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# Facile synthesis of novel α-methylene-pyrazole-carboxylate substituted imines and *trans*-β-lactams: Versatile synthons for diverse heterocyclic molecules

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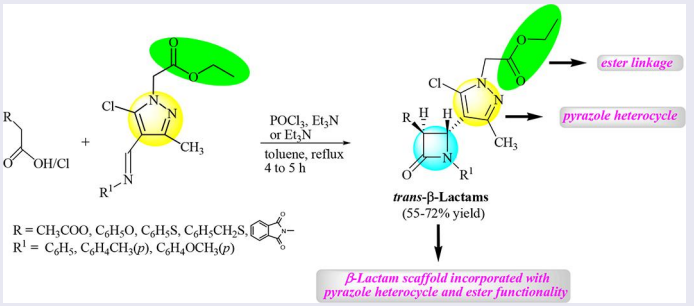
**ABSTRACT**

A simple, facile, and high yielding stereoselective approach for the integration of α-methylene-pyrazole-carboxylates at the β-lactam nucleus is described. These monocyclic β-lactams have been synthesized by treatment of 2-phenoxy/benzylthio/phenylthio ethanoic acids or acetoxyacetyl chloride/phthalimidoacetyl chloride **5a–e** with novel α-methylene-pyrazole-carboxylate imines **4a–c** using $Et_3N$ and $POCl_3$ in refluxing toluene. All of the newly synthesized α-methylene-pyrazole carboxylate imines **4a–c** and their β-lactam derivatives **6a–h** have been fully characterized by spectroscopic techniques such as FTIR, NMR ($^1H$, $^{13}C$, and $^{13}C$ DEPT-135), 2D-NMR (COSY and HSQC), and elemental analyses (CHN). The cycloaddition reaction was found to be highly stereoselective leading to the exclusive formation of *trans*-β-lactams **6a–h** and *trans* configuration was assigned with respect to coupling constant values of C3-H and C4-H. The novel β-lactams **6a–h** bearing α-methylene-pyrazole-carboxylate ring system will serve as useful synthons for highly functionalized acids, acetohydrazides/pyrazolones, alcohols, pyrazole carboxamides, peptides, and promising biologically active agents.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
β-Lactams; cycloaddition; heterocyclic β-lactams; imines; pyrazole-ester; stereoselective

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Color versions of one or more figures in this article can be found online at www.tandfonline.com/lsyc.
Supplemental data (full experimental details, their spectral data (**4a–c** and **6a–h**) and copies of $^1H$ NMR, $^{13}C$ NMR, $^{13}C$ DEPT-135, $^1H$-$^1H$ COSY, and $^1H$-$^{13}C$ COSY of representatives) can be accessed on the publisher's website.

## Introduction

Pyrazoles are well-known aromatic heterocycles that exhibit innumerable pharmacological and physiological properties.[1–3] Pyrazole-carboxylates and their derivatives show significant applications in the area of microbicides, agrochemicals, herbicides,[4–6] acts as important intermediates for the synthesis of protectants and plant growth regulators.[7] Pyrazolone-ester **(I)** demonstrates anticonvulsant effects against clonic seizures,[8] pyrazole ester **(II)** inhibits phosphodiesterase,[9] 1*H*-pyrazole carboxylate **(III)** exhibits antimicrobial effects,[10] and pyrazole-3-carboxylate **(IV)** functions as cyclooxygenase-2 inhibitor[11] (Fig. 1). Molecules **(IV–V)** have also been utilized as effective synthons for the further synthesis of acid/hydrazide[11] and carboxamide/carboxylate derivative,[12] respectively (Fig. 1).

