2976, 1627 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 9H), 2.31 (s, 3H), 5.67 (br, 1H), 6.26 (s, 1H), 7.32-7.55 (m, 4H). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.18; H, 7.58; N, 16.42.

***N*-*tert*-Butyl-2-(1,5-dimethyl-*1H*-pyrazol-3-yl)benzamide (10d-2)**

Compound (**10d-2**) was obtained accordingly, starting from **1d** (100 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 1) to give the pure **10d-2** (124 mg, 93%) as colorless prisms, mp 136-138 ^oC (CH_2Cl_2/hexane); IR (KBr) 3273, 2978, 1650 cm^{-1};

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 9H), 2.30 (s, 3H), 3.82 (s, 3H), 5.82 (br, 1H), 6.21 (s, 1H), 7.33-7.57 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 11.1, 28.5, 36.1, 51.4, 106.0, 127.7, 128.3, 129.3, 129.4, 131.3, 137.0, 139.2, 149.1, 169.0. Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found C, 70.73; H, 7.85; N, 15.38.

Compounds (**10d-3-1** and **10d-3-2**) were obtained under refluxing condition, starting from **1d** (100 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10d-3-1** (87 mg, 53%) and **10d-3-2** (59 mg, 36%).

***N-tert*-Butyl-2-(5-methyl-1-phenyl-*1H*-pyrazol-3-yl)benzamide (10d-3-1)**

Colorless prisms, mp 107-109 ^{o}C (CH_2Cl_2/hexane); IR (KBr) 3297, 2967, 1659, 1504 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 9H), 2.35 (s, 3H), 5.81 (br, 1H), 6.39 (s, 1H), 7.33-7.62 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.3, 28.4, 51.4, 107.8, 124.7, 127.6, 127.9, 128.2, 128.6, 129.0, 129.3, 130.9, 137.2, 139.5, 139.6, 150.7, 168.9. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.58; H, 6.82; N, 12.79.

***N-tert*-Butyl-2-(5-methyl-2-phenyl-*2H*-pyrazol-3-yl)benzamide (10d-3-2)**

Colorless prisms, mp 105-106 ^{o}C (CH_2Cl_2/hexane); IR (KBr) 3270, 2968, 1660, 1505 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.20 (s, 9H), 2.38 (s, 3H), 5.38 (br, 1H), 6.28 (s, 1H), 7.20-7.40 (m, 9H). Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.50; H, 6.88; N, 12.48.

***N-tert*-Butyl-2-[5-methyl-1-(4-nitrophenyl)-*1H*-pyrazol-3-yl]benzamide (10d-4)**

Compound (**10d-4**) was obtained under refluxing condition, starting from **1d** (100 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10d-4** (113 mg, 61%) as colorless prisms, mp 143-144 ^{o}C (CH_2Cl_2/hexane); IR (KBr) 3406, 2969, 1659, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 9H), 2.35 (s, 3H), 5.42 (br, 1H), 6.30 (s, 1H), 7.24 (m, 1H), 7.36-7.56 (m, 5H), 8.01 (dd, *J* = 2.0, 7.2 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.4, 28.4, 51.6, 110.4, 122.8, 124.3, 128.3, 128.4, 129.6, 130.2, 130.6, 137.5, 142.2, 144.4, 145.2, 150.9, 166.7. Anal. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.81. Found : C, 66.80; H, 5.97; N, 14.66.

***N-tert*-Butyl-2-(4,5-dimethyl-*2H*-pyrazol-3-yl)benzamide (10d-5)**

Compound (**10d-5**) was obtained accordingly, starting from **1d** (100 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10d-5** (126 mg, 95%) as colorless prisms, mp 148-150 ^{o}C (CH_2Cl_2/hexane); IR (KBr) 3269, 2924, 1678, 1432, 1388 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 9H), 1.86 (s, 3H), 2.15 (s, 3H), 5.66 (br, 1H), 7.25-7.29 (m, 1H), 7.38-7.43 (m, 2H), 7.71-7.74 (m, 1H). Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.60; H, 7.97; N, 15.28.

