A new route to 5-chloropyrazole-4-carbaldehydes and their behaviour in the Baylis–Hillman reaction

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5-Chloropyrazole-4-carbaldehydes were efficiently prepared *via* Vilsmeier reaction of 1*H*-pyrazol-5(4*H*)-ones with bis(trichloromethyl) carbonate-DMF instead of the traditional $POCl_3$–DMF system. The Baylis–Hillman reaction of these aldehydes with activated alkenes promoted by various catalysts were investigated. It was found DMAP accelerated the reaction of methyl acrylate or acrylonitrile with the aldehydes, while in the case of but-3-en-2-one, a catalyst mixture of imidazole and L-proline (1:1) was efficient. Overall, the reactivities of the aldehydes were low.

Keywords: 5-chloropyrazole-4-carbaldehyde, Baylis–Hillman reaction, Vilsmeier reaction, bis(trichloromethyl)carbonate

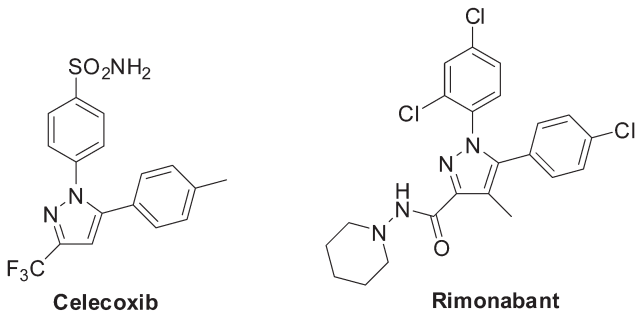
In the last 20 years, the Baylis–Hillman reaction has become a very popular carbon–carbon bond-forming reaction because it provides access to valuable classes of densely functionalised molecules, namely Baylis–Hillman adducts, which are used widely in organic synthesis and pharmaceutical chemistry.[1–3] In our previous work, we reported the efficient preparation of a new type of adduct from ketones[4] or amides[5] *via* a combination of the Vilsmeier and the Baylis–Hillman reactions. Treatment of ketones or amides with bis(trichloromethyl) carbonate [$(Cl_3CO)_2CO$, BTC]–DMF instead of the traditional $POCl_3$–DMF system afforded β-chlorovinylaldehydes or 2-chloro-3-formylquinolines, followed by reaction with activated olefins in the presence of DABCO to produce the novel adducts in satisfactory yields (Scheme 1).

Pyrazoles are important heterocycles in the pharmaceutical and agrochemical industry.[6–8] Drug discovery efforts have led to important pyrazole drugs, such as the COX-2 inhibitor Celecoxib, and the cannabinoid receptor 1 (CB-1) antagonist Rimonabant (Scheme 2).[9]

In continuation of our research on the Vilsmeier and Baylis–Hillman reactions, we wished to construct 5-chloropyrazole-4-carbaldehydes **2** from 1*H*-pyrazol-5(4*H*)-one*s* **1** *via* a Vilsmeier reaction and assess their reactivities in the Baylis–Hillman reaction (Scheme 3).

First, the Vilsmeier reaction of 1*H*-pyrazol-5(4*H*)-ones[10] **1** with BTC–DMF was investigated. When 1-phenyl-3-tolyl-1*H*-pyrazol-5(4*H*)-one **1a** (1.0 equiv.) was mixed with the Vilsmeier reagent generated from BTC (1.0 equiv.) and DMF (3.0 equiv.) in refluxing CH_2Cl_2 for 10 h, the corresponding 5-chloro-1*H*-pyrazole-4-carbaldehyde **2a** was isolated in 33% yield (Table 1, entry 1). In order to improve the yield, the molar ratios of reactants, solvents, temperatures were optimised as shown in Table 1.

It was observed that high boiling point solvents such as toluene, 1,4-dioxane and chlorobenzene could evidently increase the product yield (Table 1, entries 3 and 4). When excess

