Chlorotrimethylsilane-Mediated Synthesis of 2-Aryl-1-chloro-1-heteroarylalkenes

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Abstract: The condensation of (chloromethyl)heterarenes with aromatic aldehydes was investigated, resulting in a simple and flexible general procedure for the synthesis of 2-aryl-1-chloro-1-heteroarylalkenes. The best reaction conditions were found to be heating in *N*,*N*-dimethylformamide in the presence of chlorotrimethylsilane as a promoter and water-scavenger.

Key words: (chloromethyl)heterocycles, aromatic aldehydes, Knoevenagel condensation, 2-aryl-1-halo-1-heteroarylalkene, chlorotrimethylsilane

1-Halo-1-heteroarylalkenes **I** have attracted much attention due to their diverse biological activity.[1–4] The biological activity of this type of compound is generally defined by the nature of the heterocycle, however, the presence of the halide influences the activity parameters and is necessary for QSAR building. These compounds also have interest as dyes.[5]

There are some approaches to these substances reported in the literature (Scheme 1). These are: introduction of the halide atom into the heteroaryl-substituted alkenes **II** using halogenating agents (route 1);[1a,d,6] elimination of HHal from 1,2-dihalo-1-heteroarylalkanes **III** (route 2);[7] hydrohalogenation of alkynes **IV** (route 3);[8] elimination of HHal from 1,1-dihalo-1-heteroarylalkanes **V** (route 4);[9] from 1,1,1-trichloromethyl derivatives **VI** (route 5);[10] heteroarylation of tributylhalostannanes **VII** (route 6);[2a,11] halogenation of tributylstannanes **VIII** (route 7);[4,12] and reaction of 1,1-dihaloalkenes **IX** with heteroarylzinc compounds **X** (route 8).[13] There are also some useful approaches to 1-halo-1-heteroarylalkenes that use cyclization reactions at the last step of the synthesis.[1b,c,2b,14] However, the most facile and promising method for the preparation of these compounds is the condensation of (halomethyl)heterarenes **XII** with aldehydes (route 9).[1e,3a,15,16] The condensation should be performed under acidic conditions because under basic conditions the intermediate hydrins **XI** undergo cyclization into oxiranes via Darzens reaction.[15b] However, this approach has only been applied to a few heterocycles and has not been widely utilized.

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In the present work, the results of studying the Knoevenagel condensation using chloromethyl-substituted heterocycles and the corresponding alcohols and their tosylates are reported.

We have previously shown[17] that (benzothiazolyl)methanol **1** reacts with benzaldehyde in the presence of chlorotrimethylsilane[18,19] in a pressure tube affording (benzothiazolyl)ethanone **3** (Scheme 2). An attempt to apply this approach to (benzimidazolyl)methanol **2** resulted in the formation of (1-chlorovinyl)benzimidazole **5** as the major product instead of (benzimidazolyl)ethanone **4** under the same conditions. We hypothesized that formation of compound **5** could be rationalized by substitution of the silylated hydroxy group with chlorine in intermediates **6**. For indirect confirmation of our hypothesis we decided to perform the reaction of (chloromethyl)benzimidazole **7** with benzaldehyde under similar conditions. The sole product **5** was formed in 84% preparative yield.

The result obtained with (chloromethyl)benzimidazole **7** was extended to a set of chloromethyl derivatives of other heterocycles **8**–**22**. In all cases shown in Table 1, the reaction proceeds in high preparative yields forming the corresponding chloroalkene derivative **24**–**38** as the sole reaction product. It should be noted that these compounds have the *Z* configuration as was confirmed by NOE experiments on three compounds of this series (Figure 1).

Among the chloromethyl derivatives of π-electron-withdrawing heterocycles that were unsuccessful in this reaction was 2-(chloromethyl)-1-methyl-1*H*-imidazole. In