***N-tert*-Butyl-2-(1, 4, 5-trimethyl-*1H*-pyrazol-3-yl)benzamide (10d-6)**

Compound (**10d-6**) was obtained accordingly, starting from **1d** (100 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10d-6** (130 mg, 93%) as a yellow oil; IR (neat) 3405, 3059, 2965, 1651, 1538, 1453, 1362 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.11 (s, 9H), 1.73 (s, 3H), 2.15 (s, 3H), 3.72 (s, 3H), 5.95 (br, 1H), 7.17-7.20 (m, 1H), 7.31-7.34 (m, 2H), 7.72-7.75 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 8.1, 9.3, 28.0, 36.0, 50.8, 112.9, 128.0, 128.8, 129.4, 130.5, 131.3, 136.5, 137.3, 149.1, 166.1. Anal. Calcd for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.67; H, 8.24; N, 14.58.

Compounds (**10d-7-1** and **10d-7-2)** were obtained accordingly, starting from **1d** (100 mg, 0.49 mmol). The mixture product was isolated by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10d-7-1** (76.6 mg, 45%) and **10d-7-2** (75 mg, 44%).

***N-tert*-Butyl-2-(4,5-dimethyl-1-phenyl-*1H*-pyrazol-3-yl)benzamide (10d-7-1)**

A yellow oil; IR (KBr) 3412, 3063, 2966, 1667 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 9H), 1.88 (s, 3H), 2.31 (s, 3H), 5.88 (br, 1H), 7.34-7.46 (m, 8H), 7.80 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 8.4, 11.0, 28.3, 51.1, 115.0, 124.6, 127.5, 128.5, 128.9, 129.1, 129.7, 130.7, 131.0, 136.7, 137.6, 139.8, 151.5, 167.8. Anal. Calcd for $C_{22}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09. Found: C, 75. 80; H, 7.12; N, 12.41.

***N-tert*-Butyl-2-(4,5-dimethyl-2-phenyl-*2H*-pyrazol-3-yl)benzamide (10d-7-2)**

Colorless prisms, mp 133-134 °C (CH_2Cl_2/hexane); IR ($CHCl_3$) 3329, 2965, 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 9H), 1.91 (s, 3H), 2.32 (s, 3H), 5.35 (br, 1H), 7.10-7.22 (m, 6H), 7.43 (m, 2H), 7.79

(m, 1H). Calcd for $C_{22}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09. Found: C, 76.38; H, 7.15; N, 12.26.

***N-tert*-Butyl-2-[4,5-dimethyl-1-(4-nitrophenyl)-*1H*-pyrazol-3-yl]benzamide (10d-8)**

Compound (**10d-8**) was obtained accordingly, starting from **1d** (100 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10d-8** (167 mg, 87%) as colorless prisms; mp 152-154 ^oC (CH_2Cl_2/hexane); IR (KBr) 3352, 3085, 2918, 1639, 1594, 1507, 1330 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.20 (s, 9H), 1.93 (s, 3H), 2.34 (s, 3H), 5.29 (s, 1H), 7.26 (m, 1H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.39-7.54 (m, 2H), 7.72 (m, 1H), 8.05 (d, *J* = 7.8 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 8.2, 12.0, 28.4, 51.5, 117.6, 122.1, 124.5, 128.4, 129.0, 129.8, 130.7, 131.1, 137.8, 139.2, 144.7, 144.9, 150.5, 166.4. Anal. Calcd for $C_{22}H_{24}N_4O_3$: C, 67.33; H, 6.16; N, 14.28. Found: C, 67.43; H, 6.27; N, 14.36.

Compounds (**10d-9-1** and **10d-9-2)** were obtained accordingly, starting from **1d** (100 mg, 0.49 mmol). The mixture product was isolated by column chromatography on silica gel (EtOAc : hexane = 1 : 2) to give the pure **10d-9-1** (86 mg, 48%) and **10d-9-2** (32 mg, 18%).

***N-tert*-Butyl-2-[1-(4-fluorophenyl)-4,5-dimethyl-*1H*-pyrazol-3-yl]benzamide (10d-9-1)**

Colorless prisms, mp 102-103 °C (CH_2Cl_2/hexane); IR ($CHCl_3$) 3323, 2961, 1641, 1538 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 9H), 1.88 (s, 3H), 2.28 (s, 3H), 5.83 (br, 1H), 7.12-7.24 (m, 2H), 7.35-7.45 (m, 5H), 7.79 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 8.5, 10.9, 28.4, 51.1, 115.0, 115.9, 116.2, 126.4, 126.5, 128.5, 128.9, 129.8, 130.6, 130.9, 136.8, 137.6, 151.6, 167.8. Anal. Calcd for $C_{22}H_{24}N_3OF$: C, 72.31; H, 6.62; N, 11.50. Found: C, 72.43; H, 6.73; N, 11.66.