β-Lactam heterocyclic compounds are the integral part of numerous antibiotics including monobactams, penicillins, penams, carbapenems, and cephems.[13,14] The monocyclic β-lactams and their hetero-substituted conjugates also applied for the synthesis of many classes of compounds which include taxol derivatives, alkaloids and amino acids.[15–17] Arumugam et al.[18] reported the synthesis of pyrroloisoquinoline/indolizinoindole anchored β-lactams through pictet-spengler cyclization of ester substituted β-lactams **(VI)**. Indole- and alkenyl-carboxylate substituted β-lactams **(VII)** and **(VIII)** further transformed into their acetohydrazide/pyrazolone[19] and spiropyrrolidine/pyrrolizidine[20] grafted β-lactams, respectively (Fig. 1). Moreover, stereoselective synthesis of novel β-lactams is still the area of interest among organic chemists.[21]

Based on the above literature reports and in continuation of our ongoing research on heterocyclic substituted β-lactams and their precursors,[22] it was envisaged to accommodate β-lactam ring system and pyrazole-ester moiety in a single molecular frame work as a novel core structure which will be the versatile synthons for diverse heterocyclic molecules.

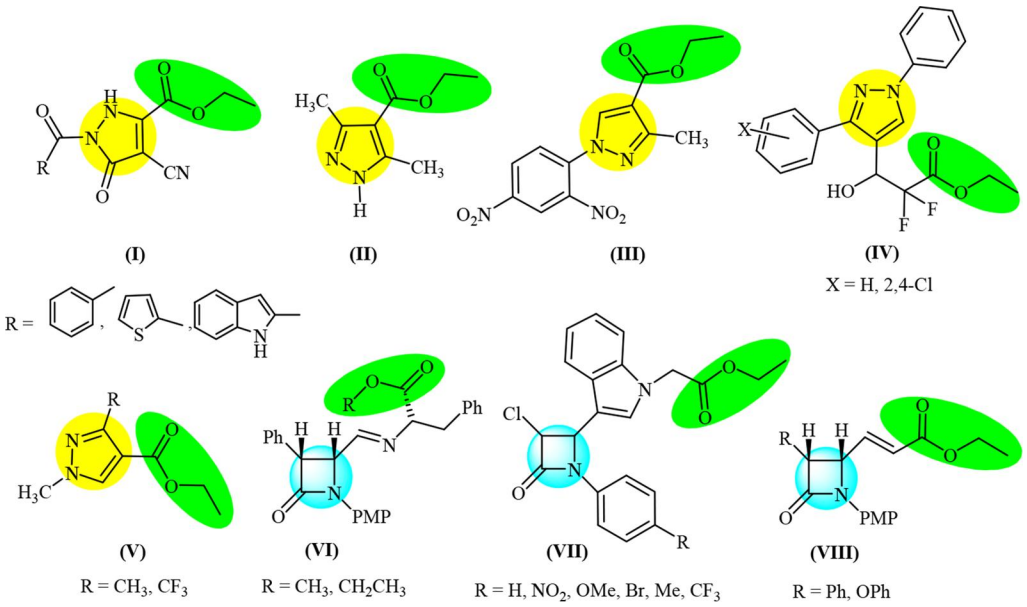



**Figure 1.** Structures of pyrazoles (**I–V**) and β-lactams (**VI–VIII**) linked with ester group.

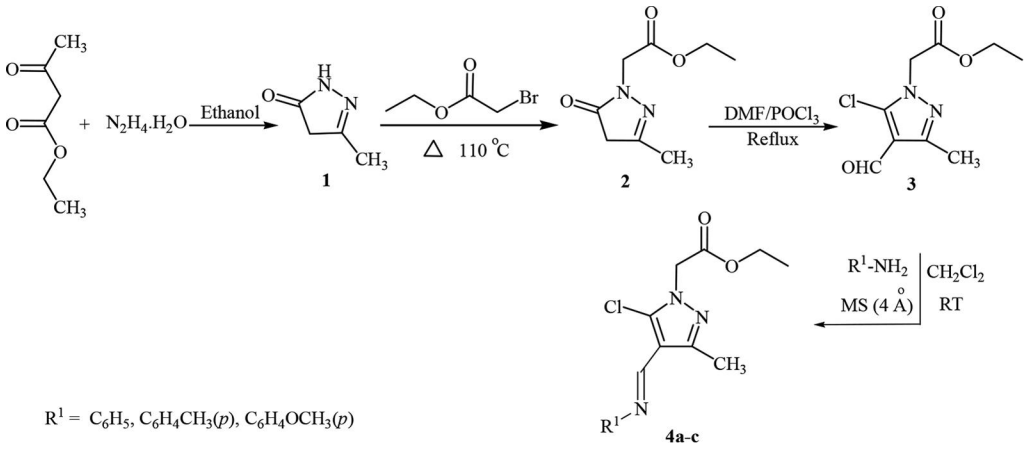
## Results and discussion

To prepare pyrazole-carboxylate aldehyde **3** as a starting substrate, pyrazolone **1** was initially prepared by the condensation of hydrazine hydrate with ethyl acetoacetate in absolute ethanol. Pyrazolone **1** on heating with ethyl bromoacetate affords ethyl-1-pyrazolacetate **2**. This when subjected to Vilsmeier–Haack reaction provides desired pyrazole-carboxylate aldehyde **3** (Scheme 1).[23]

