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A facile approach to polysubstituted pyrazoles from hydrazonyl chlorides and vinyl azides

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ABSTRACT

A novel and facile approach to polysubstituted pyrazoles from readily synthesized hydrazonyl chlorides and vinyl azides was developed. The reaction was regiospecific and proceeded under mild conditions in the presence of base.

1. Introduction

Pyrazoles are one of the most prevalent heterocyclic compounds with a wide range of biological activities, such as anti-hyperglycemic,[1] anti-inflammatory,[2] antiobesity,[3] antitumor[4] antimycobacterial,[5] molluscicidal activity,[6] and cardiac hypertrophy suppression.[7] Considering the important biological properties of pyrazole compounds, numerous methods toward pyrazoles syntheses have been developed over the past decades.[8,9] The 1,3-dipolar cycloaddition is widely used for the syntheses of pyrazoles using diverse synthons, such as nitrilimines and alkynes,[10] hydrazones and nitroolefins,[11] and azomethine imines and alkynes.[12] The most prevalent method is reacting hydrazines with 1,3-dicarbonyl compounds.[13] Despite numerous diverse approaches toward syntheses of pyrazoles developed so far, it is still challenging to prepare polysubstituted pyrazoles with various substituents from readily available building blocks.

Vinyl azides, precursors of 2*H*-azirines, have been widely utilized in cycloaddition reactions yielding heterocyclic compounds in recent years.[14] Previously, we have found a domino approach to pyrrolo[1,2-α]pyrazines from vinyl azides and 1*H*-2-pyrrolecarbaldehyde.[14a] Herein we report a facile approach to provide polysubstituted pyrazoles from vinyl azides and hydrazonyl chlorides in the presence of base with moderate to good yields. Interestingly, we observed that the nitrogen atom of the three-atom synthon in vinyl azide was not incorporated into the newly formed molecule. The azido group herein does not act in a manner that is usually reported.[14] It serves as a leaving group and stabilization of developing negative charge during the reaction in this study.

2. Results and discussion

Initially, the reaction between *N*-phenylbenzohydrazonoyl chloride **1a** and vinyl azide **2a** was selected as a model system to optimize the reaction conditions (Table 1). It was found that no reaction occurred in the absence of base. With addition of a variety of bases at room temperature, the polysubstituted pyrazole **3a** was observed as the major product (Table 1). Screening of the solvents showed that THF was the most efficient solvent producing the highest yields (Table 1, entries 2–4). It is noteworthy that the selection of the base plays a crucial role in the success of **3a** synthesis and Cs_2CO_3 was found to be the most favorable base of the ones tested (Table 1, entries 4–9). The reaction was also tested at higher temperature but with a slight decrease in the yield (Table 1, entry 10). Based on this initial study, the most suitable reaction condition for the formation of **3a** was established (Table 1, entry 4). The crude product, obtained under this reaction condition, was analyzed by LC–MS. The result showed that the 1,3-dipolar cycloaddition of **1a**

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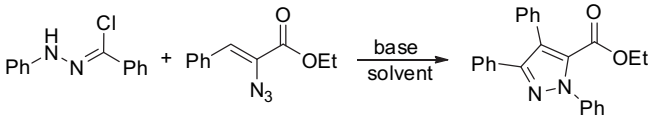
Table 1
Optimization of reaction conditions[a]



1a 2a 3a

Entry	Base	Solvent	T (°C)	Yield[b] (%)
1	—	THF	25	n.r
2	Cs_2CO_3	DMF	25	19
3	Cs_2CO_3	MeCN	25	66
4	**Cs_2CO_3**	**THF**	**25**	**91**
5	K_2CO_3	THF	25	89
6	CsF	THF	25	42
7	Cs_2SO_4	THF	25	n.r.
8	TBAF	THF	25	Trace
9	DBU	THF	25	Trace
10	Cs_2CO_3	THF	50	86

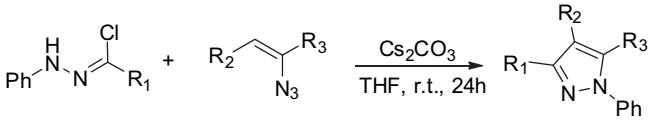
[a] Reaction conditions: vinyl azide (0.1 mmol, 1.0 equiv), hydrazonyl chloride (0.11 mmol, 1.1 equiv), base (0.1 mmol, 1.0 equiv), 1.5 mL solvent, 24 h, rt.
[b] Determined by HPLC, based on the disappearance of the starting vinyl azide. The most successful entry is highlighted in bold.

and **2a** we presented herein was regiospecific affording pyrazole with only one isomer (**3a**).

