One-pot three component synthesis of heteroarylated arylacetates *via* VNS_{Ar}-S_N reaction using N-methylpyrrolidone as general solvent†

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An efficient three component one-pot method was developed to assemble 2-heteroaryl-2-aryl acetates *via* VNS_{Ar}-S_NAr and VNS_{Ar}-S_N reaction by using N-methylpyrrolidone (NMP) as general solvent.

Introduction

2-Polyarylsubstituted acetates have been found to possess several biological activities.[1] Some derivatives were found to interact with either muscarinic receptors or butyrylcholinesterase **1**.[2] Others have been patented as herbicides **2**[3]or as potential drugs for treatment of hyperproliferative disorders **3**[4] (Fig. 1).

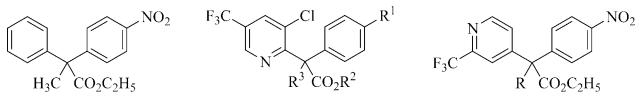


Fig. 1

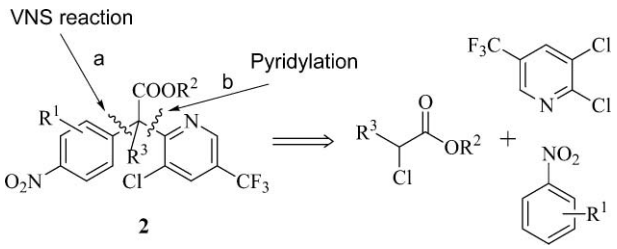
Multi-component reactions are useful and efficient methods in organic synthesis. Compared with the conventional multi-stage synthesis of the target compound, multicomponent reactions take advantage of effecting several reactions in a single synthetic operation without the need for isolation of intermediates.[5] In this paper, we wish to report a novel synthetic method for ethyl 2-heteroaryl-2-aryl acetate derivatives *via* a three-component reaction using substituted nitrobenzene, ethyl 2-chloropropionate and heteroaryl halide under mild reaction conditions.

Results and discussion

There are several conventional step-by-step methods for the synthesis of these important diaryl acetates.[6] Disadvantages of these methods include harsh reaction conditions, use of hazardous reaction chemicals, complicated workup, uncommon and expensive chemicals and solvents.

The vicarious nucleophilic substitution of hydrogen (VNS_{Ar}), developed by Makosza *et al.*, has become a useful tool for introducing C-linked substituents into electrophilic arenes.[7] Most VNS reactions reported in the literature can be further quenched by in situ with a variety of electrophiles such as alkylating reagent,[8] aldehyde,[9] oxidant[10] and π-deficient carboaromatic halide[11] to give the *para*-functionalised nitroarene.

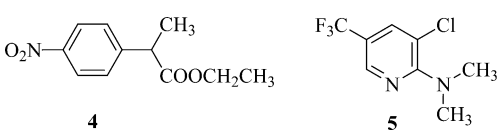
In continuation of our research on the synthesis of bioactive heterocyclic compounds, we have focused our interest on developing an efficient method for the synthesis of compounds **2** and **3**. The retrosynthetic analysis of compound **2** is shown in Scheme 1. It indicates that compound **2** can be divided into three easily available building blocks. Therefore, we propose that the synthesis of 2-polyarylsubstituted acetates **2** could be achieved *via* a process involving sequential VNS_{Ar} (step a), and followed by quenching the reaction mixture with pyridine (pyridylation, S_NAr, step b).



Scheme 1 Retrosynthetic analysis of compound **2**

According to the literature[11], most activated arenes that have been used as electrophiles are fluoronitroarenes. Up to now, there have been no reports on the use of heteroaromatic halides as electrophiles to quench the VNS reaction. Generally pyridyl chloride is a much less reactive class of π-deficient substrate[12] than fluorodinitroarenes, therefore it is necessary to reinvestigate the reaction conditions.