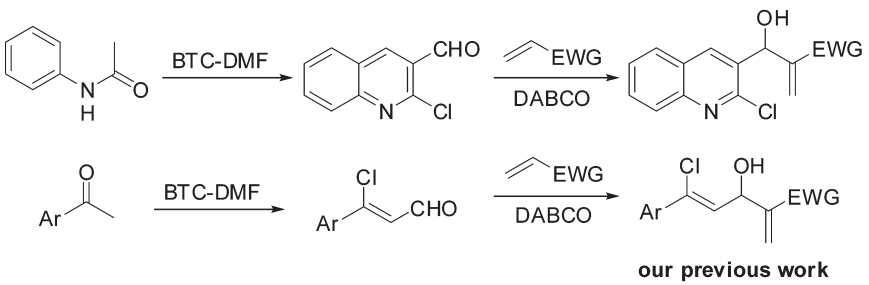


Scheme 2

Vilsmeier reagent (2 equiv. of BTC and 6 equiv. of DMF) was reacted with **1a** in chlorobenzene at 130°C for 6 h, an 85% yield of **2a** was obtained (Table 1, entry 6). Higher ratios of substrate to BTC-DMF (**1a**:BTC:DMF = 1:3:9) did not improve the yield (Table 1, entry 7). With optimal conditions to hand the formylation of several pyrazolones were investigated. The products **2a–f** were obtained in very good yields. (Table 2).

Next, we wished to assess the reactivities of the aldehydes **2** in the Baylis–Hillman reaction. Although dissimilar reactivities between isomeric pyrazolecarbaldehydes were observed in Batra's work,[11] the structure of our compounds are different. It is well known that the classical Baylis–Hillman reaction is efficiently promoted by DABCO in various solvents or under solvent-free conditions at room temperature. However, substrate **2a** revealed a lower reactivity under a variety of conditions. To improve the product yield, various factors including the nature of the catalyst, solvent and temperature were screened. The results are summarised in Table 3.

According to Table 3, it was found that DMAP accelerated the reaction of methyl acrylate or acrylonitrile with substrate **2a**, to give the corresponding product **3a** in 46% yield (Table 3, entry 5), while in the case of but-3-en-2-one, a



Scheme 1

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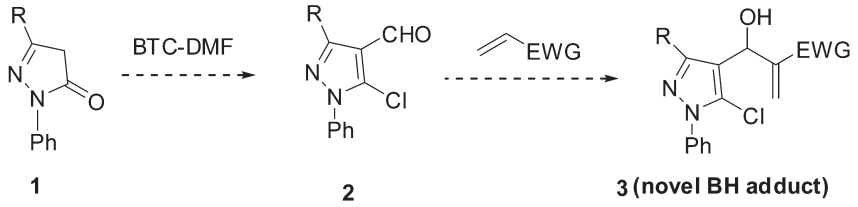
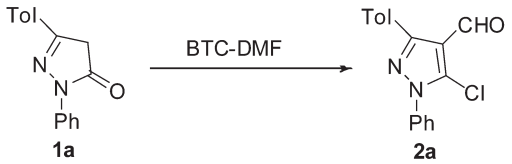


Scheme 3

Table 1 Synthesis of 5-chloro-1-phenyl-3-tolyl-1*H*-pyrazole-4-carbaldehyde **2a** under various conditions[a]



Entry	The molar ratios of pyrazolone:BTC:DMF	Solvents	Temperature /°C	Time/h	Yield[b]/%
1	1:1:3	CH_2Cl_2	40	10	33
2	1:1:3	$ClCH_2CH_2Cl$	80	7	50
3	1:1:3	Toluene	110	5	75
4	1:1:3	Chlorobenzene	130	5	80
5	1:1:3	1,4-Dioxane	100	5	79
6	1:2:6	Chlorobenzene	130	5	85
7	1:3:9	Chlorobenzene	130	4	84

[a] Conditions: **1a** (30 mmol) and solvent (25 mL) were used. [b] Isolated yields based on **1a**.

catalyst mixture of imidazole and L-proline (1:1) was efficient and a 56% yield of pyrazole **3h** was obtained (Table 3, entry 14). When the reaction was carried out with ultrasound irradiation, compound **3a** was formed in moderate yield and in a shorter reaction time, but along with some unknown byproducts (Table 3, entry 9). Meanwhile, a lower reaction temperature did not lead to a better yield (Table 3, entries 10). Although we optimised the reaction conditions in many cases, the product yields were not totally satisfactory and some of the starting materials were also recovered. These results provided further evidence that the proximity of the heteroatom influences the efficiency of the Baylis–Hillman reaction within a heterocyclic system.[11]

In order to assess the scope of this method, the reactivities of several 5-chloropyrazole-4-carbaldehydes **2** towards activated alkenes were investigated as shown in Table 4.

