Novel Syntheses of Polysubstituted Pyrroles and Oxazoles by 1,3-Dipolar Cycloaddition Reactions of Benzotriazole-Stabilized Nitrile Ylides

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1,3-Dipolar cycloadditions of benzotriazole-stabilized nitrile ylides with benzyl α,β-unsaturated-carboxylates and aldehydes as dipolarophiles proceeded smoothly and efficiently to give polysubstituted pyrroles and oxazoles, respectively, in good yields.

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Introduction.

1,3-Dipolar cycloadditions provide versatile synthetic routes to five-membered heterocycles [1]. Easy access to 1,3-dipoles and simple reaction conditions are two advantages of such reactions. An important subset involves nitrile ylides [2], which have traditionally been generated in three ways: i) treatment of imidoyl halides with base, ii) thermolysis or photolysis of phosphoric acid esters from 4,5-dihydro-1,3,5-oxazaphospholes and iii) photolysis of aryl-substituted azirines. Recent work on nitrile ylides has involved 1,3-dipolar cycloadditions to cyclic dipolarophiles, such as substituted azetines [3] and α,β-unsaturated lactones [4]. Considerable attention and effort has also been devoted to azomethine ylides, which often behave as nitrile ylide equivalents [5]. In previous work, a benzotriazole group was employed to generate or stabilize azomethine and nitrile ylide equivalents or precursors [6]. We now report further on the generation of benzotriazole-stabilized nitrile ylides and their application in the synthesis of polysubstituted pyrroles, oxazoles, and imidazoles.

Results and Discussion.

Preparation of the Nitrile Ylide Precursors.

Conventionally, nitrile ylides are generated from amides *via* imidoyl halides. The nature of the selected amide determines both the structure of the final product and the ease of nitrile ylide generation. Following the literature [7], *N*-(benzotriazol-1-ylmethyl)amides **2a-d** were prepared in 90–95% yields by refluxing a mixture of the amide **1a-d** and 1-(hydroxymethyl)benzotriazole in benzene in the presence of *p*-toluenesulfonic acid for an appropriate time, with azeotropic removal of water by a Dean-Stark apparatus. Compounds **2a-d** are all crystalline; none required column chromatography purification. Treatment of **2a-d** with phosphorus pentachloride in toluene at 70–90 °C for 4–6 hours, then evaporation to dryness, provided the corresponding imidoyl chlorides **3a-d,** which are sensitive to moisture and were used immediately for the next step.

Preparation of Pyrroles **5a-c, 5e-g, 6a-g** and **7a-f** (Table 1).

Nitrile ylides **4a-d** are not readily isolated but easily generated *in situ* from amides **2a-d**. Solutions of the imidoyl chlorides **3a-d** in THF were cooled to –40 °C, and the dipolarophiles were added, followed by 4–6 equivalents of *t*-BuOK. The reaction mixtures were allowed to warm up to 20 °C. With a variety of different substituted benzyl α,β-unsaturated carboxylates as dipolarophiles, we obtained benzyl pyrrole esters **5a-c, 5e-g** in 76–90% yields**.** The compounds **5** show a characteristic ^{1}H nmr signal in the 4.95–5.14 ppm range for the benzyl protons, and 6.51–6.61 ppm (doublet, J = 2.3 Hz) for the unsubstituted pyrrole ring proton. Pyrroles **5** can be alkylated *in situ* or