With the optimized reaction conditions in hand, the scope and limitation of the reaction were examined with a variety of hydrazonyl chlorides **1** and vinyl azides **2**. The hydrazonyl chlorides were readily prepared from hydrazones.[15] The vinyl azides presented herein were synthesized from benzaldehydes[14b–d] or styrenes.[16]

As shown in Table 2, the reaction can tolerate a range of R_1-substituents, such as alkyl, aryl, thienyl, furyl, and pyridinyl moieties. The influence of R_1-substituents in this reaction is illustrated in entries 1–10 and 17. In particular, we would like to point out entry 10 where the 3-NO_2 on the aromatic ring lead to sharp reduction in yield, **3j** (Table 2, entry 10, 36%), compared to **3a** (Table 2, entry 1, 81%). It might indicate that a strong electron-withdrawing group on the phenyl ring of R_1-substituent is not favorable for the reaction under the synthetic conditions described. When the aryl R_1-substituent was changed to isopropyl group (Table 2, entry 17), the isolated yield of the reaction decreased comparing to entry 1 (Table 2).

Table 2
Reactions of vinyl azides and hydrazonyl chlorides[a]



1 2 3

Entry	R_1	R_2	R_3	Compound	Yield[b] (%)
1	Ph	Ph	CO_2Et	**3a**	81
2	4-FC_6H_4	Ph	CO_2Et	**3b**	91
3	4-BrC_6H_4	Ph	CO_2Et	**3c**	71
4	2-BrC_6H_4	Ph	CO_2Et	**3d**	68
5	4-ClC_6H_4	Ph	CO_2Et	**3e**	72
6	4-$MeOC_6H_4$	Ph	CO_2Et	**3f**	74
7	Furyl	Ph	CO_2Et	**3g**	75.
8	2-(5-BrThiazoyl)	Ph	CO_2Et	**3h**	68
9	2-Pyridinyl	Ph	CO_2Et	**3i**	52
10	3-$NO_2C_6H_4$	Ph	CO_2Et	**3j**	36
11	Ph	4-FC_6H_4	CO_2Et	**3k**	69
12	Ph	4-BrC_6H_4	CO_2Et	**3l**	71
13	Ph	4-$MeOC_6H_4$	CO_2Et	**3m**	64
14	Ph	3-$NO_2C_6H_4$	CO_2Et	**3n**	86
15	Ph	4-BrC_6H_4	4-ClC_6H_4–CO	**3o**	55
16	Ph	H	1-Morpholinyl–CO	**3p**	n.r
17	$(CH_3)_2CH$	Ph	CO_2Et	**3q**	55
18	$(CH_3)_2CH$	4-FC_6H_4	2-Thiophenyl–CO	**3r**	67
19	Ph	C_3H_7	CO_2Et	**3s**	64
20	Ph	Ph	$CO_2{}^iBu$	**3t**	83

[a] Reactions were carried out in THF (4.0 mL) with **1** (0.33 mmol), **2** (0.3 mmol), and Cs_2CO_3 (0.3 mmol) at rt for 24 h under N_2.
[b] Isolated yield.

To extend the utility of this reaction, a set of vinyl azides were also explored (Table 2, entries 11–16 and 18–20). On the basis of these studies, we found that a range of R_2- and R_3-substituents can be tolerated in this reaction. Results from entries 11–14 indicated that the electron deficient phenyl ring of R_2-substituents was favorable for the yield. The vinyl azide **2n**, having a R_2-substituent as 3-NO_2 substituted phenyl, gave the desired product with good isolated yield (86%, Table 2, entry 14). The electron-withdrawing inductive effects of R_3-substituent were also evaluated. In this case the mild electron-withdrawing group (Table 2, entry 15) gave the product in relative lower isolated yield (55%), compared to entry 12 (Table 2, 71%). Unexpectedly, no reaction took place when R_2-substituent was just hydrogen (Table 2, entry 16).