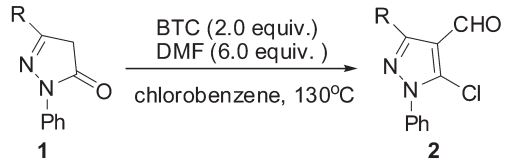
According to Table 4, most of the aldehydes **2** (except for entry 3) gave the corresponding Baylis–Hillman adducts in moderate yields. Nucleophilic displacement of the 5-chloro substituent in **2c** by treatment[12] with imidazole in DMF, in the presence of KOH, proceeded readily and provided **4** in 83% yield (Scheme 4). The Baylis–Hillman reaction of **4** with methyl acrylate gave, after 5 days at room temperature the new adduct **5** in 58% yield together with recovered **4**. It seems the substituent at the 5-position has little effect upon the reactivity of 1*H*-pyrazole-4-carbaldehydes though the reason for this is still unclear.

In summary, a new route to 5-chloropyrazole-4-carbaldehydes and their behaviour in the Baylis–Hillman reaction with activated alkenes, promoted by different catalysts, was investigated, the resulting pyrazole-containing adducts were obtained in moderate yields. Further studies on their applications are now in progress in our laboratory.

Experimental

Melting points were determined on a Büchi B-540 capillary melting point apparatus and uncorrected. IR spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ^1H and ^{13}C spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS, $\delta = 0$) as an internal standard at ambient temperature on a Varian-400 MHz spectrometer at 400 and 100 MHz. Chemical shifts (δ) are expressed

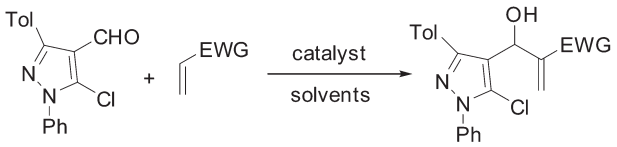
Table 2 The preparation of substituted 5-chloropyrazole-4-carbaldehydes **2** [a]



Entry	R	Time/h	Products	Yield[b]/%
1	4-MeC_6H_4	5	**2a**	85
2	Me	7	**2b**	84
3	Ph	5	**2c**	83
4	4-FC_6H_4	5	**2d**	86
5	2-ClC_6H_4	4	**2e**	57
6	2-$MeOC_6H_4$	4	**2f**	68

[a] Conditions: **1** (40 mmol), BTC (80.0 mmol), DMF (240.0 mmol) and chlorobenzene (30 mL) were used.
[b] Isolated yields based on **1**.

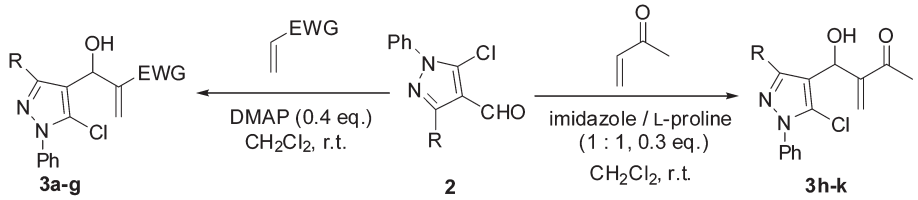
Table 3 Synthesis of novel Baylis–Hillman adducts **3a** under various conditions[a]



Entry	EWG	Catalyst	Solvents	Temp./°C	Time/days	Isolated yield[b]/%	
						Product (**3**)	Starting (**2**)
1	CO_2Me	DABCO	CH_2Cl_2	r.t.	30	**3a**/ trace	80
2	CO_2Me	Quinine	CH_2Cl_2	r.t.	30	**3a**/ trace	82
3	CO_2Me	TMEDA	CH_2Cl_2	r.t.	12	**3a/** 15	65
4	CO_2Me	Imidazole+L-Proline (1:1)	CH_2Cl_2	r.t.	7	**3a/** 17	62
5	CO_2Me	DMAP	CH_2Cl_2	r.t.	5	**3a/** 46	38
6	CO_2Me	DABCO+$LiClO_4$ (1:1)	CH_2Cl_2	r.t.	5	**3a/** 20	57
7	CO_2Me	DABCO+$Yb(OTf)_3$ (1:1)	CH_2Cl_2	r.t.	5	**3a/** 22	59
8	CO_2Me	DBU	Solvent-free	r.t.	30	**3a/** trace	81
9	CO_2Me	DMAP	CH_2Cl_2	Ultrasound (30 °C)	5	**3a/** 43	21
10	CO_2Me	DMAP	CH_2Cl_2	4 °C	5	**3a/** 45	37
11	CO_2Me	DMAP	DMF	r.t.	6	**3a/** 43	35
12	CO_2Me	DMAP	THF	r.t.	7	**3a/** 44	40
13	COMe	DMAP	CH_2Cl_2	r.t.	10	**3h/** 28	55
14	COMe	Imidazole+L-proline[c] (1:1)	CH_2Cl_2	r.t.	4	**3h/** 56	23

[a] Conditions: **2a** (1 mmol), activated olefins (3 mmol), catalysts (0.4 mmol) and solvents (1 mL) or solvent-free were used.
[b] Isolated yields based on **2a**.
[c] Imidazole and L-Proline (0.3 mmol, 1:1) were used.