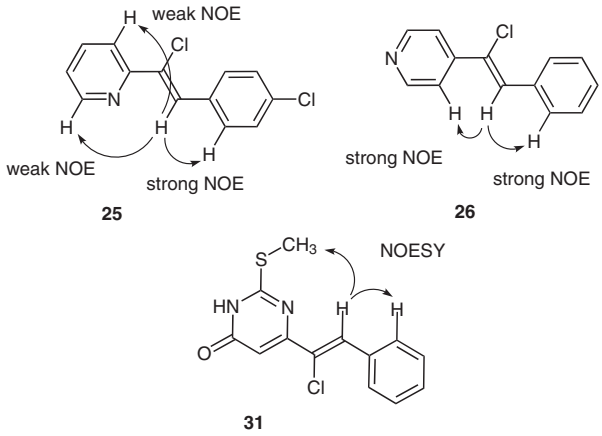
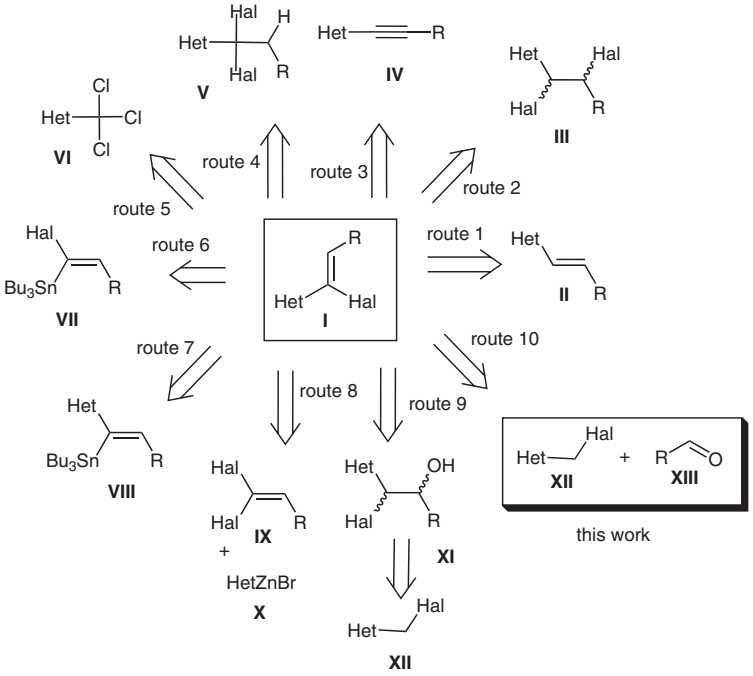
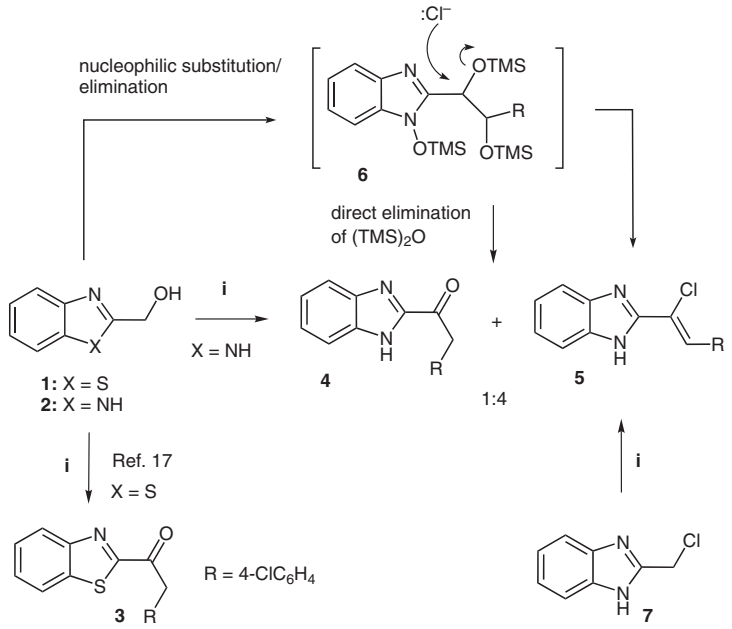


Figure 1



Scheme 1



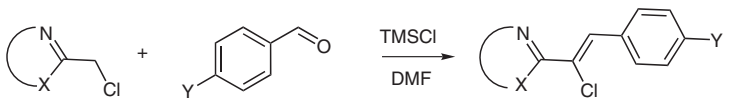
Scheme 2 *Reagents and conditions*: (i): PhCHO, DMF, TMSCl, 100 °C, 6 h, pressure tube.

this case, a complicated mixture of products with no trace of the target chlorovinyl derivative was formed. This was accounted for by the insufficiently low acceptor properties of the imidazole ring in comparison to other heterocycles in Table 1.

We propose that the process can run via two pathways. The first implies that initially formed *O*-silyl derivative **39** undergoes silylation at the heterocyclic nitrogen resulting in the formation of disilyl derivative **40**. Extrusion of hexamethyldisilazane gives the target 2-aryl-1-chloro-1-heteroarylalkenes **24**–**38**. The second pathway includes the initial silylation on heterocyclic nitrogen of the starting (halomethyl)hetarene **8**–**22** followed by addition of aldehyde to **41** resulting in the intermediate **40** (Scheme 3)

Unfortunately, we did not succeed in extending this approach to other types of CH-acidic chloromethyl derivatives. Under similar conditions 4-nitrobenzoyl chloride and monochloroacetic acid amides do not enter into the reaction with aldehydes, while chloroacetic ester and chloroacetophenones give complicated product mixtures, with no target products being detected.