The polysubstituted pyrazoles were characterized by ^1H and ^{13}C NMR, MS, and HRMS (ESI). In the presence of base the hydrazonyl chloride liberates the l,3-dipolar diphenyl-nitrilimine.[17] It is possible that either Michael addition mode could occur, initiated by the formed tautomeric electronegative carbon or nitrogen atom. For this reason it is necessary to establish the reaction pathway. In order to accomplish this, the pyrazole structures were confirmed by single-crystal X-ray diffraction studies. Pyrazole **3f** is given as an example (Fig. 1).

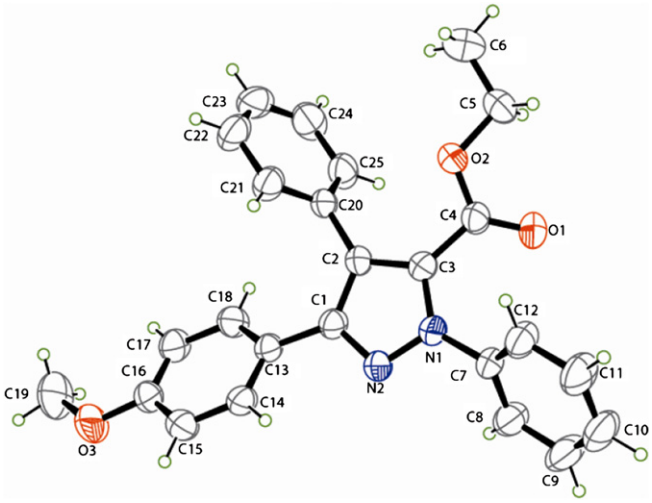
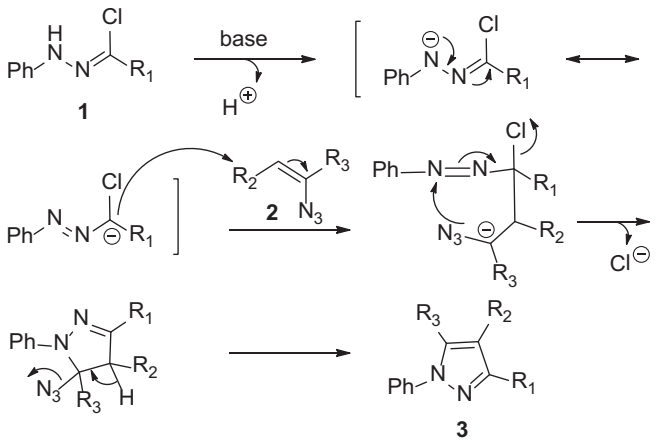


Fig. 1. Crystal structure of compound **3f**.

On the basis of the above investigations, a plausible mechanism is proposed as shown in Scheme 1. The presence of base initiates the polarization of **1** by removal of the hydrogen. The formed active hydrazonyl chloride is expected to have a Michael addition and a subsequent intramolecular cyclization with vinyl azide (**2**) to get the intermediate. A fast elimination of the intermediate, driven by excellent leaving group ability of the azido group, affords the polysubstituted pyrazole (**3**) in the presence of base.

3. Conclusions

In summary, we have reported a novel, facile, and regiospecific approach for the preparation of polysubstituted pyrazoles under mild conditions. This reaction was realized with readily available hydrazonyl chlorides and vinyl azides in moderate to good yields.



Scheme 1. Proposed reaction mechanism.

Interestingly, the azido group of the vinyl azides was not incorporated into the newly formed molecule and served as a leaving group in this study.

4. Experimental section

4.1. General

Reactions were carried out in anhydrous solvents under nitrogen atmosphere. THF was distilled from sodium-benzophenone. Purifications of reaction products were carried out by chromatography using silica gel (200–300 mesh). Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and for ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), and coupling constant(s) in Hertz. For ^{13}C NMR TMS (δ=0) or $CDCl_3$ (δ=77.26) was used as internal standard and spectra were obtained with complete proton decoupling. MS and HRMS were obtained using ESI ionization. A single crystal of compound **3f** was measured on a Rigaku RAXIS-RAPID single-crystal diffractometer. Crystallographic data (excluding structure factors) for **3f** in this paper have been deposited at the Cambridge Crystallographic Data Center with a deposition number CCDC 804343. Copy of the data can be obtained free of charge on application to CCDC by e-mail (deposit@ccdc.cam.ac.uk).