Table 1

Preparation of Pyrroles **5, 6** and **7**

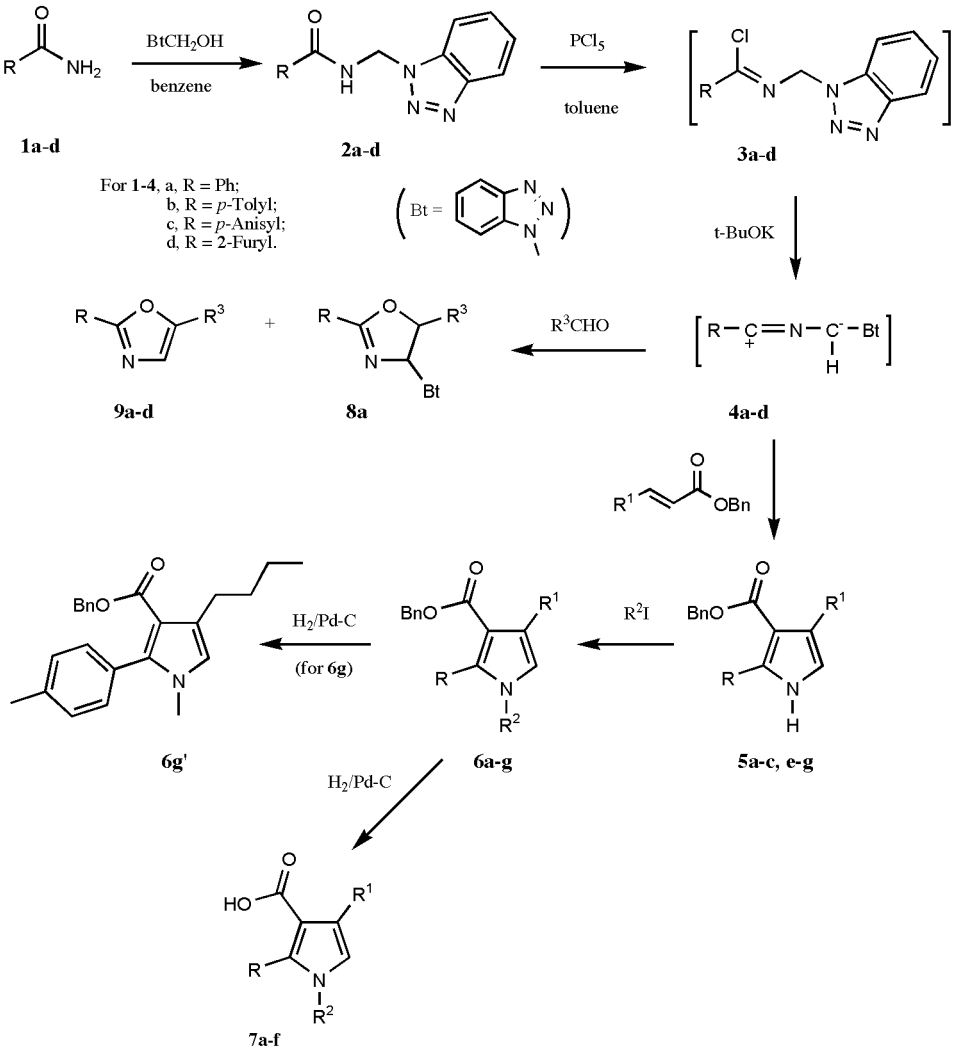
Entry	Amide (R)	Dipolarophile (R^1)	R^2	**5** (%)	**6** (%)	**7** (%)
a	Ph	Ph	Me	90	90	96
b	*p*-Tolyl	Ph	Me	81	93	99
c	*p*-Anisyl	Ph	Me	85	95	90
d	*p*-Anisyl	Ph	Et	- [a]	88	96
e	2-Furyl	Ph	Me	76	85	93
f	*p*-Tolyl	Propyl	Me	81	91	97
g	*p*-Tolyl	2-Thienyl	Me	86	96	_

[a] Compound **5** does not contains R^2, hence **5d** is identical to **5c**.

after isolation, to provide *N*-alkylpyrroles **6a-g** in 85–96% yields. Pyrrole carboxylic acids **7a-f** were readily obtained in 90–99% yield by the hydrogenation of **6** with 5% Pd/C in dioxane under at least 40 bar pressure (Scheme 1). This hydrogenolytic removal of the benzyl group provides a more efficient method for the preparation of pyrrole acids than the traditional hydrolysis of pyrrolecarboxylic acid esters, since strongly acidic or basic conditions at elevated temperatures usually result in incomplete conversion [8] or decarboxylation [9].

of a large excess of Pd/C did not result in cleavage of the benzyl group, but led to desulfurization and formation of product **6g'** in 70% yield. The structure of **6g'** was unambiguously established by X-ray crystallography. Figure 1 shows a perspective view of the structure, which has the *n*-butyl substituent disordered over two conformations with approximately equal occupancies. Desulfurization of thiophenes is important in the petroleum and natural gas industry [10], where hydrodesulfurization (HDS) is typically catalyzed by metal sulfides.

Scheme 1



(For designation of R, R^1, R^2, R^3 in compounds **5**, **6** and **7**, see Table 1)

Certain heteroatoms, and particularly sulfur, can considerably decrease the activity of the hydrogenation catalyst Pd/C. In the case of the thienyl derivative **6g**, the standard reaction conditions resulted in the total recovery of the starting material. The hydrogenation of **6g** in the presence

Preparation of Oxazoles **9a-d**.