Table 1 Preparation of 2-Aryl-1-chloro-1-heteroarylalkenes[a]



8–22 **23a–e** **24–38**

Y = **a**: H, **b**: OMe, **c**: Cl, **d**: NO_2, **e**: COOMe

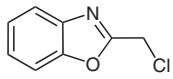
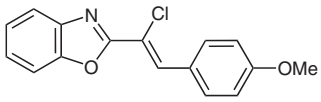
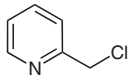
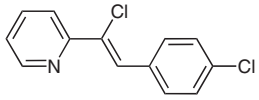
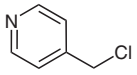
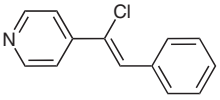
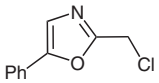
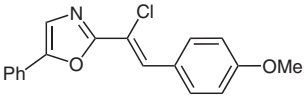
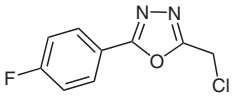
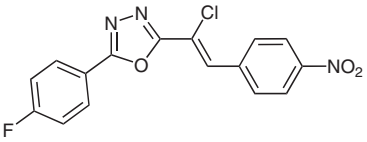
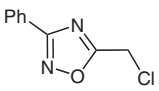
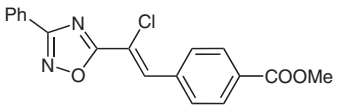
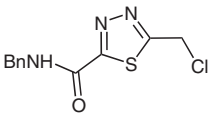
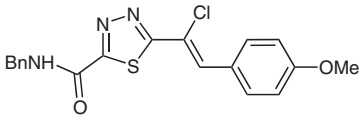
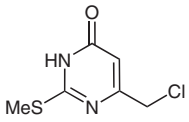
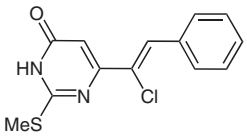
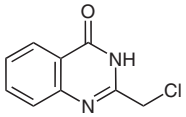
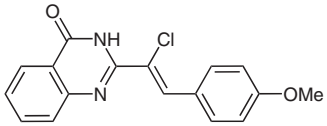
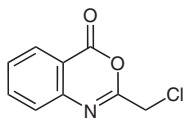
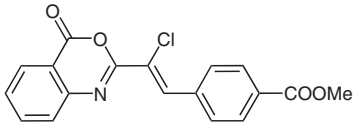
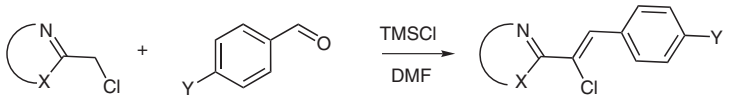
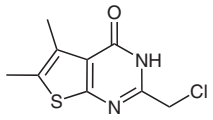
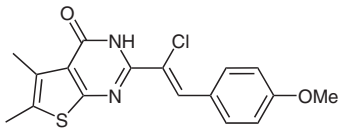
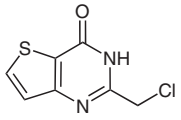
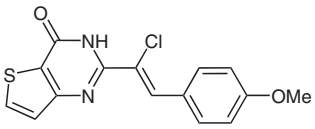
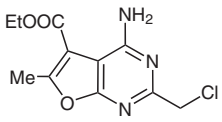
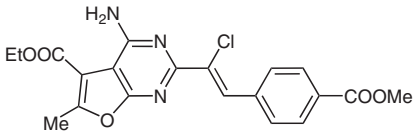
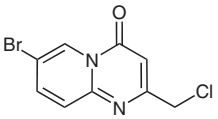
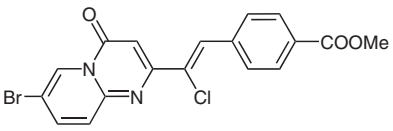
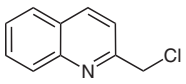
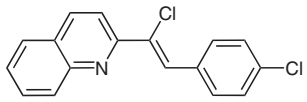
Starting material	23	Product	Yield[b] (%)
 **8**	**23b**	 **24**	82
 **9**	**23c**	 **25**	78
 **10**	**23a**	 **26**	75
 **11**	**23b**	 **27**	74
 **12**	**23d**	 **28**	83
 **13**	**23e**	 **29**	85
 **14**	**23b**	 **30**	87
 **15**	**23a**	 **31**	77
 **16**	**23b**	 **32**	96
 **17**	**23e**	 **33**	86

Table 1 Preparation of 2-Aryl-1-chloro-1-heteroarylalkenes[a] (continued)



8–22 **23a–e** **24–38**

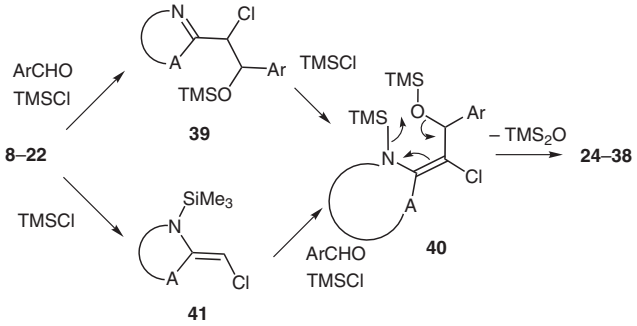
Y = **a**: H, **b**: OMe, **c**: Cl, **d**: NO_2, **e**: COOMe

Starting material	23	Product	Yield[b] (%)
 **18**	**23b**	 **34**	91
 **19**	**23b**	 **35**	95
 **20**	**23e**	 **36**	78
 **21**	**23e**	 **37**	75
 **22**	**23c**	 **38**	89

[a] Satisfactory microanalysis obtained: C ±0.33; H ±0.45; N ±0.25.
[b] Yields refer to pure isolated products.