It is well known that the selection of solvent is important for the VNS reaction. The common polar aprotic solvents are DMF, DMSO, THF, liquid ammonia *etc*. Following the literature procedures, reaction of nitrobenzene with ethyl 2-chloropropionate in the presence of NaH in DMF at 0 °C, and then quenching with 5-trifluoromethyl-2,3-dichloropyridine at room temperature gave just two major side products **4** and **5** (Scheme 2). No desired product was separated. It is obvious that compound **4** was obtained by the vicarious nucleophilic substitution (VNS_{Ar}) reaction, and the 2-dimethylamino compound **5** was obtained by reaction of 5-trifluoromethyl-2,3-dichloropyridine with solvent



Scheme 2

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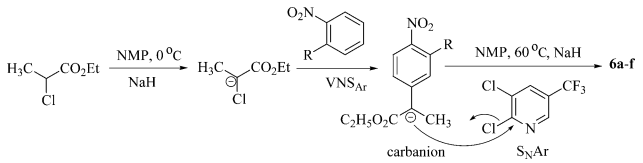
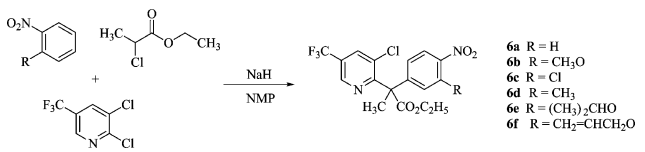
dimethylformamide which acted as a nucleophile.[13] Therefore, DMF cannot be used as solvent when 5-trifluoromethyl-2,3-dichloropyridine is reacted with a VNS carbanion.

Because the reaction of nitrobenzene with ethyl 2-chloropropionate is an exothermic reaction, it is best to cool the flask with an ice bath. Although dimethyl sulfoxide (DMSO) is a good solvent for VNS reactions, a practical disadvantage in certain important situations is that DMSO cannot conveniently be used in cold environments (mp: 18 °C). Attempts to try THF as solvent were also unsuccessful. Finally, we tested another good polar aprotic solvent N-methylpyrrolidone to perform this reaction at 0 °C and ambient temperature. But only a few expected products were obtained. Considering that 5-trifluoromethyl-2,3-dichloropyridine is a relatively weak electrophile, we carried out the S_NAr reaction at a higher temperature (60 °C). To our delight, the reaction proceeded smoothly in NMP at 60 °C after the carbanion has been formed. (Scheme 3).



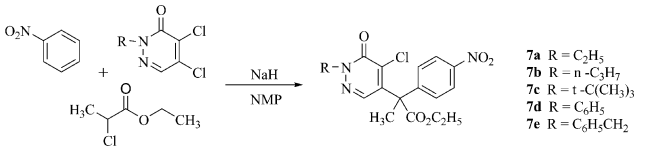
Scheme 3

The position of the substituents on the nitrobenzene derivatives played an important role in this reaction. When groups such as chloro, methyl and methoxy were substituted at the *ortho* position to the nitro group, both the VNS_{Ar} and S_NAr reactions proceeded satisfactorily, and the final products were obtained (Scheme 4, **6a–f**). But when the *meta* position of the nitro group was substituted by other substituents, no matter whether it is electron-withdrawing group or electron-donating group, the reaction stopped at the first step, and gave VNS product. This is due to the steric effect of the substituent attached at the *meta* position relative to the nitro group, and the anion failed to undergo further S_NAr reactions. This reaction mechanism is supposed to be VNS_{Ar}-S_NAr (nucleophilic aromatic heterocyclic substitution) two step process.



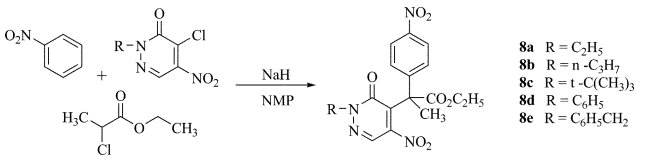
Scheme 4

After the successful application of NMP as solvent in the synthesis of 2-polysubstituted acetates containing a pyridine ring, we next wished to synthesize 2-polysubstituted acetates containing other heterocyclic rings. So, 4,5-dichloropyridazinone was used as electrophile to react with the carbanion. Unlike fluorodinitroarenes and 5-trifluoromethyl-2,3-dichloropyridine, 4,5-dichloropyridazinone lacks strong electron-withdrawing substituents such as nitro, trifluoromethyl, cyano on the pyridazinone ring. Even more significantly, pyridazinone is not an aromatic ring. The π electrons in the ring are localized, and cannot form a delocalized big π bond to stabilize the transition state. Theoretically, it might be difficult for 4,5-dichloro-pyridazinone to undergo the S_NAr reaction with carbanion. Fortunately, quenching the VNS reaction with 4,5-dichloropyridazinone in NMP gave the expected product in a moderate yield (Scheme 5, **7a–e**). It is also necessary to heat the mixture at this stage to effect formation of the final compounds.