A similar procedure to that applied for pyrroles **5**, also gave satisfactory results for the preparation of oxazoles **9a-d** (Scheme 1). While the reaction of imidoyl chloride **3a** and isobutyraldehyde with base at low temperatures (0

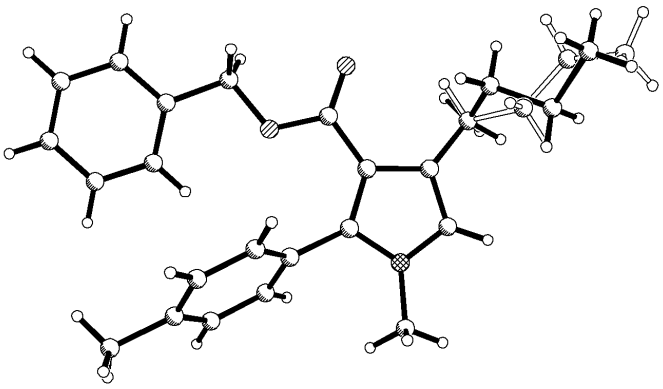


Figure 1**.** Perspective view of the X-ray crystal structure of **6g'**, showing the disorder of the *n*-butyl side chain.

°C to 20 °C) produced a mixture of oxazoline **8a** and oxazole **9a**, a single product **9a** was formed at reflux in THF, which presumably facilitates aromatization by elimination of benzotriazole from **8a**. This observation led to the development of one-pot conditions, which avoided the formation and separation of oxazolines **8a-d** and allowed the production of oxazoles **9a-d** in good yields (Table 2).

Table 2

Preparation of Oxazoles **9**

Entry	Amide (R)	Aldehyde (R^3)	Yield (%)
a	Ph	Isopropyl	77
b	Ph	Ethyl	80
c	*p*-Tolyl	*p*-Anisyl	73
d	*p*-Tolyl	Ph	94

Preparation of Imidazoles **15a-d**.

Under conditions similar to those used to prepare pyrroles **5a-c, 5e-g** and oxazoles **9a-d**, reactions of nitrile ylides **4a-d** with *N*-benzylideneaniline failed to give the corresponding imidazoles. The use of imines possessing strongly electron-withdrawing substituents, *e.g. N*-[(*E*)-phenylmethylidene]benzenesulfonamide, also failed.

Concomitantly, we also prepared substituted amides **12a-d** that did not carry a benzotriazole group from the corresponding acid chlorides **10** and benzylamines **11** in methylene chloride at 0–20 °C in 90–95% yields. Interestingly, treatment of imidoyl chloride **13a**, prepared from **12a** *in situ*, with i) imines, ii) activated olefins and iii) aldehydes afforded none of the expected imidazoles, pyrroles, and oxazoles, but gave, in good yield, imidazole **15a**, which is a self [3+2] condensation product of the imidoyl chloride **13a**. In addition to **15a**, a minor amount of product **16a** was also obtained; **16a** is presumably formed by self [3+3] condensation of the imidoyl chloride **13a** *via* air oxidation (Scheme 2). Indeed, direct treatment of imidoyl chlorides **13a-d** with *t*-BuOK in THF at a decreased temperature and shorter reaction time avoided the formation of pyrazines of type **16** and gave only imidazoles **15a-d** as listed in Table 3. This was thus indicative that the difference between nitrile ylides **4** and **14** in behavior towards imines, activated olefins and aldehydes is related to the ability of benzotriazolyl to act as a leaving group.

Scheme 2

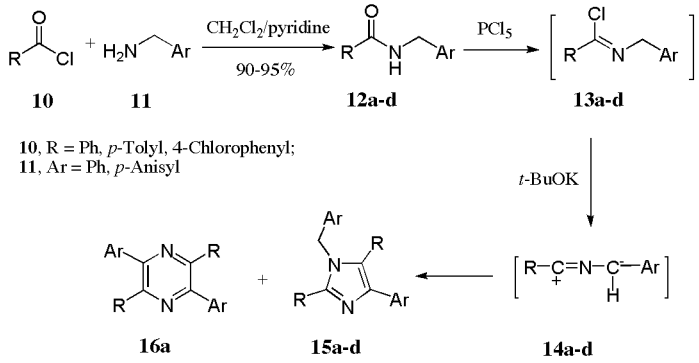


Table 3

Preparation of Imidazoles **15**

Entry	Amide **12**		**15**
	R	Ar	Yield (%)
a	Ph	Ph	53
b	*p*-Tolyl	*p*-Anisyl	66
c	4-Chlorophenyl	*p*-Anisyl	71
d	4-Chlorophenyl	Ph	62

Conclusions.