A further disadvantage of this approach is that some (chloromethyl)hetarenes are difficult to access or have low stability. For example, the 2-(chloromethyl)benzothiazole possesses low stability under the reaction conditions. In this case, to obtain the corresponding chlorovinyl derivative we decided to use an approach similar to that used for the preparation of vinyl chloride **5** from (benzimidazolyl)methanol **2** (Scheme 2). In order to increase the nucleofugicity of the leaving group in intermediates of type **6**, the hydroxylic group of the starting (benzothiazolyl)methanol **1** was tosylated. Using the tosylate **42** gave chloro derivative **43** in 93% preparative yield. We assume that the reaction proceeds via an intermediate **44**, the nucleophilic substitution of the tosylate group leads to intermediate **45**. The confirmation of the generality of this reaction is the transformation of tosylate **46**, which is a quinoline derivative, into chlorovinyl derivative **38** in 95% yield (Scheme 4). Compound **38** has also had its *Z* configuration confirmed by NOE experiments.

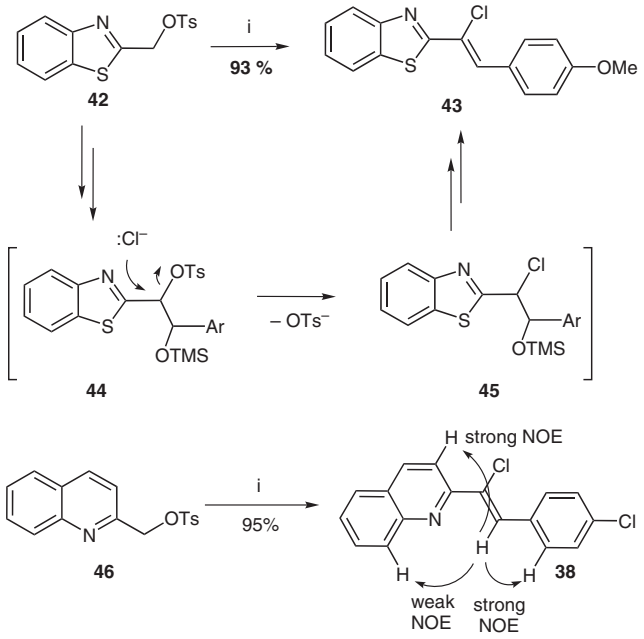
We also tried to use fluorine as a nucleofuge for which a trimethylsilyl group is a good acceptor due to the high affinity of fluorine to silicon. We carried out the reaction of (fluoromethyl)benzothiazole **47** with aldehyde **23b**. However, substitution of fluorine does not occur and the fluorovinyl derivative **48** was isolated in 85% yield (Scheme 5).



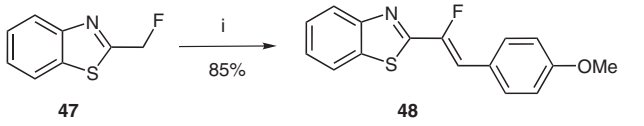
Scheme 3

We attempted to extend this approach and introduce, through the tosyl derivative, bromine and iodine to the

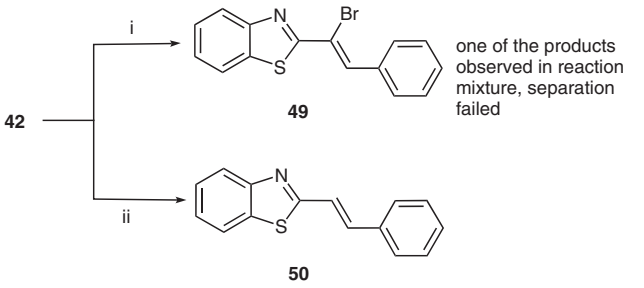
double bond using bromotrimethylsilane and iodotrimethylsilane (generated in situ from TMSCl and NaI in DMF),[20] respectively, instead of chlorotrimethylsilane. However, in the case of bromotrimethylsilane the reaction proceeds unselectively giving a mixture of products. The target bromovinyl **49** was identified by HPLC MS spectra of the product mixture; however it could not be isolated. In the case of iodotrimethylsilane, the reduction to alkene **50** occurs in 72% yield (Scheme 6).