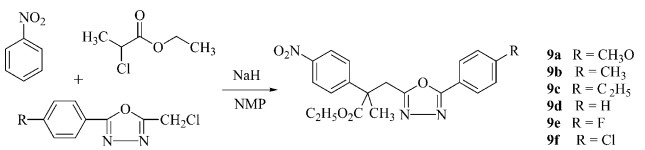
Scheme 5

In order to explore the scope of the reaction, a series of 4-chloro-5-nitro-pyridazinones were used as substrates for this study. Generally, a chloro group at the 4-position in the pyridazinone ring is less reactive toward nucleophile than a chloro group at the 5-position. But due to the strong electron-withdrawing nitro group attached at the 5-position of the pyridazinone ring, the chloro group at the 4-position is doubly activated by nitro group and carbonyl group. Therefore, a higher temperature may probably not be needed. The second step S_NAr reaction proceeded efficiently at room temperature using NMP as a solvent with a short reaction time, and gave a slightly higher yield (Scheme 6, **8a–e**).



Scheme 6

Finally, we also used a series of 5-aryl-2-(chloromethyl)-1,3,4-oxadiazoles as electrophiles for this reaction in NMP. Because there is an electron-withdrawing heterocyclic ring neighboring the methylene, the reaction is easy to perform (Scheme 7, **9a–f**).



Scheme 7

In summary, we have developed a new efficient method to construct ethyl 2-heteroaryl-2-arylacetates by quenching the VNS reaction with heteroaromatic halides in a one-pot three-component reaction using N-methylpyrrolidone (NMP) as general solvent.

Experimental

General methods

Melting points were recorded in an open capillary using a Büchi melting point B-540 apparatus. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with UV light. All chemicals used were reagent grade procured commercially and used with further

purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 MHz) or a Bruker WP-500SY (500 MHz) spectrometer in $CDCl_3$ using TMS as internal standard. High-resolution mass spectra were recorded under electron impact conditions using a MicroMass GCT CA055 instrument.

General procedure for compounds 6a–f

To a solution of sodium hydride (60% dispersion in oil, 9 mmol) in dry NMP (3 mL) was added dropwise a solution of ethyl 2-chloropropionate (3 mmol) and the appropriate nitrobenzene (3 mmol) in dry NMP (3 mL) at 0° C under nitrogen atmosphere and the mixture was stirred for 30 min. 5-Trifluoromethyl-2,3-dichloropyridine (3 mmol) in anhydrous NMP (2 mL) was then added, the reaction mixture was allowed to warm to 60° C and stirred for a further 2–4 h (monitored by TLC). After the reaction was complete, the solution was poured onto ice and hydrochloric acid (15 mL, 1 M) and extracted three times with 15 mL of dichloromethane. The combined organic layers were washed with distilled water and then saturated aqueous sodium bicarbonate solution (3 × 15 mL) and dried on magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using a petroleum ether/ethyl acetate (3:1) mixture as eluent to afford the pure target compound.

Ethyl 2-(3′-chloro-5′-trifluoromethyl-pyridin-2′-yl)-2-(4″-nitrophenyl)propanoate (6a)

Yellow viscous liquid. Yield: 68%. ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.92 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 4.25 (q, J = 7.0 Hz, 2H), 2.12 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.7, 162.2, 147.6, 146.9, 143.2, 135.6, 131.9, 128.9, 126.8, 123.1, 122.5, 62.2, 58.4, 25.0, 13.8; HRMS: calcd. for $C_{17}H_{14}ClF_3N_2O_4$ (M^+): 402.0594, found: 402.0596.