In conclusion, we have developed a general methodology for the preparation of polysubstituted pyrroles and oxazoles by the cycloaddition of Bt-stabilized nitrile ylides with dipolarophiles. In contrast to Bt-stabilized nitrile ylides **4a-d**, the aryl stabilized nitrile ylides **14a-d** gave only the imidazoles **15a-d** by self condensation.

EXPERIMENTAL

Melting points were determined on a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were taken in $CDCl_3$ (unless stated otherwise) with tetramethylsilane as the internal standard for ^1H (300 MHz) or a solvent as the internal standard for ^{13}C (75MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon or nitrogen atmosphere.

General Procedure for Pyrroles **5a-c, 5e-g**.

Amide **2** (2 mmol) was treated with an equimolar amount of PCl_5 (0.42g, 2 mmol) in toluene at 70–90 °C for 4–6 hours. The

reaction mixture was evaporated *in vacuo* to dryness. The purple residue was dissolved in 20 mL of THF. Under N_2, the solution was cooled below –40 °C, a benzyl α,β-unsaturated carboxylate (2 mmol) was added followed by *t*-BuOK (0.90g, 8 mmol). The mixture was stirred and allowed to warm up to room temperature over 12 hours. The reaction mixture was diluted with EtOAc and washed with saturated aqueous NaCl and water. The organic phase was dried over $MgSO_4$. Purification of the crude product by means of column chromatography provided the desired benzyl pyrrolecarboxylates **5.**

Benzyl 2,4-Diphenyl-1*H*-pyrrole-3-carboxylate (**5a**).

Yellow needles from hexane-ethyl acetate (90%), mp 94–95 °C; ^{1}H nmr: δ 8.58 (s, 1H), 7.41–7.12 (m, 13H), 6.87 (d, *J* = 7.4 Hz, 2H), 6.61 (s, 1H), 5.00 (s, 2H); ^{13}C nmr: δ 165.6, 137.2, 135.7, 135.3, 132.2, 129.0, 128.7, 128.2, 128.1, 128.0 (2C), 127.8, 127.7, 127.6, 126.4, 117.4, 110.5, 65.7.

Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.20; H, 5.42; N, 3.96.

Benzyl 2-(4-Methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (**5b**).

Yellow needles from hexane-ethyl acetate (81%), mp 153–154 °C; ^{1}H nmr: δ 8.61 (s, 1H), 7.36–7.22 (m, 7H), 7.18–7.10 (m, 3H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 6.5 Hz, 2H), 6.55 (d, *J* = 2.6 Hz, 1H), 4.97 (s, 2H), 2.29 (s, 3H); ^{13}C nmr: δ 165.7, 137.9, 137.6, 135.7, 135.5, 129.4, 129.0, 128.8, 128.7, 128.0 (2C), 127.8, 127.5 (2C), 126.3, 117.2, 110.1, 65.7, 21.2.

Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.26; H, 5.88; N, 3.82.

Benzyl 2-(4-Methoxyphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (**5c**).

White prisms from hexane-ethyl acetate (85%), mp 126–127 °C; ^{1}H nmr: δ 8.59 (s, 1H), 7.36–7.12 (m, 10H), 6.87 (d, 2H, *J* = 6.2 Hz), 6.77 (d, 2H, *J* = 3.1 Hz), 6.53 (d, 1H, *J* = 2.3 Hz), 4.98 (s, 2H), 3.71 (s, 3H); ^{13}C nmr: δ 165.8, 159.3, 137.4, 135.6, 135.5, 130.0, 129.0, 128.0 (2C), 127.7, 127.5, 127.3, 126.2, 124.6, 117.2, 113.4, 109.6, 65.6, 55.0.

Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.19; H, 5.91; N, 3.63.

Benzyl 2-(2-Furyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (**5e**).