Table 4 The preparation of pyrazole-containing Baylis–Hillman adducts **3** [a]



Entry	R	EWG	Method	Time/days	Isolated yield[b]/%	
					Product (**3**)	Starting (**2**)
1	4-MeC_6H_4	CO_2Me	**A**	5	**3a /** 46	38
2	4-MeC_6H_4	CN	**A**	4	**3b/** 52	30
3	4-MeC_6H_4	CO_2Et	**A**	30	**–/** NR	90
4	Me	CO_2Me	**A**	10	**3c/** 43	42
5	2-ClC_6H_4	CO_2Me	**A**	5	**3d/** 49	35
6	Ph	CO_2Me	**A**	6	**3e/** 46	38
7	2-$MeOC_6H_4$	CO_2Me	**A**	4	**3f/** 52	31
8	Ph	CN	**A**	5	**3g/** 50	34
9	4-MeC_6H_4	COMe	**B**	4	**3h/** 56	23
10	Ph	COMe	**B**	5	**3i/** 53	30
11	4-FC_6H_4	COMe	**B**	6	**3j/** 55	31
12	2-ClC_6H_4	COMe	**B**	4	**3k/** 56	30

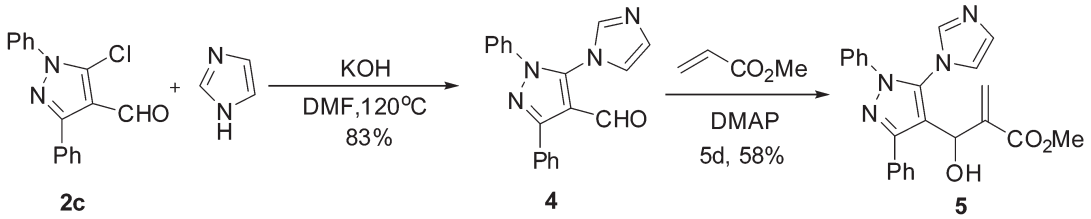
[a] Method A: **2** (1 mmol), activated olefins (3 mmol), DMAP (0.4 mmol) and dichloromethane (1 mL) were used; method B: **2** (1 mmol), but-3-en-2-one (3 mmol), imidazole and L-proline (0.3 mmol, 1:1), dichloromethane (1 mL) were used.
[b] Isolated yield based on **2**. NR = No reaction.

in ppm and coupling constants *J* are given in Hz. Mass spectra were obtained on a Trace DSQ mass spectrometer. High resolution mass spectra were recorded using an Agilent 6210 TOF mass spectrometer.

*General procedure for synthesis of 5-chloro-1*H*-pyrazole-4-carbaldehydes* (**2a–f**): A mechanically stirred solution of BTC (23.76 g, 80.0 mmol) in chlorobenzene (30 mL) was cooled in an ice bath while DMF (17.52 g, 240.0 mmol) was added dropwise over a period of 30 min. After stirring at room temperature for 1 h, 1*H*-pyrazol-5(4*H*)-one (**1**, 40 mmol) was added and the mixture was then stirred at 130 °C for the time given in Table 2 and then poured in saturated sodium bicarbonate solution and filtrated. The crude solid was recrystallised from petroleum ether-ethyl acetate, 8:1 to give **2a–f**.

*5-Chloro-1-phenyl-3-p-tolyl-1*H*-pyrazole-4-carbaldehyde* (**2a**): White solid; m.p. 93.7–95.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (3H, s, C*H*$_3$), 7.29 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.50–7.57 (3H, m, Ar*H*), 7.63 (2H, dd, *J* = 6.8, 7.6 Hz, Ar*H*), 7.72 (2H, d, *J* = 8.0 Hz, Ar*H*), 10.06 (1H, s, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 116.3, 125.4(2C), 127.8, 128.8(2C), 129.3(2C), 129.4(3C), 133.1, 137.0, 139.6, 154.3, 184.0; IR (KBr): 2729, 1683, 1503 cm^{-1}. MS (EI) *m/z* 298 (^{37}Cl-M$^+$, 35), 296 (^{35}Cl-M$^+$, 100), 281 (50); HRMS (EI) *m/z* Calcd for $C_{17}H_{13}{}^{35}ClN_2O$: 296.0176. Found: 296.0182.