Scheme 4 *Reagents and conditions*: (i) **23b** (for **43**) or **23c** (for **38**), DMF, TMSCl, 100 °C, 6 h, pressure tube.



Scheme 5 *Reagents and conditions*: (i) **23b**, DMF, TMSCl, 100 °C, 6 h, pressure tube.



Scheme 6 *Reagents and conditions*: (i) **23a**, DMF, TMSBr, 100 °C, 6 h, pressure tube; (ii) **23a**, DMF, TMSI, 100 °C, 6 h, pressure tube.

In summary, we have developed efficient methodology for the preparation of 2-aryl-1-chloro-1-heteroarylalkenes from (chloromethyl)heterarenes or (tosyloxymethyl)hetarenes and aldehydes using chlorotrimethylsilane as a promoter and water-scavenger. The methodology is applicable to a wide variety of (chloromethyl)heterarenes and delivers the target products in good yields. The chemical procedure is very simple and could be easily adapted to semi-automated solution-phase parallel synthesis of 2-aryl-1-chloro-1-heteroarylalkene libraries.

All commercially available starting materials (Aldrich, Fluka, Enamine Ltd) were used without additional purification. All solvents were purified by standard methods. All procedures were carried out under open atmosphere with no precautions taken to exclude ambient moisture. Melting points were measured with a Buchi melting points apparatus and are uncorrected. ^{1}H NMR (400 MHz and 500 MHz) were recorded on a Varian Mercury-400 spectrometer and Bruker Avance DRX 500 spectrometer with TMS as an internal standard. ^{13}C NMR (125 MHz) were recorded on a Bruker Avance DRX 500 spectrometer with TMS as an internal standard. ^{19}F NMR (470 MHz) were recorded on a Bruker Avance DRX 500 spectrometer with $CFCl_3$ as an internal standard. NOE and NOESY experiments were recorded on a Bruker Avance DRX 500 spectrometer. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph Agilent 1100 Series equipped with diode-matrix and mass-selective detector Agilent LC\MSD SL. The parameters of chromatography-mass analysis: column: Zorbax SB-C18, 1.8 μm, 4.6 mm × 15 mm; eluent, A: MeCN–H_2O (95:5) + 0.1% TFA; B: H_2O + 0.1% TFA; flow rate: 3 mL/sec; volume of injected sample: 1 μL; UV detectors: 215, 254, and 265 nm; ionization method: CI under atmospheric pressure (APCI); ionization mode, simultaneous scanning of positive and negative ions in the mass range of 80–1000. According to HPLC-MS data all the synthesized compounds have purity >98%. Branson 2510E-MT ultrasonic bath was used.

2-Aryl-1-halo-1-heteroarylalkenes 5, 24–38, and 48, and 1-Aryl-2-heteroarylalkene 50; General Procedure

(Chloromethyl)heterocycle **7**, **8**–**22** or (fluoromethyl)benzothiazole **47** (2 mmol) and an appropriate aromatic aldehyde **23a**–**e** (2 mmol) were placed in a 15-mL pressure tube and dissolved in DMF (2–3 mL). TMSCl (6 mmol) (TMSI in the case of **50**) was added dropwise to the soln. The tube was thoroughly sealed and heated on a water bath for 6–15 h. After cooling the flask was opened (*Caution! Excessive pressure.*) and the mixture was poured into H_2O (15 mL) and allowed to stand at 20 °C in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with small amount of *i*-PrOH. Recrystallization from an appropriate solvent yielded target compounds **5**, **24**–**38**, **48**, and **50** (see Table 1 and Schemes 5 and 6).

2-[(*Z*)-1-Chloro-2-(4-chlorophenyl)vinyl]-1*H*-benzimidazole Hydrochloride (5)

Yield: 84%; mp 242–243 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36 (m, 2 H, 5,6-H_{BIm}), 7.60 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 3,5-H_{Ar}), 7.67 (m, 2 H, 4,7-H_{BIm}), 7.94 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 2,6-H_{Ar}), 8.18 (s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 115.0, 117.0, 125.7, 129.5, 132.1, 132.4, 133.5, 134.7, 135.5, 147. 7.

MS (APSI): *m*/*z* = 289 $[M + 1]^+$.

2-[(*Z*)-1-Chloro-2-(4-methoxyphenyl)vinyl]benzoxazole (24)

Yield: 82%; mp 123–124 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.83 (s, 3 H, OCH_3), 7.08 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 3,5-H_{Ar}), 7.44 (m, 2 H, 5,6-H_{BOx}), 7.76 (d,

$^3J_{H,H}$ = 7.6 Hz, 1 H, 4-H_{BOx}), 7.80 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 7-H_{BOx}), 8.01 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 2,6-H_{Ar}), 8.07 (s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.9, 111.3, 114.8, 114.9, 120.5, 125.6, 125.9, 126.5, 132.9, 133.6, 141.8, 150.9, 160.8, 161.2.