Dark oil (76%); ^{1}H nmr: δ 9.11 (s, 1H), 7.27–7.11 (m, 10H), 6.96–6.93 (m, 2H), 6.51 (d, *J* = 2.3 Hz, 1H), 6.36–6.34 (m, 1H), 5.12 (s, 2H); ^{13}C nmr: δ 164.9, 145.8, 141.4, 135.8, 135.4, 129.2, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 126.4, 117.4, 112.1, 110.0, 109.3, 65.7.

HRMS (FAB) Calcd for $C_{22}H_{17}NO_3$ $[M]^+$: 343.1208. Found: 343.1208.

Benzyl 2-(4-Methylphenyl)-4-propyl-1*H*-pyrrole-3-carboxylate (**5f**).

White needles from hexane-ethyl acetate (81%), mp 125–126 °C; ^{1}H nmr: δ 8.14 (s, 1H), 7.33–7.25 (m, 5H), 7.18–7.10 (m, 4H), 6.53 (s, 1H), 5.14 (s, 2H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.35 (s, 3H), 1.63–1.55 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C nmr: δ 165.4, 138.1, 137.8, 136.4, 130.2, 129.0, 128.7, 128.2 (2C), 127.7, 127.6, 115.7, 110.3, 65.3, 29.0, 23.6, 21.2, 14.1.

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.17; H, 7.04; N, 4.22.

Benzyl 2-(4-Methylphenyl)-4-(2-thienyl)-1*H*-pyrrole-3-carboxylate (**5g**).

White prisms from hexane-ethyl acetate (86%), mp 159–160 °C; ^{1}H nmr: δ 8.45 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.24–7.10 (m, 7H), 6.99–6.97 (m, 3H), 6.81 (d, *J* = 2.3 Hz, 1H), 5.08 (s, 2H), 2.35 (s, 3H); ^{13}C nmr: δ 165.1, 138.2, 137.8, 136.4, 135.8, 129.3, 128.9, 128.6, 128.1, 128.1, 127.6, 127.0, 126.1, 124.0, 120.0, 117.9, 110.7, 65.8, 21.3.

Anal. Calcd for $C_{23}H_{19}NO_2S$: C, 73.97; H, 5.13; N, 3.75. Found: C, 73.57; H, 5.18; N, 3.76

General Procedure for Benzyl *N*-Alkylpyrrole Carboxylates **6a-g**.

To a solution of **5** (2 mmol) in 20 mL of THF, sodium hydride was added, followed by a solution of alkyl halide (2.2 mmol) in 5 mL of THF at 0 °C. After the addition, the reaction mixture was stirred at 0 °C to room temperature overnight. The reaction mixture was diluted with EtOAc and washed with saturated aqueous NaCl and water. The organic phase was dried over $MgSO_4$. Purification of the crude product by means of column chromatography gave pure products **6**.

Benzyl 1-Methyl-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (**6a**).

Compound **6a** was obtained as a yellow oil (90%); ^{1}H nmr: δ 7.40 (d, *J* = 6.7 Hz, 2H), 7.36–7.21 (m, 8H), 7.14–7.07 (m, 3H), 6.76 (d, *J* = 6.1 Hz, 2H), 6.60 (s, 1H), 4.96 (s, 2H), 3.31 (s, 3H); ^{13}C nmr: δ 164.6, 138.9, 135.9, 135.2, 131.9, 130.4, 129.0, 128.1, 127.9 (2C), 127.6 (2C), 127.2, 126.3, 126.1, 121.6, 111.4, 65.1, 34.4.

HRMS (FAB) Calcd for $C_{25}H_{21}NO_2$ $[M]^+$: 367.1572. Found: 367.1578.

Benzyl 1-Methyl-2-(4-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (**6b**).

Compound **6b** was obtained as a yellow oil (93%); ^{1}H nmr: δ 7.40 (d, *J* = 6.9 Hz, 2H), 7.30–7.11 (m, 10H), 6.78 (d, *J* = 6.7 Hz, 2H), 6.61 (s, 1H), 4.97 (s, 2H), 3.35 (s, 3H), 2.37 (s, 3H); ^{13}C nmr: δ 164.7, 139.2, 137.9, 135.9, 135.3, 130.3, 129.1, 128.9, 128.7, 127.8, 127.7, 127.6, 127.2, 126.3, 126.1, 121.4, 111.3, 65.1, 34.4, 21.1.