The novel α-methylene-pyrazole-carboxylate substituted imines **4a–c** were prepared by condensation of appropriate primary amines and α-methylene-pyrazole-carboxylate aldehyde **3** using molecular sieves (4 Å) in dichloromethane at room temperature (Scheme 1, Table 1). The structure of α-methylene-pyrazole-carboxylate substituted imines **4a–c** were confirmed on the basis of spectroscopic techniques viz., FTIR, NMR ($^{1}$H, $^{13}$C), and CHN elemental analysis.

Further, a series of novel *trans*-3-oxy/thio/phthalimido-4-pyrazole-carboxylate-β-lactams **6a–h** were synthesized by reacting α-methylene-pyrazole-carboxylate substituted imines **4a–c** with 2-substituted ethanoic acids or acid chlorides **5a–e** (Scheme 2).

Initial studies were performed through annealation of ethyl 2-(5-chloro-3-methyl-4-((phenylimino)methyl)-1*H*-pyrazol-1-yl) acetate **4a** with ketenes, generated in situ from acetoxyacetyl chloride **5a** in dry $CH_2Cl_2$ at 0 °C, using triethylamine as a base and phosphorus oxychloride as a condensing agent. However, the reaction did not afford the anticipated product. Then the reaction was performed at higher temperature in refluxing toluene under nitrogen atmosphere and the progress of the reaction was monitored by thin-layer chromatography (TLC) (Scheme 2, Table 2, entry 1).

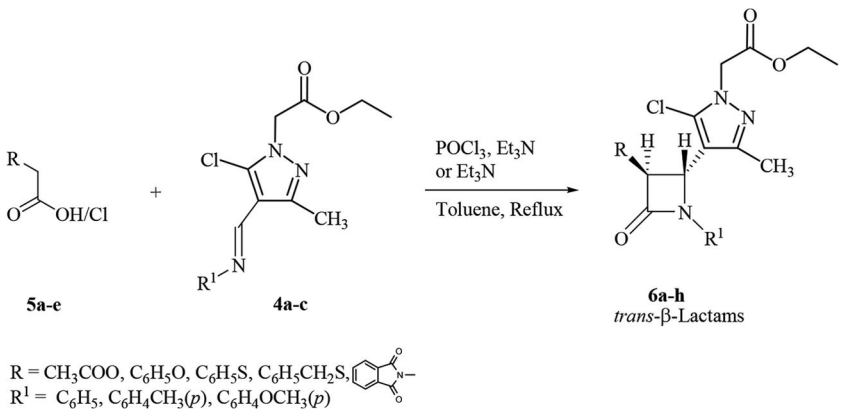



**Scheme 1.** Preparation of α-methylene-pyrazole-carboxylate substituted imines **4a–c**.

**Table 1.** Synthesis of α-methylene-pyrazole-carboxylate substituted imines **4a–c**.

| Entry | $R^1$ | Schiff's base 4 | Yield[a] (%) |
|---|---|---|---|
| 1 | $-C_6H_5$ | **4a** | 85 |
| 2 | $-C_6H_4CH_3(p)$ | **4b** | 79 |
| 3 | $-C_6H_4OCH_3(p)$ | **4c** | 80 |

[a]Yield of pure isolated product with correct analytical and spectral data.