MS (APSI): *m*/*z* = 286 [M + 1]$^+$.

2-[(*Z*)-1-Chloro-2-(4-chlorophenyl)vinyl]pyridine Hydrochloride (25)
Yield: 78%; mp 82–83 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.44 (m, 1 H, 5-H_{Py}), 7.53 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, 3,5-H_{Ar}), 7.89 (m, 2 H, 2,6-H_{Ar}), 7.94 (m, 2 H, 3,4-H_{Py}), 8.07 (s, 1 H, CH), 8.66 (m, 1 H, 6-H_{Py}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 121.2, 124.3, 127.0, 129.0, 130.7, 132.0, 133.6, 133.7, 138.1, 149.7, 153.7.

MS (APSI): *m*/*z* = 250 [M + 1]$^+$.

4-[(*Z*)-1-Chloro-2-phenylvinyl]pyridine Hydrochloride (26)
Yield: 75%; mp 214–215 °C (EtOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.46 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-H_{Ph}), 7.51 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, 3,5-H_{Ph}), 7.92 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, 2,6-H_{Ph}), 8.09 (s, 1 H, CH), 8.27 (d, $^3J_{H,H}$ = 5.4 Hz, 2 H, 3,5-H_{Py}), 8.90 (d, $^3J_{H,H}$ = 5.4 Hz, 2 H, 2,6-H_{Py}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 122.5, 126.8, 129.1, 130.3, 130.6, 133.4, 134.2, 145.6, 150.3.

MS (APSI): *m*/*z* = 216 [M + 1]$^+$.

2-[(*Z*)-1-Chloro-2-(4-methoxyphenyl)vinyl]-5-phenyloxazole (27)
Yield: 74%; mp 95–96 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.86 (s, 3 H, OCH_3), 6.99 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 3,5-H_{Ar}), 7.35 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H, 4-H_{Ph}), 7.46 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, 3,5-H_{Ph}), 7.64 (s, 1 H, 4-H_{Ox}), 7.76 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, 2,6-H_{Ph}), 7.88 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 2,6-H_{Ar}), 7.91 (s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.9, 114.7, 115.1, 124.7, 125.0, 126.3, 127.5, 129.4, 129.6, 130.5, 132.4, 151.9, 158.6, 160.8.

MS (APSI): *m*/*z* = 312 [M + 1]$^+$.

2-[(*Z*)-1-Chloro-2-(4-nitrophenyl)vinyl]-5-(4-fluorophenyl)-1,3,4-oxadiazole (28)
Yield: 83%; mp 181–182 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.37 (d, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.5 Hz, 2 H, 3,5-H_{Ar}), 8.16–8.26 (m, 5 H, 2,6-H_{Ar}, 2,6-$H_{Ar'}$,CH), 8.33 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 3,5-$H_{Ar'}$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 117.3 ($^2J_{C,F}$ = 22.1 Hz), 117.6, 120.0 ($^4J_{C,F}$ = 3.1 Hz), 124.3, 130.2 ($^3J_{C,F}$ = 9.4 Hz), 131.7, 132.0, 139.5, 148.0, 162.6, 164.5, 165.0 ($^1J_{C,F}$ = 250.8 Hz).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –106.9.

MS (APSI): *m*/*z* = 346 [M + 1]$^+$.

Methyl 4-[(*Z*)-2-Chloro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)vinyl]benzoate (29)
Yield: 85%; mp 146–147 °C (EtOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.91 (s, 3 H, OCH_3), 7.50–7.59 (m, 3 H, 2,6-H_{Ar}, 4-H_{Ph}), 8.04–8.12 (m, 6 H, 3,5-H_{Ar}, 2,3,5,6-H_{Ph}), 8.24 (s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.9, 116.7, 126.2, 127.7, 128.8, 129.9, 131.3, 132.4, 133.8, 136.0, 137.2, 166.1, 169.0, 173.7.

MS (APSI): *m*/*z* = 341 [M + 1]$^+$.

***N*-Benzyl-5-[(*Z*)-1-chloro-2-(4-methoxyphenyl)vinyl]-1,3,4-thiadiazole-2-carboxamide (30)**
Yield: 87%; mp 165–166 °C (MeCN).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.82 (s, 3 H, OCH_3), 4.47 (d, $^3J_{H,H}$ = 5.4 Hz, 2 H, CH_2), 7.07 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, 3,5-H_{Ar}), 7.25 (m, 1 H, 4-H_{Ph}), 7.33 (s, 4 H, 2,3,5,6-H_{Ph}), 7.95 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, 2,6-H_{Ar}), 8.06 (s, 1 H, CH), 9.85 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 43.2, 55.9, 114.8, 116.8, 125.7, 127.5, 128.0, 128.8, 132.88, 132.92, 139.1, 157.9, 161.3, 165.8, 172.3.