***N-tert*-Butyl-2-[2-(4-fluorophenyl)-4,5-dimethyl-*2H*-pyrazol-3-yl]benzamide (10d-9-2)**

Colorless prisms, mp 155-156 ºC (CH_2Cl_2/hexane); IR (KBr) 3414, 2966, 1661, 1516, 1364, 1224 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 9H), 1.91 (s, 3H), 2.31 (s, 3H), 5.35 (br, 1H), 6.86 (t like, *J* = 8.5 Hz, 2H), 7.13-7.24 (m, 3H), 7.59 (m, 2H), 7.78 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 8.2, 11.9, 28.5, 51.3, 115.5, 115.6, 115.7, 125.0, 125.03, 128.4, 129.3, 129.4, 130.3, 131.4, 137.4, 138.9, 148.6, 166.1. Anal. Calcd for $C_{22}H_{24}N_3OF$: C, 72.31; H, 6.62; N, 11.50. Found: C, 72.18; H, 6.58; N, 11.62.

The reaction of **1d** (100 mg, 0.49 mmol) with 2-buynylmagnesium bromide (0.74 mL, 0.74 mmol, 1M solution in Et_2O) at 0 ^oC gave a mixture of the ring-chain tautomers of the hydroxy lactam (**5d**) and ketoamide (**6d**) with a 6 to 1 ratio, which was purified by column chromatography on silica gel to give **5d** (103 mg, 86%) and **6d** (17 mg, 14%).

2-*tert*-Butyl-3-hydroxy-3-prop-2-ynyl-2,3-dihydroisoindol-1-one (5d)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 9H), 1.76 (t, *J* = 2.4 Hz, 1H), 3.18 (dd, *J* = 2.4, 17.3 Hz, 2H), 4.06 (br, 1H, -OH), 7.4 (m, 4H).

2-Buta-2,3-dienoyl-*N*-*tert*-butylbenzamide (6d)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 9H), 5.05 (d, *J* = 6.4 Hz, 2H), 5.70 (br, 1H, -NH), 6.10 (t, *J* = 6.4 Hz, 1H), 7.34-7.53 (m, 4H).

***N*-*tert*-Butyl-2-(2-methylbuta-2,3-dienoyl)benzamide (8)**

To a mixture of *N*-*tert*-butylphthalimide (**1d**) (1.0 g, 4.92 mmol), magnesium flakes (180 mg, 7.38 mmol), and mercury(II) chloride (85 mg, 0.3 mmol) in THF (30 mL) was added slowly a solution of 1-bromo-2-butyne (0.65 ml, 7.38 mmol) in THF (3 mL) under N_2 atmosphere, and then the mixture was vigorously stirred at 0 °C for 2 h. The reaction mixture was quenched with excess water and then extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to afford the crude **8** (1.27 g, 100%) as colorless needles, mp 89-90 °C (CH_2Cl_2/hexane); IR (KBr) 3346, 3061, 2970, 1937, 1659 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 9H), 1.95 (t, *J* = 2.9 Hz, 3H), 4.87 (q, *J* = 2.9 Hz, 2H), 5.71 (br, 1H), 7.29-7.50 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.63, 28.49, 51.87, 78.86, 104.98, 126.83, 127.52, 129.57, 129.73, 136.62, 139.21,167.51, 197.92, 218.10. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.80; H, 7.59, N, 5.38.

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8. Crystal data for **10d-2**: $C_{16}H_{21}N_3O$, M = 271.36, monoclinic, a = 9.0026(2) *Å*, b = 17.7091(5) *Å*, c = 9.9930(3) *Å*, β = 110.503(1)º, V = 1492.24(7) *Å*^{3}, space group $P2_1/a$ (#14), Z = 4, D*calc* = 1.208 g/cm^3, F_{000} = 584.00, μ(MoKα) = 0.77 cm^{-1}.