Ethyl 2-(3′-chloro-5′-trifluoromethyl-pyridin-2′-yl)-2-(3″-methoxy-4″-nitrophenyl)propanoate (6b)

White solid. Yield: 61%. Mp: 95.1–96.2 °C. ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.46 (s, 1H), 6.85 (dd, J = 8.6 Hz, J = 1.3 Hz, 1H), 4.27–4.22 (m, 2H, nonequivalent geminal hydrogens), 3.94 (s, 3H), 2.09 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 162.2, 152.6, 147.5, 143.2, 138.3, 135.5, 132.0, 126.8, 125.3, 121.5, 119.7, 113.8, 62.1, 58.3, 56.5, 25.4, 13.9; HRMS: calcd. for $C_{18}H_{16}ClF_3N_2O_5$ (M^+): 432.0700, found: 432.0681.

Ethyl 2-(3′-chloro-5′-trifluoromethyl-pyridin-2′-yl)-2-(3″-chloro-4″-nitrophenyl)propanoate (6c)

Yellow solid. Yield: 65%. Mp: 75.0–75.6 °C. ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 7.93 (s, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.6 Hz, J = 2.0 Hz, 1H), 4.27–4.22 (m, 2H, nonequivalent geminal hydrogens), 2.09 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 161.6, 146.6, 146.5, 143.3, 135.7, 131.8, 131.5, 127.3, 127.0, 126.9, 125.1, 122.4, 62.4, 58.0, 24.9, 13.8; HRMS: calcd. for $C_{17}H_{13}Cl_2F_3N_2O_4$ (M^+): 436.0204, found: 436.0205.

Ethyl 2-(3′-chloro-5′-trifluoromethyl-pyridin-2′-yl)-2-(3″-methyl-4″-nitrophenyl)propanoate (6d)

Yellow viscous liquid. Yield: 60%. ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.41 (s, 1H), 7.34 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 4.27–4.21 (m, 2H, nonequivalent geminal hydrogens), 2.60 (s, 3H), 2.10 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 162.3, 147.9, 145.8, 143.2, 135.6, 133.3, 132.2, 131.9, 126.7, 126.6, 124.4, 122.5, 62.1, 58.2, 24.9, 20.9, 13.8; HRMS: calcd. for $C_{18}H_{17}ClF_3N_2O_4$ ([M + H]$^+$): 417.0829, found: 417.0848.

Ethyl 2-(3′-chloro-5′-trifluoromethyl-pyridin-2′-yl)-2-(3″-isopropoxy-4″-nitrophenyl)propanoate (6e)

Yellow viscous liquid. Yield: 61%. ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 7.91 (s, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 1.6 Hz, 1H), 6.85 (dd, J = 8.8 Hz, J = 1.6 Hz, 1H), 4.65–4.58 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 2.08 (s, 3H), 1.36 (d, J = 6.4 Hz, 6H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 162.3, 150.8, 146.8, 143.1, 139.6, 135.5, 132.0, 126.7, 125.0, 122.5, 118.5, 116.8, 72.7, 62.1, 58.2, 25.4, 21.8, 13.9; HRMS: calcd. for $C_{20}H_{21}ClF_3N_2O_5$ ([M + H]$^+$): 461.1091, found: 461.1099.

Ethyl 2-(3′-chloro-5′-trifluoromethyl-pyridin-2′-yl)-2-(3″-allyloxy-4″-nitrophenyl)propanoate (6f)

Orange–yellow viscous liquid. Yield: 63%. ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 7.91 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 1.2 Hz, 1H), 6.91 (dd, J = 8.8 Hz, J = 1.6 Hz, 1H), 6.04–5.95 (m, 1H), 5.42 (dd, J = 17.2 Hz, J = 0.8 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 4.65 (d, J = 4.8 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 2.08 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 162.2, 151.5, 147.3, 143.1, 138.6, 135.5, 132.0, 131.8, 126.8, 125.2, 122.5, 119.8, 118.3, 115.3, 70.1, 62.1, 58.2, 25.4, 13.8; HRMS: calcd. for $C_{20}H_{19}ClF_3N_2O_5$ ([M + H]$^+$): 459.0935, found: 459.0919.

Compounds 7a–e

Compounds **7a–e** were prepared by the same procedure as that for compounds **6a–f**, using 4,5-dichloropyridazinone as electrophile to quench the VNS reaction.

Ethyl 2-(4′-chloro-2′-ethyl-3′-oxopyridazin-5′-yl)-2-(4″-nitrophenyl)propanoate (7a)

Viscous liquid. Yield: 63%. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.19 (s, 1H), 4.34–4.18 (m, 4H), 2.05 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 156.7, 147.6, 145.6, 143.3, 135.4, 134.7, 129.1, 123.8, 62.8, 54.6, 48.3, 22.3, 13.8, 13.2; HRMS: calcd. for $C_{17}H_{18}ClN_3O_5$ (M^+): 379.0935, found: 379.0936.