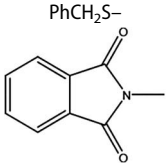



**Scheme 2.** Synthetic route for *trans*-4-α-methylene-pyrazole-carboxylate β-lactam derivatives **6a–h**.

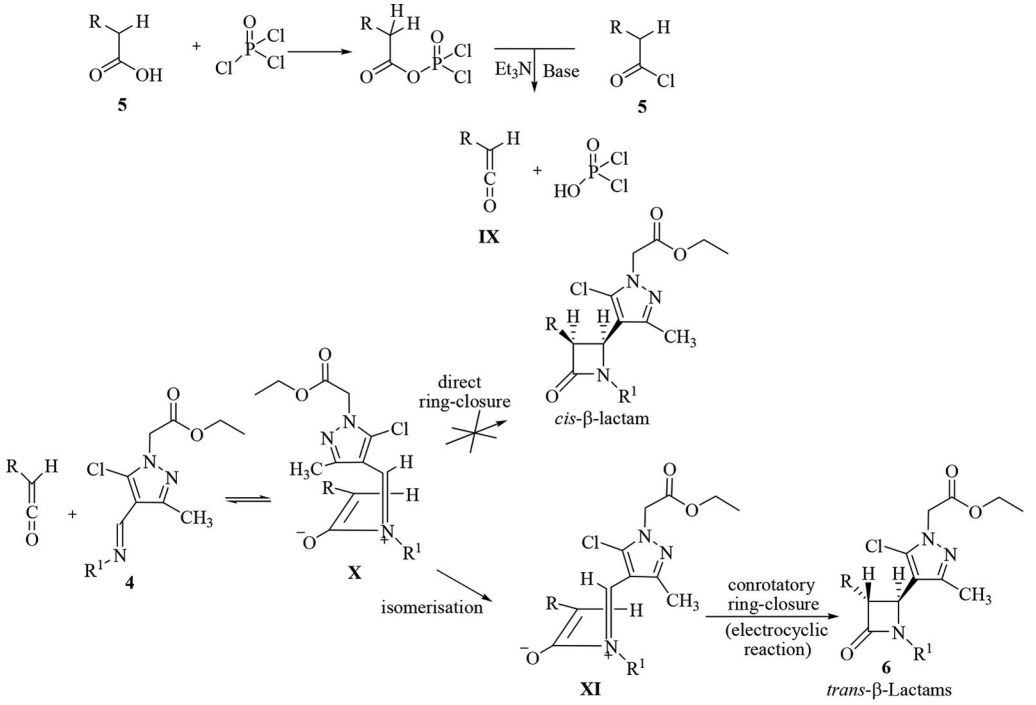
After completion of the reaction, solvent was evaporated under vacuum and crude product was purified by silica gel column chromatography using 10% EtOAc/hexane as eluant. The product was identified as *trans*-ethyl-2-(4-(1-phenyl-3-acetoxy-4-oxo-azetidin-2-yl)-5-chloro-3-methyl-1*H*-pyrazol-1-yl)acetate **6a** on the basis of various spectroscopic techniques viz., FTIR, $^{1}$H NMR, $^{13}$C NMR, and elemental analysis. The reaction was found to be highly stereoselective and it resulted in the exclusive formation of only *trans*-β-lactam **6a** in excellent yield.

Further, the protocol was extended to synthesize other 4-α-methylene-pyrazole-carboxylate β-lactam derivatives **6b–h** by altering R and $R^1$ substituents (R=$CH_3COO$, $C_6H_5O$, $C_6H_5S$, $C_6H_5CH_2S$, phthamlimido; $R^1 = C_6H_5$, $(p)CH_3OC_6H_4$, $(p)CH_3C_6H_4$) (Table 2, entries 2–8). The highly pure novel *trans* monocyclic β-lactams **6b–h** were isolated by workup of the reaction, purified by silica gel column chromatography using 10% EtOAc/hexane followed by crystallization in dichloromethane-hexane (1:3). The structures of all these *trans*-4-α-methylene-pyrazole-carboxylate β-lactams **6a–h** were established on the basis of various spectroscopic techniques viz., FTIR, NMR ($^{1}$H and $^{13}$C), $^{13}$C DEPT-135, $^{1}$H-$^{1}$H COSY, and $^{1}$H-$^{13}$C COSY in representative cases and their elemental analysis. The $^{1}$H NMR spectra of **6a–h** exhibited two doublets for vicinal methine protons between δ = 4.05–5.64 ppm ($J$ = 1.8–2.7 Hz; C3-H and C4-H) which confirms the formation