HRMS (FAB) Calcd for $C_{26}H_{23}NO_2$ $[M]^+$: 381.1729. Found: 381.1719.

Benzyl 2-(4-Methoxyphenyl)-1-methyl-4-phenyl-1*H*-pyrrole-3-carboxylate (**6c**).

White prisms from hexane-ethyl acetate (95%), mp 87–88 °C; ^{1}H nmr: δ 7.40 (d, *J* = 6.8 Hz, 2H), 7.29–7.21 (m, 5H), 7.15–7.10 (m, 3H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.81–6.78 (m, 2H), 6.58 (s, 1H), 4.96 (s, 2H), 3.76 (s, 3H), 3.31 (s, 3H); ^{13}C nmr: δ 164.7, 159.4, 138.9, 135.9, 135.3, 131.6, 129.0, 127.8, 127.6, 127.6, 127.2, 126.2, 126.0, 123,9, 121.3, 113.3, 111.2, 65.1, 54.9, 34.3.

Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.37; H, 6.31; N, 3.50.

Benzyl 1-Ethyl-2-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (**6d**).

White prisms from hexane-ethyl acetate (88%), mp 70–72 °C; ^{1}H nmr: δ 7.44–7.42 (m, 2H), 7.33–7.25 (m, 5H), 7.19–7.12 (m, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.83–80 (m, 2H), 6.72 (s, 1H), 4.98 (s, 2H), 3.84 (s, 3H), 3.74 (q, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 3H); ^{13}C nmr: δ 164.5, 159.2, 138.1, 135.7, 135.2, 131.4, 128.8, 127.6, 127.4 (2C), 127.0, 126.2, 125.8, 123.9, 119.2, 113.1, 111.0, 64.8, 54.7, 41.4, 16.1.

Anal. Calcd for $C_{27}H_{25}NO_3$: C, 78.81; H, 6.12; N, 3.40. Found: C, 78.55; H, 6.25; N, 3.40.

Benzyl 2-(2-Furyl)-1-methyl-4-phenyl-1*H*-pyrrole-3-carboxylate (**6e**).

Compound **6e** was obtained as a dark oil (85%); ^{1}H nmr: δ 7.45 (d, *J* = 1.1 Hz, 1H), 7.37–7.34 (m, 2H), 7.29–7.18 (m, 6H), 6.99–6.97 (m, 2H), 6.65 (s, 1H), 6.61 (d, *J* = 3.3 Hz, 1H), 6.44 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.07 (s, 2H), 3.55 (s, 3H); ^{13}C nmr: δ 164.5, 144.1, 142.8, 135.9, 134.9, 128.9, 128.0, 128.0, 127.8, 127.7, 127.5, 126.4, 126.3, 122.9, 113.7, 112.3, 110.8, 65.6, 35.3.

Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 76.85; H, 5.41; N, 4.22.

Benzyl 1-Methyl-2-(4-methylphenyl)-4-propyl-1*H*-pyrrole-3-carboxylate (**6f**).

White needles from hexane-ethyl acetate (91%), mp 46–47 °C; ^{1}H nmr: δ 7.17–7.11 (m, 7H), 6.97–6.95 (m, 2H), 6.38 (s, 1H), 5.04 (s, 2H), 3.24 (s, 3H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 1.68–1.54 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C nmr: δ 164.8, 138.9, 137.4, 136.2, 130.1, 129.5, 128.4, 127.8, 127.5, 127.1, 126.1, 120.1, 111.0, 64.7, 34.0, 28.6, 23.5, 21.1, 14.0.

Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.45; H, 7.70; N, 4.04.

Benzyl 1-Methyl-2-(4-methylphenyl)-4-(2-thienyl)-1*H*-pyrrole-3-carboxylate (**6g**).

White prisms from hexane-ethyl acetate (96%), mp 96–98 °C; ^{1}H nmr: δ 7.24–7.13 (m 9H), 7.01–6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.87–6.82 (m, 2H), 6.79 (s, 1H), 5.01 (s, 2H), 3.39 (s, 3H), 2.39 (s, 3H); ^{13}C nmr: δ 164.5, 139.5, 138.1, 136.4, 136.0, 130.3, 128.9, 128.8, 127.9, 127.8, 127.4, 127.0, 126.1, 123.8, 122.2, 118.6, 111.6, 65.4, 34.6, 21.3.

Anal. Calcd for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.61. Found: C, 74.22; H, 5.53; N, 3.59.