4.2. General procedure for the synthesis of 3

A mixture of hydrazonyl chloride **1** (0.3 mmol, 1.0 equiv), vinyl azide **2** (0.33 mmol, 1.1 equiv) and Cs_2CO_3 (0.3 mmol, 1.0 equiv) was stirred in anhydrous THF (4 mL) at room temperature under nitrogen overnight. The reaction mixture was quenched with water (5 mL), then extracted three times with EtOAc (10 mL×3). The combined organic extracts were washed with water (10 mL×3), brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired product **3**.

*4.2.1. 1,3,4-Triphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3a**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.549 (2H, d, J=8.0 Hz), 7.499–7.417 (6H, m), 7.368–7.324 (5H, m), 7.251–7.237 (2H, m), 4.052 (2H, q, J=7.0 Hz), 0.912 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 150.2, 140.5, 132.6, 132.3, 132.2, 130.5, 128.8, 128.4, 128.2, 128.1, 128.0, 127.9, 127.5, 125.3, 125.7, 61.2, 13.4; LC–MS (ESI): m/z [M+H]$^+$: 369.3; HRMS (ESI): m/z calcd for $C_{24}H_{20}N_2O_2$ (M)$^+$ 368.1525, found: m/z 368.1530.

*4.2.2. 3-(4-Fluorophenyl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3b**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.549–7.531 (2H, m), 7.504–7.474 (2H, m), 7.458–7.412 (3H, m), 7.376–7.353 (3H, m), 7.333–7.313 (2H, m), 6.934 (2H, t, J=9.0 Hz), 4.050 (2H, q, J=7.5 Hz), 0.909 (3H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6 (d, J=246 Hz), 160.0, 149.3, 140.4, 132.6, 132.1, 130.4, 129.9 (d, J=8 Hz), 128.8, 128.5, 128.3 (d, J=3 Hz), 128.1, 127.7, 125.3, 124.9, 115.2 (d, J=21 Hz), 61.3, 13.4; LC–MS (ESI): m/z [M+H]$^+$: 387.2; HRMS (ESI): m/z calcd for $C_{24}H_{19}N_2O_2F$(M)$^+$ 386.1431, found: m/z 386.1435.

*4.2.3. 3-(4-Bromophenyl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3c**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.548–7.529 (2H, m), 7.508–7.478 (2H, m), 7.465–7.431 (1H, m), 7.381–7.364 (5H, m), 7.337–7.312 (4H, m), 4.048 (2H, q, J=7.0 Hz), 0.907 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 149.2, 140.6, 133.0, 132.2, 131.6, 131.4, 130.6, 129.8, 129.0, 128.8, 128.4, 127.9, 125.5, 125.2, 122.4, 61.5, 13.6; LC–MS (ESI): m/z [M+H]$^+$: 447.2; HRMS (ESI): m/z calcd for $C_{24}H_{19}N_2O_2Br$(M)$^+$ 446.0630, found: m/z 446.0635.

*4.2.4. 3-(2-Bromophenyl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3d**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.572–7.545 (3H, m), 7.494–7.464 (2H, t, J=7.5 Hz), 7.426 (1H, t, J=7.5 Hz), 7.335 (1H, d, J=7.5 Hz), 7.273–7.245 (6H, m), 7.175 (1H, t, J=7.5 Hz), 4.125 (2H, q, J=7.0 Hz), 0.988 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 150.9, 140.6, 133.9, 133.1, 132.7, 131.7, 130.3, 130.1, 129.0, 128.7, 127.9, 127.5, 127.2, 126.5, 125.5, 124.4, 61.7, 13.7; LC–MS (ESI): m/z [M+H]$^+$: 447.2; HRMS (ESI): m/z calcd for $C_{24}H_{19}N_2O_2Br$(M)$^+$ 446.0630, found: m/z 446.0634.

*4.2.5. 3-(4-Chlorophenyl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3e**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.547–7.528 (2H, m), 7.506–7.476 (2H, m), 7.459–7.430 (1H, m), 7.404–7.366 (5H, m), 7.331–7.312 (2H, m), 7.211 (2H, dt, J=9.0, 2.0 Hz), 4.050 (2H, q, J=7.5 Hz), 0.909 (3H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 149.2, 140.6, 134.1, 132.9, 132.2, 130.9, 130.6, 129.6, 129.0, 128.8, 128.6, 128.4, 127.9, 125.6, 125.3, 61.5, 13.6; LC–MS (ESI): m/z [M+H]$^+$: 403.2; HRMS (ESI): m/z calcd for $C_{24}H_{19}N_2O_2Cl$(M)$^+$ 402.1135, found: m/z 402.1130.