**Table 2.** *trans*-4-α-Methylene-pyrazole-carboxylate β-lactams **6a–h**.

| Entry | R | $R^1$ | *trans*-β-Lactams 6 | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $CH_3COO$– | $-C_6H_5$ | **6a** | 60 |
| 2 | $CH_3COO$– | $-C_6H_4OCH_3(p)$ | **6b** | 64 |
| 3 | PhO– | $-C_6H_4OCH_3(p)$ | **6c** | 70 |
| 4 | PhS– | $-C_6H_5$ | **6d** | 58 |
| 5 | PhS– | $-C_6H_4OCH_3(p)$ | **6e** | 72 |
| 6 | PhS– | $-C_6H_4CH_3(p)$ | **6f** | 69 |
| 7 | $PhCH_2S$– | $-C_6H_4OCH_3(p)$ | **6g** | 62 |
| 8 |  | $-C_6H_4OCH_3(p)$ | **6h** | 55 |

[a]Yield of pure isolated product after chromatographic purification with correct analytical and spectral data.




**Scheme 3.** Plausible mechanism for the formation of *trans*-4-α-methylene-pyrazole-carboxylate β-lactams **6**.

of *trans*-β-lactams as the only product.[21] CHN elemental analysis data of all the synthesized molecules **6a–h** were also in full support with their depicted structures. These α-methylene pyrazole-carboxylate-β-lactams **6a–h** are air- and moisture-stable, soluble in solvents such as dichloromethane, chloroform, acetone, toluene, ethyl acetate and obtained as stable solids.

A plausible mechanism for **6a–h** is depicted below (Scheme 3) and is in accordance with the literature reports.[22,24] The reaction of 2-substituted ethanoic acid **5** with phosphorus oxychloride or 2-substituted acetylchloride **5** in the presence of triethylamine generate the corresponding ketene **IX** (Scheme 3). Then the nucleophilic attack of imine nitrogen of novel pyrazole-carboxylate imines **4** to the carbonyl carbon of the ketene, which is generated in situ, leading to a zwitterionic intermediate **X**. This zwitterionic intermediate **X** upon direct conrotatory electrocyclic ring closure yields thermodynamically less stable *cis*-β-lactams which is highly unfavorable due to steric factors associated with bulky group at C-4. As α-methylene pyrazole-carboxylate is a large group, steric hindrance between Ar-group of the ketene and the α-methylene pyrazole-ester chain of imine in the intermediate **X** causes isomerization to generate intermediate **XI**. Further, electrocyclic ring closure reaction of zwitterionic intermediate **XI** through conrotatory mode leads to the formation of *trans* isomer of β-lactams **6**.

## Conclusion

In conclusion, we have synthesized stereoselectively novel *trans*-4-α-methylene-pyrazole-carboxylate β-lactams **6a–h** from the reaction of various 2-substituted-ethanoic

acids/acetylchloride and novel hetero-ester substituted imines **4a–c** using $Et_3N$. The structures and stereochemistry of all the novel compounds were established on the basis of various spectroscopic techniques such as FTIR, NMR ($^1H$ and $^{13}C$ NMR), $^{13}C$ DEPT-135, $^1H$–$^1H$ COSY, $^1H$–$^{13}C$ COSY, and elemental analysis. In addition, efforts are in progress to synthesize corresponding acid, hydrazide, pyrazolone, alcohol, pyrazole carboxamide, and peptide substituted β-lactams through modifications of these novel pyrazole-ester substituted β-lactam analogues **6** in accordance with literature reports[11,19,25–27] (Fig. 2). Further, detailed results of these synthetic applications with complete spectroscopic analysis and structure activity relationship studies of newly synthesized imines **4a–c** and β-lactams **6a–h** will be reported in due course of time.