*5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde* (**2b**): Yellow solid; m.p. 146.2–147.1 °C (lit.[13] 146.0–147.0 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (3H, s, C*H*$_3$), 7.48–7.57 (5H, m, Ar*H*), 9.99 (1H, s, C*H*O).



Scheme 4

*5-Chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde* (**2c**): Yellow solid; m.p. 107.0–108.5 °C (lit.[14], 104.0–110.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.57 (6H, m, Ar*H*), 7.64 (2H, m, Ar*H*), 7.83 (2H, m, Ar*H*), 10.07 (1H, s, C*H*O).

*5-Chloro-3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde* (**2d**): Yellow solid; m.p. 117.5–118.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.19 (2H, m, Ar*H*), 7.50–7.59 (3H, m, Ar*H*), 7.61–7.64 (2H, m, Ar*H*), 7.86–7.91 (2H, m, Ar*H*), 10.05 (1H, s, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.4, 115.6(2C), 125.4(2C), 126.9, 129.3, 129.5(2C), 130.8(2C), 130.9, 136.8, 152.8, 163.6($J_{C\text{-}F}$ = 247 Hz), 183.5; IR (KBr): 2782, 1683, 1503, 1454 cm^{-1}. MS (EI) *m/z* 302 (^{37}Cl-M$^+$, 30), 300 (^{35}Cl-M$^+$, 100), 299 (80); HRMS (ESI) *m/z* Calcd for $C_{16}H_{10}{}^{35}ClFN_2O$: 300.0466. Found: 301.0523 [M+H]$^+$.

*5-Chloro-3-(2-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde* (**2e**): Yellow solid; m.p. 105.7–106.9°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.44 (2H, m, Ar*H*), 7.46–7.56 (5H, m, Ar*H*), 7.64 (2H, d, *J* = 7.6 Hz, Ar*H*), 10.05 (1H, s, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ117.6, 125.3(2C), 126.9, 129.3, 129.4(2C), 129.9, 130.2, 130.8, 131.4, 131.8, 133.8, 136.8, 152.0, 183.5; IR (KBr): 2775, 1679, 1540, 1478 cm^{-1}; MS (NCI) 316(^{35}Cl-M$^+$, 16), 315(55), 279 (100); HRMS (ESI) *m/z* Calcd for $C_{16}H_{10}{}^{35}Cl_2N_2O$: 316.0170. Found: 317.0254 [M+H]$^+$.

*5-Chloro-3-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde* (**2f**): Yellow solid; m.p. 113.3–115.1 °C. ^{1}H NMR(400 MHz, $CDCl_3$): δ 3.84 (1H, s, OCH_3), 7.01–7.10 (2H, m, Ar*H*), 7.44–7.55 (5H, m, Ar*H*), 7.64 (2H, d, *J* = 7.6 Hz, Ar*H*), 9.82 (1H, s, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 111.0, 117.4, 119.9, 121.0, 125.4(3C), 129.2(3C), 131.0, 131.2, 137.0, 151.9, 157.0, 184.9; IR (KBr): 2843, 1684, 1522, 1498 cm^{-1}; MS (EI) 315 (^{37}Cl-M$^+$, 33), 313 (^{35}Cl-M$^+$, 100).; HRMS (ESI) *m/z* Calcd for $C_{17}H_{13}{}^{35}ClN_2O_2$: 312.0666. Found: 313.0738 [M+H]$^+$.

Preparation of Baylis–Hillman adducts **3a–k** *and* **5**

A mixture of **2** (4.0 mmol), methyl acrylate or but-3-en-2-one, (12.0 mmol), DMAP (1.6 mmol) or imidazole and L-proline (1.2 mmol, 1:1) and dichloromethane (2 mL) was kept at room temperature for the given time in Table 4. The reaction was monitored by TLC. After completion, the reaction was quenched with saturated brine and extracted with ethyl acetate (3 × 10 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 6:1) to give **3a–k** and **5**.