MS (APSI): *m*/*z* = 386 [M + 1]$^+$.

6-[(*Z*)-1-Chloro-2-phenylvinyl]-2-(methylsulfanyl)pyrimidin-4(3*H*)-one (31)
Yield: 77%; mp 244–245 °C (EtOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.60 (s, 3 H, SCH_3), 7.42 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H, 4-H_{Ph}), 7.47 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, 3,5-H_{Ph}), 7.84 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, 2,6-H_{Ph}), 8.22 (s, 1 H, CH), 12.88 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.6, 107.0, 127.7, 129.1, 130.0, 130.7, 131.6, 134.1, 157.3, 163.2, 165.7.

MS (APSI): *m*/*z* = 279 [M + 1]$^+$.

2-[(*Z*)-1-Chloro-2-(4-methoxyphenyl)vinyl]quinazolin-4(3*H*)-one (32)
Yield: 96%; mp 213–214 °C (DMF–MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.86 (s, 3 H, OCH_3), 6.98 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 3,5-H_{Ar}), 7.46 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, 7-H_{Qnz}), 7.70 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, 6-H_{Qnz}), 7.77 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 8-H_{Qnz}), 7.89 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 2,6-H_{Ar}), 7.91 (s, 1 H, CH), 8.14 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 5-H_{Qnz}), 12.08 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.8, 114.7, 121.5, 126.3, 126.40, 126.42, 127.6, 128.0, 132.6, 133.2, 135.2, 148.5, 150.8, 160.8, 162.2.

MS (APSI): *m*/*z* = 313 [M + 1]$^+$.

Methyl 4-[(*Z*)-2-Chloro-2-(4-oxo-4*H*-3,1-benzoxazin-2-yl)vinyl]benzoate (33)
Yield: 86%; mp 264–265 °C (DMF–MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 3 H, OCH_3), 7.24 (t, $^3J_{H,H}$ = 8.5 Hz, 1 H, 6-H_{Het}), 7.67 (t, $^3J_{H,H}$ = 8.5 Hz, 1 H, 7-H_{Het}), 7.98 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, 2,6-H_{Ar}), 8.04 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, 3,5-H_{Ar}), 8.05 (m, 1 H, 8-H_{Het}), 8.10 (s, 1 H, CH), 8.66 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, 4-H_{Het}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.8, 117.4, 120.4, 124.2, 126.1, 129.8, 130.8, 130.9, 131.8, 133.8, 134.8, 137.7, 140.6, 160.3, 166.1, 170.1.

MS (APSI): *m*/*z* = 342 [M + 1]$^+$.

2-[(*Z*)-1-Chloro-2-(4-methoxyphenyl)vinyl]-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (34)
Yield: 91%; mp 257–258 °C (DMF–MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 6.96 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 3,5-H_{Ar}), 7.86 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 2,6-H_{Ar}), 11.98 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.2, 13.3, 55.8, 114.6, 120.7, 122.4, 126.3, 129.4, 131.1, 132.5, 133.0, 150.3, 159.0, 160.8, 161.9.

MS (APSI): *m*/*z* = 347 [M + 1]$^+$.

2-[(*Z*)-1-Chloro-2-(4-methoxyphenyl)vinyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (35)
Yield: 95%; mp 260–261 °C (DMF–MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3 H, OCH_3), 6.96 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 3,5-H_{Ar}), 7.36 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, 4-H_{Th}), 7.84–7.91 (m, 3 H, 2,6-H_{Ar}, CH), 7.99 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, 4-H_{Th}), 12.35 (br s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.8, 114.7, 121.2, 122.2, 125.8, 126.3, 132.5, 133.2, 136.0, 152.8, 157.7, 158.5, 160.9.

MS (APSI): m/z = 319 $[M + 1]^+$.

Ethyl 4-Amino-2-{(*Z*)-1-chloro-2-[4-(methoxycarbonyl)phenyl]vinyl}-6-methylfuro[2,3-*d*]pyrimidine-5-carboxylate (36)
Yield: 78%; mp 189–190 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, OCH_2CH_3), 2.67 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 4.33 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2CH_3), 7.95 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 2,6-H_{Ar}), 7.97–8.05 (m, 4 H, 3,5-H_{Ar}, NH_2), 8.20 (s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.4, 15.1, 52.7, 62.1, 98.3, 108.5, 129.7, 129.8, 130.5, 132.1, 139.0, 157.5, 158.2, 160.5, 162.8, 164.6, 165.8, 166.2.

MS (APSI): m/z = 416 $[M + 1]^+$.