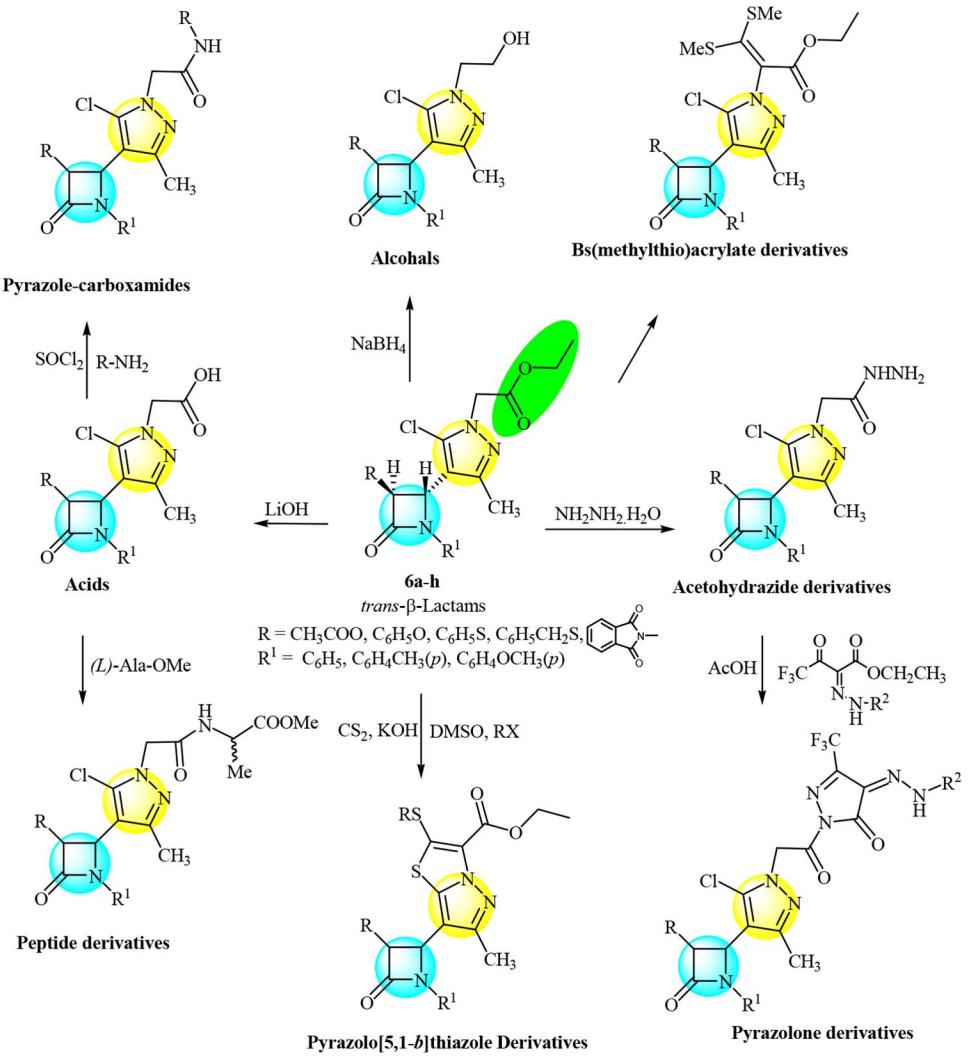



**Figure 2.** Synthetic utility of synthesized *trans*-4-α-methylene-pyrazole-carboxylate β-lactams **6**.

## Experimental

Melting points were determined in an open capillary on melting point apparatus (Perfit GSI-MP-3) and are uncorrected. IR spectra were recorded using Thermo scientific Nicolet iS50 (FTIR) spectrophotometer ($\upsilon_{max}$ in $cm^{-1}$). $^{1}H$ and $^{13}C$ NMR spectra were recorded on JEOL AL 300 MHz and BRUKER AVANCE II 400 MHz spectrometer using TMS as an internal standard. The elemental analysis (C, H, N) were recorded on Flash 2000 Organic elemental analyzer. All the reactions were monitored by TLC using precoated silica 60 F254, 0.25 mm aluminum plates (Merck) with visualization under UV light. Column chromatography was performed using Merck Silica Gel (60–120 mesh) using ethyl acetate-hexanes (10:90) as an eluant system.