*Methyl 2-[(5-chloro-1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl)(hydroxy)methyl]acrylate* (**3a**): Yellow solid; m.p. 120.1–121.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 5.84–5.86 (2H, m, =CH_2), 6.36 (1H, s, C*H*OH), 7.22 (2H, d, *J* = 7.6 Hz, Ar*H*), 7.40–7.44 (1H, m, Ar*H*), 7.48–7.52 (2H, m, Ar*H*), 7.58–7.63 (4H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 52.1, 65.2, 115.5, 117.4, 125.3(2C), 126.7, 128.4, 128.6(2C), 129.0(2C), 129.1(2C), 129.6, 138.1, 138.3, 139.2, 152.1, 166.8; IR (KBr): 3440, 2950, 2913, 1717, 1628 cm^{-1}; MS (ESI) 385 (^{37}Cl-M$^+$, 33), 383 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{21}H_{19}{}^{35}ClN_2O_3$: 382.1084. Found: 383.1156 [M+H]$^+$.

*2-[(5-Chloro-1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl)(hydroxy)methyl] acrylonitrile* (**3b**): Yellow solid; m.p. 61.4–62.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (3H, s, CH_3), 2.90 (1H, t, *J* = 6.4, O*H*), 5.43 (1H, t, *J* = 1.8 Hz, C*H*OH), 6.00 (1H, d, *J* = 1.6 Hz, =CH_2), 6.08 (1H, d, *J* = 1.6 Hz, =CH_2), 7.20 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.41–7.58 (7H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 65.2, 114.4, 116.9, 125.3(2C), 123.5, 127.2, 128.7(4C), 129.0(2C), 129.1(2C), 130.4, 137.7, 138.8, 152.2; IR (KBr): 3445, 2239, 1622, 1499 cm^{-1}. MS (ESI) 352 (^{37}Cl-M$^+$, 31), 350 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{20}H_{16}{}^{35}ClN_3O$: 349.0982. Found: 350.1051 [M+H]$^+$.

*Methyl 2-[(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(hydroxy) methyl]acrylate* (**3c**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 5.67 (1H, s, C*H*OH), 5.95 (1H, s, =CH_2), 6.40 (1H, s, =CH_2), 7.38–7.40 (1H, m, Ar*H*), 7.44–7.52 (4H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 51.9, 64.8, 116.2, 124.9(2C), 125.5, 126.0, 128.1, 128.9(2C), 138.1, 139.7, 148.8, 166.6; IR (KBr): 3428, 2916, 2835, 1693, 1544, 1421 cm^{-1}; MS (ESI) 309 (^{37}Cl-M$^+$, 34), 307 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{15}H_{15}{}^{35}ClN_2O_3$: 306.0771. Found: 307.0872 [M+H]$^+$.

*Methyl 2-[(5-chloro-3-(2-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl) (hydroxy)methyl] acrylate* (**3d**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (3H, s, OCH_3), 5.59 (1H, t, *J* = 1.6 Hz, =CH_2), 5.82–5.83 (1H, m, =CH_2), 6.23 (1H, d, *J* = 1.2 Hz, C*H*OH), 7.29–7.37 (2H, m, Ar*H*), 7.41–7.51 (5H, m, Ar*H*), 7.62–7.65 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 65.2, 117.9, 125.5(2C), 126.3, 126.8, 126.9, 128.8, 129.3(2C), 129.7, 130.5, 132.2, 132.8, 134.4, 138.2, 139.0, 149.8, 166.6; IR (KBr): 3399, 2946, 2924, 2848, 1721, 1499 cm^{-1}; MS (ESI) 405 (^{37,35}Cl-M$^+$, 62), 403 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{20}H_{16}{}^{35}Cl_2N_2O_3$:402.0538. Found: 403.0635 [M+H]$^+$.

*Methyl 2-[(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)(hydroxy)methyl] acrylate* (**3e**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (3H, s, OCH_3), 5.84–5.86 (2H,m, =CH_2), 6.35 (1H, s, C*H*OH), 7.37–7.44 (4H, m, Ar*H*), 7.48–7.52 (2H, m, Ar*H*), 7.61–7.63 (2H, m, Ar*H*), 7.69–7.72 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0, 65.0, 115.7, 125.3(2C), 126.7, 127.0, 128.3(3C), 128.5(2C), 128.8(2C), 129.0, 132.5, 138.0, 139.1, 152.0, 166.7; IR (KBr): 3382, 1716, 1596, 1500 cm^{-1}; MS (ESI) 371 (^{37}Cl-M$^+$, 33), 369 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{20}H_{17}{}^{35}ClN_2O_3$: 368.0928. Found: 369.1016 [M+H]$^+$.