*4.2.6. 3-(4-Methoxyphenyl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3f**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.550–7.531 (2H, m), 7.490–7.460 (2H, m), 7.437–7.415 (1H, m), 7.401–7.372 (2H, m), 7.372–7.329 (5H, m), 6.776 (2H, dt, J=8.5, 3.0 Hz), 4.043 (2H, q, J=7.0 Hz), 3.763 (3H, s), 0.904 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 159.6, 150.2, 140.8, 132.7, 130.7, 129.6, 129.0, 128.5, 128.3, 127.7, 125.5, 125.0, 124.9, 113.9, 61.4, 55.4, 13.6; LC–MS (ESI): m/z [M+H]$^+$: 399.3; HRMS (ESI): m/z calcd for $C_{25}H_{22}N_2O_3$ (M)$^+$ 398.1630, found: m/z 398.1634.

*4.2.7. 3-(Furan-2-yl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3g**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.536–7.521 (2H, d, J=7.5 Hz), 7.487–7.400 (9H, m), 6.288 (1H, dd, J=3.5, 1.5 Hz), 6.025 (1H, d, J=3.5 Hz), 4.021 (2H, q, J=7.0 Hz), 0.873 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 147.0, 142.7, 142.4, 140.5, 132.7, 132.1, 130.4, 128.9, 128.8, 128.3, 128.1, 125.8, 124.7, 111.1, 109.0, 61.4, 13.5; LC–MS (ESI): m/z [M+H]$^+$: 359.2; HRMS (ESI): m/z calcd for $C_{22}H_{18}N_2O_3$ (M)$^+$ 358.1317, found: m/z 358.1322.

*4.2.8. 3-(5-Bromothiophen-2-yl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3h**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.532–7.423 (8H, m), 7.414–7.384 (2H, m), 6.820 (1H, d, J=3.5 Hz), 6.611 (1H, d, J=3.5 Hz), 4.023 (2H, q, J=7.0 Hz), 0.875 (3H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 144.8, 140.4, 136.4, 132.9, 131.8,

130.6, 130.2, 129.0, 128.9, 128.5, 128.4, 126.2, 125.7, 124.6, 112.7, 61.5, 13.6; LC–MS (ESI): *m/z* $[M+H]^+$: 453.2; HRMS (ESI): *m/z* calcd for $C_{22}H_{17}N_2O_2BrS(M)^+$ 452.0194, found: *m/z* 452.0189.

*4.2.9. 3-(Pyridine-2-yl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3i**).* ^1H NMR (500 MHz, $CDCl_3$): δ 8.610 (1H, d, *J*=4.5 Hz), 7.562 (2H, d, *J*=7.5 Hz), 7.529–7.414 (4H, m), 7.375–7.363 (5H, m), 7.270 (1H, d, *J*=7.5 Hz), 7.153 (1H, dd, *J*=7.5, 4.5 Hz), 4.050 (2H, q, *J*=7.0 Hz), 0.901 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 151.5, 150.0, 149.8, 140.6, 136.2, 133.1, 132.3, 130.7, 128.9, 128.8, 128.2, 127.8, 126.2, 125.9, 123.5, 122.8, 61.5, 13.6; LC–MS (ESI): *m/z* $[M+H]^+$: 370.4; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}N_3O_2$ $(M)^+$ 369.1477, found: *m/z* 369.1479.

*4.2.10. 3-(3-Nitrophenyl)-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3j**).* ^1H NMR (500 MHz, $CDCl_3$): δ 8.396 (1H, s), 8.090 (1H, dd, *J*=8.0, 2.0 Hz), 7.730 (1H, d, *J*=7.5 Hz), 7.561–7.461 (5H, m), 7.417–7.370 (4H, m), 7.353–7.335 (2H, m), 4.060 (2H, q, *J*=7.0 Hz), 0.912 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 148.5, 147.9, 140.5, 134.3, 133.9, 133.3, 131.7, 130.5, 129.3, 129.1, 129.0, 128.7, 128.4, 125.7, 125.6, 123.1, 122.8, 61.6, 13.6; LC–MS (ESI): *m/z* $[M+H]^+$: 414.2; HRMS (ESI): *m/z* calcd for $C_{24}H_{19}N_3O_4$ $(M)^+$ 413.1376, found: *m/z* 413.1372.