Ethyl 2-(4′-chloro-2′-propyl-3′-oxopyridazin-5′-yl)-2-(4″-nitrophenyl)propanoate (7b)

Viscous liquid. Yield: 63%. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 9.2 Hz, 2H), 7.71 (d, J = 9.2 Hz, 2H), 7.19 (s, 1H), 4.32–4.09 (m, 4H), 2.05 (s, 3H), 1.88–1.78 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 156.9, 147.6, 145.6, 143.2,

135.4, 134.5, 129.1, 123.8, 62.8, 54.7, 54.6, 22.4, 21.4, 13.8, 11.1; HRMS: calcd. for $C_{18}H_{20}ClN_3O_5$ (M^+): 393.1091, found: 393.1099.

Ethyl 2-(2′-*tert*-butyl-4′-chloro-3′-oxopyridazin-5′-yl)-2-(4″-nitrophenyl)propanoate (7c)

White solid. Yield: 60%. Mp: 121.4–122.6 °C. ^{1}H NMR ($CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.27 (s, 1H), 4.31–4.18 (m, 2H, nonequivalent geminal hydrogens), 2.05 (s, 3H), 1.64 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 157.1, 147.6, 145.7, 142.6, 136.1, 132.9, 129.1, 123.8, 66.7, 62.7, 54.5, 27.6, 22.1, 13.8; HRMS: calcd. for $C_{19}H_{22}ClN_3O_5$ (M^+): 407.1248, found: 407.1249.

Ethyl 2-(4′-chloro-2′-phenyl-3′-oxopyridazin-5′-yl)-2-(4″-nitrophenyl)propanoate (7d)

Yellow solid. Yield: 65%. Mp: 130.1–130.8 °C. ^{1}H NMR ($CDCl_3$) δ 8.30 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.65–7.43 (m, 5H), 7.33 (s, 1H), 4.33–4.20 (m, 2H, nonequivalent geminal hydrogens), 2.12 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 156.5, 147.7, 145.4, 143.3, 141.1, 136.6, 135.4, 129.1, 128.8, 128.7, 123.9, 123.4, 62.9, 54.7, 22.2, 13.8; HRMS: calcd. for $C_{21}H_{18}ClN_3O_5$ (M^+): 427.0935, found: 427.0941.

Ethyl 2-(2′-benzyl-4′-chloro-3′-oxopyridazin-5′-yl)-2-(4″-nitrophenyl)propanoate (7e)

White solid. Yield: 64%. Mp: 115.8–116.9 °C. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 9.2 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.50–7.35 (m, 5H), 7.17 (s, 1H), 5.33 (dd, J = 13.6 Hz, 2H, nonequivalent geminal hydrogens), 4.30–4.12 (m, 2H, nonequivalent geminal hydrogens), 2.03 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 156.8, 147.6, 145.4, 143.5, 135.7, 135.1, 135.0, 129.4, 129.1, 128.7, 128.4, 123.9, 62.8, 56.5, 54.6, 22.2, 13.8; HRMS: calcd. for $C_{22}H_{20}ClN_3O_5$ (M^+): 441.1091, found: 441.1096.

Compounds 8a–e

Compounds **8a–e** were prepared by the same procedure as that for compounds **6a–f**, using 4-chloro-5-nitro-pyridazinone as electrophile to quench the VNS reaction. Except that the second step was carried out at room temperature.

Ethyl 2-(2′-ethyl-5′-nitro-3′-oxopyridazin-4′-yl)-2-(4″-nitrophenyl)propanoate (8a)

Yellow solid. Yield: 72%. Mp: 99.7–100.9 °C. ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J = 9.2 Hz, 2H), 7.95 (s, 1H), 7.65 (d, J = 9.2 Hz, 2H), 4.30–4.21 (m, 2H, nonequivalent geminal hydrogens), 4.14–4.05 (m, 2H, nonequivalent geminal hydrogens), 2.18 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.3, 158.7, 147.5, 144.5, 136.6, 129.9, 128.1, 123.4, 62.4, 53.6, 48.6, 19.7, 13.7, 13.2; HRMS: calcd. for $C_{17}H_{18}N_4O_7$ (M^+): 390.1175, found: 390.1156.