Preparation of novel pyrazole-carboxylate linked *trans*-3-oxy/thio/phth-β-lactams was performed under dry and deoxygenated nitrogen atmosphere. Phosphorus oxychloride (Merck), triethylamine (Qualigen), hydrazine hydrate (Qualigen) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. Dimethylformamide and dichloromethane were dried and distilled over anhydrous calcium chloride ($CaCl_2$) and phosphorus pentoxide ($P_2O_5$) respectively. Toluene was distilled under $N_2$ from sodium-benzophenone immediately before use.

### *General procedure for the preparation of imines 4a–c*

Solution of aromatic amine (1 mmol) and pyrazole-carboxylate aldehyde (1 mmol) in the presence of molecular sieves (4 Å) in dry methylene chloride (15 mL) was stirred at room temperature. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered and solvent was evaporated under vacuum to yield crude product as colorless oil.

### *Ethyl 2-(5-chloro-3-methyl-4-((phenylimino)methyl)-1H-pyrazol-1-yl) acetate 4a*

Colorless oil; yield 85%; FTIR ($\nu_{max}$, $cm^{-1}$): 1740, 1624; $^{1}H$ NMR (300 MHz, $CDCl_3$): 1.18 (3H, t, $J = 7.2$ Hz, $CH_2CH_3$), 2.46 (3H, s, $CH_3$), 4.09 (2H, q, $J = 7.2$ Hz, $CH_2CH_3$), 4.73 (2H, s, $NCH_2$), 6.46–7.24 (5H, m, Ar*H*), 8.20 (1H, s, -N=CH); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 14.00, 14.47, 49.71, 61.76, 114.66, 114.73, 116.53, 118.10, 120.57, 125.33, 128.84, 128.99, 130.76, 134.09, 146.29, 149.88, 150.81, 151.03, 152.65, 165.56, 166.11; Anal. calcd for $C_{15}H_{16}ClN_3O_2$: C 58.92, H 5.27, N 13.74%. Found: C 58.84, H 5.19, N 13.61%.

### *General procedure for synthesis of trans-4-α-methylene-pyrazole-carboxylate β-lactams 6a–h*

A solution of phosphorus oxychloride ($POCl_3$, 0.69 mmol, 1.5 equiv.) in dry toluene (10 mL) was added dropwise to a stirred solution of 2-substituted ethanoic acid (0.55 mmol, 1.2 equiv.), imine (0.46 mmol, 1 equiv.), and distilled triethyl amine (1.38 mmol, 3 equiv.) in dry toluene (20 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 3–4 h. The solvent was evaporated and crude product was extracted with $CH_2Cl_2$. The organic layer was washed with water (3 × 10 mL), 1N HCl (3 × 10 mL), 5% $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL), then dried ($Na_2SO_4$) and

concentrated. The crude product was then isolated by column chromatography over silica gel using hexane/EtOAc (90:10) as eluent to afford pure products.

### *Trans-ethyl-2-(4-(1-phenyl-3-acetoxy-4-oxo-azetidin-2-yl)-5-chloro-3-methyl-1H-pyrazol-1-yl)acetate 6a*

Yellowish white solid; yield: 60%; mp 64–66 °C; FTIR ($\nu_{max}$, $cm^{-1}$): 1730, 1725, 1700; $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.28 (3H, t, $J = 7.2$ Hz, $CH_2CH_3$), 2.02 (3H, s, $CH_3$), 2.12 (3H, s, $CH_3COO$), 4.23 (1H, d, $J = 1.8$ Hz, C4-H), 4.25 (2H, q, $J = 7.1$ Hz, $CH_2CH_3$), 4.85 (2H, s, $NCH_2$), 5.6 (1H, d, j = 1.8 Hz, C3-H), 7.15–7.35 (m, 5H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 12.47, 14.13, 20.51, 44.71, 50.16, 54.17, 62.15, 79.71, 109.32, 127.82, 128.06, 128.87, 128.92, 134.07, 148.55, 163.70, 166.76, 169.61; Anal. calcd for $C_{20}H_{22}ClN_3O_5$: C 57.21, H 5.28, N 10.01%. Found: C 57.11, H 5.20, N 9.86%.

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