*Methyl 2-[(5-chloro-3-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)(hydroxy)methyl] acrylate* (**3f**): Yellow solid; m.p. 129.4–130.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (3H, s, CO_2CH_3), 3.83 (3H, s, OCH_3), 5.57 (1H, d, *J* = 1.6 Hz, C*H*OH), 5.80 (1H, t, *J* = 1.6 Hz, =CH_2), 6.13 (1H, t, *J* = 1.6 Hz, =CH_2), 6.95 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.01–7.05 (1H, m, Ar*H*), 7.32 (2H, dd, *J* = 6.0, 7.6 Hz, Ar*H*), 7.36–7.42 (2H, m, Ar*H*), 7.46–7.50 (2H, m, Ar*H*), 7.63–7.65 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 55.8, 64.6, 111.0, 118.2, 121.4, 122.2, 124.7, 125.1(2C), 126.4, 128.2, 128.9(2C), 130.4, 131.6, 138.1, 139.4, 148.5, 156.7, 166.2; IR (KBr): 3428, 1715, 1680, 1491, 1326 cm^{-1}; MS (APCI) 401 (^{37}Cl-M$^+$, 33), 399 (^{35}Cl-M$^+$, 100); HRMS (APCI) *m/z* Calcd for $C_{21}H_{19}{}^{35}ClN_2O_4$: 398.1033. Found: 399.1131 [M+H]$^+$.

*2-[(5-Chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)(hydroxy)methyl]acryl onitrile* (**3g**): Yellow solid; m.p. 85.8–87.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (1H, s, O*H*), 5.35 (1H, s, C*H*OH), 5.92 (1H, d, *J* = 2.0 Hz, =CH_2), 6.01 (1H, d, *J* = 2.0 Hz, =CH_2), 7.36–7.48 (6H, m, Ar*H*), 7.53–7.56 (2H, m, Ar*H*), 7.61–7.64 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.8, 114.6, 116.9, 123.3, 125.2(2C), 127.4, 128.3(2C), 128.6, 128.7, 128.8(2C), 129.0(2C), 130.4, 131.6, 137.5, 152.1; IR (KBr): 3396, 2222, 1530, 1452, 1360 cm^{-1}; MS (ESI) 338 (^{37}Cl-M$^+$, 30), 336 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{19}H_{14}{}^{35}ClN_3O$: 335.0825. Found:336.0905 [M+H]$^+$.

*3-[(5-Chloro-1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl)(hydroxy)methyl] but-3-en-2-one* (**3h**): Yellow solid; m.p. 68.5–70.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s, COCH_3), 2.38 (3H, s, CH_3), 5.89 (1H, s, C*H*OH), 6.03 (1H, s, =CH_2), 6.19 (1H, s, =CH_2), 7.20 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.43 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.49 (2H, t, *J* = 8.0 Hz, Ar*H*), 7.60 (4H, t, *J* = 8.0 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 26.5, 64.8, 115.8, 125.3(2C), 126.9, 127.3, 128.4, 128.7(2C), 129.0(4C), 129.6, 138.1, 138.3, 147.0, 152.0, 200.5; IR (KBr): 3420, 2247, 1675, 1499 cm^{-1}; MS (ESI) 369 (^{37}Cl-M$^+$, 33), 367 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{21}H_{19}{}^{35}ClN_2O_2$: 366.1135. Found: 367.1225 [M+H]$^+$.

*3-[(5-Chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)(hydroxy)methyl]but-3-en-2-one* (**3i**): Yellow solid; m.p. 113.5–115.7 °C. ^{1}H NMR (400

MHz, $CDCl_3$): δ 2.32 (3H, s, C*H*$_3$), 5.89 (1H, s, C*H*OH), 6.03 (1H, s, =C*H*$_2$), 6.18 (1H, s, =C*H*$_2$), 7.37–7.52 (6H, m, Ar*H*), 7.62 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.71 (2H, t, *J* = 2.0 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 64.8, 115.9, 125.3(2C), 127.0, 127.3, 128.3(3C), 128.4(2C), 128.9(2C), 129.0, 132.5, 138.0, 147.0, 152.0, 200.4; IR (KBr): 3410, 2925, 2357, 1685 cm^{-1}; MS (ESI) 355 (^{37}Cl-M$^+$, 38), 353 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{20}H_{17}{}^{35}ClN_2O_2$: 352.0979. Found: 353.1173 [M+H]$^+$.