*4.2.11. 4-(4-Fluorophenyl)-1,3-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3k**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.547–7.528 (2H, m), 7.498–7.468 (2H, m), 7.449–7.429 (3H, m), 7.339–7.302 (2H, m), 7.266–7.248 (3H, m), 7.061 (2H, t, *J*=9.0 Hz), 4.061 (2H, q, *J*=7.0 Hz), 0.936 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6 (d, *J*=245 Hz), 160.2, 150.5, 140.7, 132.8, 132.5 (d, *J*=8 Hz), 132.2, 129.1, 128.7, 128.5, 128.4 (d, *J*=4 Hz), 128.4, 128.3, 125.6, 124.2, 115.3 (d, *J*=22 Hz), 61.5, 13.7; LC–MS (ESI): *m/z* $[M+H]^+$: 387.2; HRMS (ESI): *m/z* calcd for $C_{24}H_{19}N_2O_2F$ $(M)^+$ 386.1431, found: *m/z* 386.1435.

*4.2.12. 4-(4-Bromophenyl)-1,3-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3l**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.529 (2H, d, *J*=8.0 Hz), 7.501–7.467 (4H, t, *J*=8.5 Hz), 7.449–7.426 (3H, m), 7.275–7.248 (3H, m), 7.231–7.214 (2H, d, *J*=8.5 Hz), 4.066 (2H, q, *J*=7.0 Hz), 0.944 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 150.4, 140.6, 132.7, 132.4, 132.1, 131.5, 131.4, 129.0, 128.7, 128.5, 128.4, 128.3, 125.6, 124.0, 122.0, 61.6, 13.7; LC–MS (ESI): *m/z* $[M+H]^+$: 447.2; HRMS (ESI): *m/z* calcd for $C_{24}H_{19}N_2O_2Br$ $(M)^+$ 446.0630, found: *m/z* 446.0633.

*4.2.13. 4-(4-Methoxyphenyl)-1,3-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3m**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.548–7.531 (2H, m), 7.485–7.458 (4H, m), 7.433–7.404 (1H, m), 7.272–7.245 (5H, m), 6.908–6.891 (2H, m), 4.065 (2H, q, *J*=7.0 Hz), 3.835 (3H, s), 0.944 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 159.4, 150.5, 140.9, 132.8, 132.6, 131.8, 128.9, 128.5, 128.4, 128.0, 125.5, 125.0, 124.6, 113.8, 61.4, 55.4, 13.7; LC–MS (ESI): *m/z* $[M+H]^+$: 399.3; HRMS (ESI): *m/z* calcd for $C_{25}H_{22}N_2O_3$ $(M)^+$ 398.1630, found: *m/z* 398.1634.

*4.2.14. 4-(3-Nitrophenyl)-1,3-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3n**).* ^1H NMR (500 MHz, $CDCl_3$): δ 8.307 (1H, t, *J*=2.0 Hz), 8.221 (1H, ddd, *J*=8.0, 2.0, 1.0 Hz), 7.636 (1H, dt, *J*=8.0, 1.5 Hz), 7.556–7.451 (6H, m), 7.404–7.385 (2H, m), 7.303–7.262 (3H, m), 4.070 (2H, q, *J*=7.0 Hz), 0.925 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 150.6, 148.3, 140.6, 137.0, 134.5, 132.9, 131.6, 129.2, 129.1, 129.0, 128.7, 128.6, 128.5, 126.0, 125.8, 122.8, 61.7, 13.7; LC–MS (ESI): *m/z* $[M+H]^+$: 414.2; HRMS (ESI): *m/z* calcd for $C_{24}H_{19}N_3O_4$ $(M)^+$ 413.1376, found: *m/z* 413.1373.