Methyl 4-[(*Z*)-2-(7-Bromo-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)-2-chlorovinyl]benzoate (37)
Yield: 75%; mp 222–223 °C (DMF–MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.89 (s, 3 H, OCH_3), 6.91 (s, 1 H, 3-H_{Het}), 7.67 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, 9-H_{Het}), 7.98 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2,6-H_{Ar}), 8.04 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 3,5-H_{Ar}), 8.10 (dd, $^3J_{H,H}$ = 9.5 Hz, $^4J_{H,H}$ = 2.3 Hz, 1 H, 8-H_{Het}), 8.34 (s, 1 H, CH), 8.96 (d, $^4J_{H,H}$ = 2.3 Hz, 1 H, 6-H_{Het}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.7, 100.6, 126.5, 127.26, 127.32, 128.1, 128.9, 129.6, 129.7, 129.9, 130.7, 140.2, 158.1, 159.6, 161.8, 173.1.

MS (APSI): m/z = 419 $[M + 1]^+$.

2-[(*Z*)-1-Chloro-2-(4-chlorophenyl)vinyl]quinoline Hydrochloride (38)
Yield: 89%; mp 95–96 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 3,5-H_{Ar}), 7.65 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, 6-H_{Qn}), 7.82 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, 7-H_{Qn}), 7.96 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 2,6-H_{Ar}), 8.03 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-H_{Qn}), 8.08 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 8-H_{Qn}), 8.12 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 3-H_{Qn}), 8.15 (s, 1 H, CH), 8.51 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 4-H_{Qn}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 119.1, 127.7, 127.8, 128.3, 128.8, 129.1, 129.5, 130.9, 131.5, 132.1, 133.7, 133.9, 137.9, 147.3, 154.0.

MS (APSI): m/z = 300 $[M + 1]^+$.

2-[(*Z*)-1-Fluoro-2-(4-methoxyphenyl)vinyl]benzothiazole (48)
Yield: 85%; mp 113–114 °C (EtOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.80 (s, 3 H, OCH_3), 7.03 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 3,5-H_{Ar}), 7.18 (d, $^3J_{H,F}$ = 41.0 Hz, 1 H, CH), 7.49 (t, $^3J_{H,H}$ = 8.1 Hz, 1 H, 5-H_{BTz}), 7.58 (t, $^3J_{H,H}$ = 8.1 Hz, 1 H, 6-H_{BTz}), 7.74 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2,6-H_{Ar}), 8.04 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, 7-H_{BTz}), 8.17 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, 4-H_{BTz}).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.7, 111.2 ($^2J_{C,F}$ = 5.5 Hz), 115.0, 123.0, 123.3, 124.5 ($^4J_{C,F}$ = 3.1 Hz), 126.2, 127.5, 132.0 ($^3J_{C,F}$ = 7.9 Hz), 134.6, 150.1 ($^1J_{C,F}$ = 249.2 Hz), 153.7, 160.4 ($^4J_{C,F}$ = 3.2 Hz), 160.8 ($^2J_{C,F}$ = 37.0 Hz).

^{19}F NMR (470 MHz, DMSO-d_6): δ = 119.5 ($^3J_{H,F}$ = 40.7 Hz).

MS (APSI): m/z = 286 $[M + 1]^+$.

2-[(*E*)-2-Phenylvinyl]benzothiazole (50)
Mp 104–105 °C (EtOH) (Lit. 104,[21a] 112,[21b] 109–110,[21c] 98–100[21d]).

^{1}H NMR data of this compound were in agreement with previously reported data.[21]

APSI-MS: $[M + 1]^+$ = 238.

2-Aryl-1-chloro-1-heteroarylalkenes 38 and 43; General Procedure
2-(Tosyloxymethyl)hetarenes **42** or **46** (2 mmol) and an appropriate aromatic aldehyde **23b**,**c** (2 mmol) were placed in a 15-mL pressure tube and dissolved in DMF (2–3 mL). TMSCl (6 mmol) was added dropwise to the soln. The tube was thoroughly sealed and heated on a water bath for 8 h. After cooling the flask was opened (*Caution! Excessive pressure.*) and the mixture was poured into H_2O (15 mL) and allowed to stand at 20 °C in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with small amount of *i*-PrOH. Recrystallization from an appropriate solvent yielded target compounds **38** (95% yield) and **43** (93% yield).

2-[(*Z*)-1-Chloro-2-(4-methoxyphenyl)vinyl]benzothiazole (43)
Yield: 93%; mp 121–122 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 3 H, OCH_3), 6.98 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 3,5-H_{Ar}), 7.39 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H, 5-H_{BTz}), 7.50 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H, 6-H_{BTz}), 7.89 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H, 2,6-H_{Ar}), 7.96 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, 4,7-H_{BTz}), 8.05 (s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.9, 114.8, 121.2, 122.8, 123.4, 126.0, 126.1, 127.4, 130.3, 132.7, 135.4, 153.8, 161.0, 167.2.

MS (APSI): m/z = 302 $[M + 1]^+$.

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