Ethyl 2-(2′-propyl-5′-nitro-3′-oxopyridazin-4′-yl)-2-(4″-nitrophenyl)propanoate (8b)

Yellow solid. Yield: 72%. Mp: 119.9–120.7 °C. ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J = 9.2 Hz, 2H), 7.95 (s, 1H), 7.65 (d, J = 9.2 Hz, 2H), 4.23–4.02 (m, 4H), 2.17 (s, 3H), 1.87–1.82 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.3, 158.9, 147.5, 147.4, 144.5, 136.6, 129.8, 128.1, 123.4, 62.4, 54.8, 53.6, 21.6, 19.7, 13.7, 11.0; HRMS: calcd. for $C_{18}H_{20}N_4O_7$ (M^+): 404.1332, found: 404.1336.

Ethyl 2-(2′-*tert*-butyl-5′-nitro-3′-oxopyridazin-4′-yl)-2-(4″-nitrophenyl)propanoate (8c)

Yellow solid. Yield: 72%. Mp: 99.7–100.9 °C. ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 7.64 (d, J = 9.2 Hz, 2H), 4.16–3.98 (m, 2H, nonequivalent geminal hydrogens), 2.19 (s, 3H), 1.65 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 159.5, 147.5, 147.1, 144.7, 137.0, 128.1, 127.9, 123.3, 67.5, 62.3, 53.5, 27.6, 20.1, 13.7; HRMS: calcd. for $C_{19}H_{22}N_4O_7$ (M^+): 418.1521, found: 418.1523.

Ethyl 2-(2′-phenyl-5′-nitro-3′-oxopyridazin-4′-yl)-2-(4″-nitrophenyl)propanoate (8d)

Yellow solid. Yield: 75%. Mp: 194.5–195.8 °C. ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J = 8.8 Hz, 2H), 8.08 (s, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.56–7.45 (m, 5H), 4.18–4.03 (m, 2H, nonequivalent geminal hydrogens), 2.23 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 158.9, 147.6, 147.2, 144.4, 140.5, 138.3, 130.6, 129.3, 129.1, 128.1, 125.1, 123.5, 62.5, 53.9, 19.8, 13.7; HRMS: calcd. for $C_{21}H_{18}N_4O_7$ (M^+): 438.1175, found: 438.1173.

Ethyl 2-(2′-benzyl-5′-nitro-3′-oxopyridazin-4′-yl)-2-(4″-nitrophenyl)propanoate (8e)

Yellow viscous liquid. Yield: 75%. ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 2H), 7.95 (s, 1H), 7.61 (d, J = 9.2 Hz, 2H), 7.45–7.35 (m, 5H), 5.34 (dd, J = 13.6 Hz, 2H, nonequivalent geminal hydrogens), 4.10–3.92 (m, 2H, nonequivalent geminal hydrogens), 2.16 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H);^{13}C NMR ($CDCl_3$) δ 170.1, 158.8, 147.5, 147.4, 144.4, 137.2, 134.7, 130.1, 129.1, 128.8, 128.6, 128.0, 123.4, 62.4, 56.7, 53.6, 19.7, 13.6; HRMS: calcd. for $C_{22}H_{20}N_4O_7$ (M^+): 452.1332, found: 452.1332.

Compounds 9a–f

Compounds **9a–f** were prepared by the same procedure as that for compounds **6a–f**, using 4,5-dichloropyridazinone as electrophile to quench the VNS reaction. Except that the second step was carried out at 40° C.

Ethyl 2-{[5′-(4″-methoxyphenyl)-1′,3′,4′-oxadiazol-2′-yl]methyl}-2-(4‴-nitrophenyl)propanoate (9a)

Yellow solid. Yield: 74%. Mp: 123.6–124.5 °C. ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 9.2 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.28–4.20 (m, 2H, nonequivalent geminal hydrogens), 3.87 (s, 3H), 3.67 (dd, J = 15.2 Hz, 2H, nonequivalent geminal hydrogens), 1.83 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 164.8, 162.6, 162.4, 148.6, 147.2, 128.4, 127.2, 123.8, 115.9, 114.5, 62.1, 55.5, 49.7, 35.4, 22.4, 13.9; HRMS: calcd. for $C_{21}H_{21}N_3O_6$ (M^+): 411.1430, found: 411.1431.