General Procedure for *N*-Alkylpyrrole Acids **7a-f**.

To a pressure-resistant hydrogenation bottle charged with a mixture of **6** (1 mmol) and equal amount of 5% Pd/C (in weight) in 30 mL of dioxane was introduced hydrogen. After air was replaced with hydrogen 3-4 times, the bottle was sealed and the reaction was carried out under at least 40 bar pressure of H_2 overnight. Filtration to remove catalyst, concentration *in vacuo* to remove dioxane and purification by recrystallization gave pure products **7**.

1-Methyl-2,4-diphenyl-1*H*-pyrrole-3-carboxylic Acid (**7a**).

White needles from ethanol (96%), mp 184–185 °C; ^{1}H nmr (DMSO-d_6): δ 11.5 (s, 1H), 7.48–7.36 (m, 6H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.24–7.16 (m, 1H), 6.99 (s, 1H), 3.41 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 166.5, 137.7, 135.6, 132.0, 130.7, 128.6, 128.2 (2C), 128.0, 126.1, 124.7, 122.5, 112.4, 34.7.

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.62, H, 5.85; N, 5.01.

1-Methyl-2-(4-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (**7b**).

White needles from ethanol (99%), mp 218–219 °C; ^{1}H nmr (DMSO-d_6): δ 11.5 (s, 1H), 7.38 (d, *J* = 7.1 Hz, 2H), 7.33–7.20 (m, 7H), 6.97 (s, 1H), 3.41 (s, 3H), 2.36 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 166.2, 137.4, 137.2, 135.5, 130.3, 128.9, 128.5, 128.3, 127.7, 125.7, 124.4, 122.1, 112.0, 34.4, 20.9.

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.07; H, 6.39; N, 4.80.

2-(4-Methoxyphenyl)-1-methyl-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (**7c**).

White prisms from ethanol (90%), mp 223–224 °C; ^{1}H nmr (DMSO-d_6); δ 11.47 (s, 1H), 7.40–7.26 (m, 6H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.95 (s, 1H), 3.80 (s, 3H), 3.40 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 166.7, 159.4, 137.8, 136.0, 132.2, 128.8, 128.2, 126.1, 124.9, 124.4, 122.4, 113.8, 112.4, 55.5. 34.9.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.26; H, 5.76; N, 4.54.

1-Ethyl-2-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (**7d**).

White prisms from ethanol (96%), mp 178–179 °C; ^{1}H nmr (DMSO-d_6): δ 11.45 (s, 1H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.33–7.26 (m, 4H), 7.24–7.17 (m, 1H), 7.04–6.96 (m, 3H), 3.80 (s, 3H), 3.71 (q, *J* = 7.3 Hz, 2H), 1.16 (t, *J* = 7.3 Hz, 3H); ^{13}C nmr (DMSO-d_6): δ 167.0, 159.8, 137.9, 136.5, 132.6, 129.3, 128.5, 126.5, 125.6, 124.9, 120.9, 114.3, 112.8, 55.9, 42.2, 17.2.

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.48; H, 6.09; N, 4.33.

2-(2-Furyl)-1-methyl-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (**7e**).

Compound **7e** was obtained as a white solid (93%), mp 157–158 °C; ^{1}H nmr (DMSO-d_6): δ 11.95 (s, 1H), 7.80–7.78 (m, 1H), 7.40–7.29 (m, 4H)), 7.25–7.19 (m, 1H), 7.08 (s, 1H), 6.70 (d, *J* = 3.3 Hz, 1H), 6.61 (dd, *J* = 3.3, 1.9 Hz, 1H), 3.58 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 166.1, 144.2, 143.3, 134.9, 128.1, 127.9, 126.0, 125.9, 124.3, 123.4, 114.5, 111.2, 111.1, 35.0.

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.64; H, 5.07; N, 5.22.

1-Methyl-2-(4-methylphenyl)-4-propyl-1*H*-pyrrole-3-carboxylic Acid (**7f**).

White prisms from ethanol (97%), mp 189–191 °C; ^{1}H nmr (DMSO-d_6): δ 11.24 (s, 1H), 7.24–7.15 (m, 4H), 6.62 (s, 1H), 3.29 (s, 3H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 1.62–1.48 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C nmr (DMSO-d_6): δ 166.2, 138.1, 137.1, 130.6, 129.7, 128.4, 124.9, 121.0, 111.5, 34.3, 28.6, 23.3, 21.0, 14.3.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.54; H, 7.71; N, 5.42.