*4.2.15. [4-(4-Bromophenyl)-1,3-diphenyl-1H-pyrazole-5-yl]-4-chlorophenyl-methanone (**3o**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.625–7.608 (2H, d, *J*=8.5 Hz), 7.521–7.503 (2H, m), 7.455–7.440 (2H, d, *J*=7.5 Hz), 7.358–7.270 (8H, m), 7.254–7.225 (2H, m), 7.06 (2H, d, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.6, 150.4, 140.8, 139.6, 138.7, 134.9, 132.0, 131.9, 131.8, 131.2, 130.5, 129.5, 129.1, 128.7, 128.6, 128.5, 128.4, 124.2, 122.7, 122.1; LC–MS (ESI): *m/z* $[M+H]^+$: 513.4; HRMS (ESI): *m/z* calcd for $C_{28}H_{18}N_2OBrCl$ $(M)^+$ 512.0291, found: *m/z* 512.0295.

*4.2.16. 3-Isopropyl-1,4-diphenyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3q**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.454 (4H, m), 7.396 (3H, m), 7.349 (3H, m), 4.009 (2H, q, *J*=7.0 Hz), 3.012 (1H, m, *J*=7.0 Hz), 1.245 (6H, d, *J*=7.0 Hz), 0.876 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 157.1, 140.6, 132.6, 131.2, 130.2, 128.7, 128.1, 127.9, 129.3, 125.4, 125.2, 61.0, 26.2, 22.6, 13.4; LC–MS (ESI): *m/z* $[M+H]^+$: 335.3; HRMS (ESI): *m/z* calcd for $C_{28}H_{18}N_2OBrCl$ $(M)^+$ 334.1681, found: *m/z* 334.1684.

*4.2.17. [4-(4-Fluorophenyl)-3-isopropyl-1-phenyl-1H-pyrazol-5-yl]-(thiophen-2-yl)-methanone (**3r**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.558 (1H, d, *J*=4.5 Hz), 7.450 (2H, d, *J*=8.0 Hz), 7.348 (2H, t, *J*=8.0 Hz), 7.298 (1H, d, *J*=4.0 Hz), 7.247 (3H, m), 6.976 (2H, t, *J*=8.5 Hz), 6.864 (1H, t, *J*=4.5 Hz), 3.135 (1H, m, *J*=7.0 Hz), 1.319 (6H, d, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.7, 162.0 (d, *J*=245 Hz), 156.8, 143.6, 139.8, 137.7, 135.7, 131.4 (d, *J*=8 Hz), 129.2, 128.1, 127.9 (d, *J*=3 Hz), 127.6, 123.8, 122.5, 115.4 (d, *J*=21 Hz), 26.2, 22.6; LC–MS (ESI): *m/z* $[M+H]^+$: 391.2; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}FN_2OS$ $(M)^+$ 390.1202, found: *m/z* 390.1206.

*4.2.18. 1,3-Diphenyl-4-propyl-1H-pyrazole-5-carboxylic acid ethyl ester (**3s**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.650 (2H, d, *J*=7.5 Hz), 7.453–7.358 (8H, m), 4.227 (2H, q, *J*=7.0 Hz), 2.834 (2H, t, *J*=8.0 Hz), 1.644 (2H, m), 1.168 (3H, t, *J*=7.0 Hz), 0.964 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 151.5, 141.1, 133.1, 131.8, 128.6, 128.5, 128.3, 128.1, 128.0, 125.9, 125.7, 26.3, 24.5, 14.2, 13.8; LC–MS (ESI): *m/z* $[M+H]^+$: 335.3; HRMS (ESI): *m/z* calcd for $C_{21}H_{22}N_2O_2$ $(M)^+$ 334.1681, found: *m/z* 334.1686.

*4.2.19. 1,3,4-Triphenyl-1H-pyrazole-5-carboxylic acid tert-butyl ester (**3t**).* ^1H NMR (500 MHz, $CDCl_3$): δ 7.547 (2H, d, *J*=7.5 Hz), 7.494–7.405 (5H, m), 7.376–7.321 (5H, m), 7.238–7.225 (3H, m), 1.196 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 149.9, 140.6, 134.0, 132.6, 132.4, 130.5, 128.8, 128.3, 128.2, 128.1, 127.8, 127.4, 125.4, 124.5, 82.6, 27.6; LC–MS (ESI): *m/z* $[M+H]^+$: 397.5; HRMS (ESI): *m/z* calcd for $C_{26}H_{24}N_2O_2$ $(M)^+$ 396.1838, found: *m/z* 396.1830.

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Supplementary data

Copies of NMR spectra for all products and single-crystal X-ray diffraction analysis of **3f** (CCDC 804343). Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.04.103.

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