*3-[(5-Chloro-3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)(hydroxy) methyl]but-3-en-2-one* (**3j**): Yellow solid; m.p. 60.3–61.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (3H, s, C*H*$_3$), 3.28 (1H, s, O*H*), 5.84 (1H, s, C*H*OH), 6.02 (1H, d, *J* = 1.2 Hz, =C*H*$_2$), 6.16 (1H, s, =C*H*$_2$), 7.08 (2H, t, *J* = 8.8 Hz, Ar*H*), 7.41–7.51 (3H, m, Ar*H*), 7.59 (2H, t, *J* = 6.0 Hz, Ar*H*),7.71–7.75 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 64.5, 115.0(2C), 115.3(2C), 125.2(2C), 127.1, 128.5, 128.7(2C), 129.0, 130.7, 130.8, 137.9, 146.9, 151.0, 162.9 ($J_{C\text{-}F}$ = 245 Hz, 1C), 200.2; IR (KBr): 3440, 3007, 1676, 1499 cm^{-1}; MS (ESI) 373 (^{37}Cl-M$^+$, 37), 371 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{20}H_{16}{}^{35}ClFN_2O_2$: 370.0884. Found: 371.0975 [M+H]$^+$.

3-[(5-Chloro-3-(2-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)(hydroxy) methyl]but-3-en-2-one (**3k**): White solid; m.p. 106.8–108.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (3H, s, C*H*$_3$), 5.61 (1H, t, *J* = 1.6 Hz, C*H*OH), 6.04 (2H, d, *J* = 7.6 Hz, =C*H*$_2$), 7.31–7.36 (2H, m, Ar*H*), 7.42–7.51 (5H, m, Ar*H*), 7.64 (2H, m, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1l, 64.5, 117.9, 125.1(2C), 126.5, 126.5, 128.4, 128.9, 129.2(3C), 130.1, 132.0, 132.7, 134.2, 137.9, 146.6, 149.3, 199.4; IR (KBr): 3415, 1666, 1441, 1365 cm^{-1}; MS (ESI) 389 (^{37,35}Cl-M$^+$, 66), 387 (^{35}Cl-M$^+$, 100); HRMS (ESI) *m/z* Calcd for $C_{20}H_{16}{}^{35}Cl_2N_2O_2$: 386.0589. Found: 387.0657 [M+H]$^+$.

*5-(1*H*-Imidazol-1-yl)-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde* (**4**): A mixture of **2c** (2.8 g, 10 mmol), imidazole (2.0 g, 30 mmol) and KOH (0.84 g, 15 mmol) in DMF (5 mL) was stirred at 120°C for 4 h. The reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed successively with brine and water, dried over Na_2SO_4, and then evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 3:1) to give 83% yield of **4** (2.62 g).

*5-(1*H*-Imidazol-1-yl)-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde* (**4**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.17–7.25 (3H, m, Ar*H*), 7.33 (2H, d, *J* = 7.6 Hz, Ar*H*), 7.40–7.43 (3H, m, Ar*H*), 7.65 (1H, s, =C*H*), 7.75–7.80 (2H, m, C*H*=C*H*), 9.95 (1H, s, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.3, 121.5, 124.6(2C), 128.0, 128.5(2C), 129.1(4C), 130.3, 137.2, 158.7, 189.4; IR (KBr): 2793, 1725, 1492 cm^{-1}; MS (ESI) 315 [M+1]$^+$; HRMS (ESI) *m/z* Calcd for $C_{19}H_{14}N_4O$: 314.1168. Found: 315.1239 [M+H]$^+$.

*Methyl 2-[(5-(1*H*-imidazol-1-yl)-1,3-diphenyl-1*H*-pyrazol-4-yl) (hydroxy)methyl]acrylate* (**5**): White solid; m.p. 165.8–166.5 °C. ^{1}H NMR(400 MHz, $CDCl_3$): δ 3.62 (3H, s, OC*H*$_3$), 5.66 (2H, t, *J* = 4.0 Hz, C*H*OH), 5.77 (1H, d, *J* = 1.6 Hz, =C*H*$_2$), 6.05 (1H, d, *J* = 1.6 Hz, =CH2), 7.03–7.17 (m, 3H, Ar*H*), 7.28–7.41 (m, 6H, Ar*H*), 7.57 (1H, s, =C*H*), 7.81–7.83 (2H, m, C*H*=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 64.0, 117.5, 121.4, 122.9(2C), 125.3, 126.6(3C), 129.4(4C), 129.5, 130.3, 132.6, 137.4, 138.6, 138.8, 149.1(2C), 165.9; IR (KBr): 3540, 1692 1457, 1326 cm^{-1}; MS (ESI) 401 [M+1]$^+$; HRMS (ESI) *m/z* Calcd for $C_{23}H_{20}N_4O_3$: 400.1535. Found: 401.1603 [M+H]$^+$.

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