Ethyl 2-{[5′-(4″-methylphenyl)-1′,3′,4′-oxadiazol-2′-yl]methyl}-2-(4‴-nitrophenyl)propanoate (9b)

Yellow solid. Yield: 72%. Mp: 69.6–70.5 °C. ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 4.26–4.19 (m, 2H, nonequivalent geminal hydrogens), 3.67 (dd, J = 15.2 Hz, 2H, nonequivalent geminal hydrogens), 2.40 (s, 3H), 1.82 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 165.0, 162.9, 148.6, 147.2, 142.4, 129.8, 127.2, 126.6, 123.8, 120.7, 62.1, 49.7, 35.3, 22.4, 21.6, 13.9; HRMS: calcd. for $C_{21}H_{21}N_3O_5$ (M^+): 395.1481, found: 395.1482.

Ethyl 2-{[5′-(4″-ethylphenyl)-1′,3′,4′- oxadiazol-2′-yl]methyl}-2-(4‴-nitrophenyl)propanoate (9c)

Orange viscous liquid. Yield: 72%. ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 4.27–4.21 (m, 2H, nonequivalent geminal hydrogens), 3.67 (dd, J = 15.2 Hz, 2H, nonequivalent geminal hydrogens), 2.71 (q, J = 7.6 Hz, 2H), 1.83 (s, 3H), 1.28–1.21 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.4, 165.0, 162.9, 148.6, 148.6, 147.2, 128.6, 127.2, 126.7, 123.8, 120.9, 62.1, 49.7, 35.4, 28.9, 22.4, 15.2, 14.0; HRMS: calcd. for $C_{22}H_{23}N_3O_5$ (M^+): 409.1638, found: 409.1623.

Ethyl 2-[(5′-phenyl-1′,3′,4′-oxadiazol-2′-yl)methyl]-2-(4″-nitrophenyl)propanoate (9d)

Yellow viscous liquid. Yield: 70%. ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.51–7.44 (m, 3H), 4.27–4.19 (m, 2H, nonequivalent geminal hydrogens), 3.68 (dd, J = 15.2 Hz, 2H, nonequivalent geminal hydrogens), 1.83 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 164.9, 163.2, 148.6, 147.2, 131.8, 129.1, 127.2, 126.6, 123.8, 123.5, 62.1, 49.7, 35.4, 22.5, 13.9; HRMS: calcd. for $C_{20}H_{19}N_3O_5$ (M^+): 381.1325, found: 381.1313.

Ethyl 2-{[5′-(4″-fluorophenyl)-1′,3′,4′-oxadiazol-2′-yl]methyl}-2-(4‴-nitrophenyl)propanoate (9e)

Orange viscous liquid. Yield: 68%. ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 2H), 7.85 (dd, J = 8.8 Hz, J = 5.6 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.15 (t, J = 8.4 Hz, 2H), 4.28–4.17 (m, 2H, nonequivalent geminal hydrogens), 3.67 (dd, J = 15.2 Hz, 2H, nonequivalent geminal hydrogens), 1.84 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 166.0, 164.1, 163.3, 148.5, 147.2, 128.9, 127.2, 123.8, 119.8, 116.5, 62.2, 49.7, 35.3, 22.4, 14.0; HRMS: calcd. for $C_{20}H_{18}FN_3O_5$ (M^+): 399.1230, found: 399.1226.

Ethyl 2-{[5′-(4″-chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl]methyl}-2-(4‴-nitrophenyl)propanoate (9f)

Yellow solid. Yield: 68%. Mp: 85.0–85.9 °C. ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.27–4.17 (m, 2H, nonequivalent geminal hydrogens), 3.67 (dd, J = 15.2 Hz, 2H, nonequivalent geminal hydrogens), 1.84 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 164.1, 163.4, 148.5, 147.2, 138.1, 129.5, 127.9, 127.2, 123.8, 122.0, 62.2, 49.7, 35.4, 22.4, 13.9; HRMS: calcd. for $C_{20}H_{18}ClN_3O_5$ (M^+): 415.0935, found: 415.0935.

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