Benzyl 4-Butyl-1-methyl-2-(4-methylphenyl)-1*H*-pyrrole-3-carboxylate (**6g'**).

The procedure is similar to that of **7a-f** except for the use of 15 times the amount of 5% Pd/C. Recrystallization from hexane-ethyl acetate furnished white needles (70%), mp 82–83 °C; ^{1}H nmr: δ 7.23–7.12 (m, 7H), 7.10–6.96 (m, 2H), 6.41 (s, 1H), 5.05 (s, 2H), 3.31(s, 3H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.37 (s, 3H), 1.63–1.51 (m, 2H), 1.42–1.30 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C nmr: δ 165.0, 139.2, 137.6, 136.4, 130.3, 129.7, 128.6, 127.9, 127.7, 127.3, 126.5, 120.1, 111.1, 64.9, 34.2, 32.7, 26.4, 22.7, 21.3, 14.0.

Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.70; H, 7.78; N, 3.88.

Crystal data for **6g'**: $C_{24}H_{27}NO_2$, MW 361.47, monoclinic, space group $P2_1/c$, *a* = 13.770(6), *b* 14.080(6), *c* = 10.676(4) Å, β = 96.425(5) °, V = 2057(1) Å^3, F(000) = 776, Z = 4, T =

-105 °C, μ (MoKα) = 0.073 mm^{-1}, D_{calcd} = 1.167 $g.cm^{-3}$, $2\theta_{max}$ 46° (CCD area detector, MoKα radiation, 99.9% completeness), GOF = 1.029, wR(F^2) = 0.1779 (all 2859 data), R = 0.0514 (2038 data with I > 2σI).

General Procedure for Oxazoles **9a-d**.

Oxazoles **9a-d** were prepared using the same procedure as pyrroles **5** with aldehydes as dipolarophiles.

5-Isopropyl-2-phenyl-1,3-oxazole (**9a**).

Compound **9a** was obtained as a yellow oil (77%); ^{1}H nmr: δ 7.78 (s, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.31–7.26 (m, 1H), 3.45–3.30 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 6H); ^{13}C nmr: δ 152.2, 148.7, 132.3, 132.1, 128.4, 127.2, 126.9, 25.6, 21.0.

HRMS (FAB) Calcd for $C_{12}H_{14}NO$ $[M+1]^+$: 188.1075. Found: 188.1074.

5-Ethyl-2-phenyl-1,3-oxazole (**9b**) [11].

Compound **9b** was obtained as a yellow oil (80%); ^{1}H nmr: δ 7.79 (s, 1H), 7.67–7.62 (m, 2H), 7.44–7.37 (m, 2H), 7.32–7.26 (m, 1H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H); ^{13}C nmr: δ 148.9, 148.9, 133.3, 132.0, 128.5, 127.2, 126.7, 19.2, 12.3.

5-(4-Methoxyphenyl)-2-(4-methylphenyl)-1,3-oxazole (**9c**) [12].

White prisms from hexane (73%), mp 126–128 °C; lit. mp 127 °C; ^{1}H nmr: δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.28 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.38 (s, 3H); ^{13}C nmr: δ 160.7, 159.6, 150.9, 140.2, 129.4, 126.0, 125.5, 124.8, 121.7, 120.8, 114.3, 55.2, 21.4.

2-(4-Methylphenyl)-5-phenyl-1,3-oxazole (**9d**) [13].

White prisms from hexane (90%), mp 75 °C; lit. mp 75 °C; ^{1}H nmr: δ 7.97 (d, *J* = 8.1 Hz, 2H); 7.67 (d, *J* = 7.6 Hz, 2H); 7.43–7.37 (m, 3H); 7.30 (d, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 2.37 (s, 3H); ^{13}C nmr: δ 161.2, 150.8, 140.5, 129.4, 128.8, 128.2, 128.0, 126.1, 124.6, 124.0, 123.2, 21.4.

1-(5-Isopropyl-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl)-1*H*-1,2,3-benzotriazole (**8a**).

Compound **8a** was obtained as a yellow oil (10%); ^{1}H nmr: δ 8.11-8.07 (m, 3H), 7.61–7.56 (m, 1H), 7.51–7.33 (m, 5H), 6.90 (d, *J* = 5.5 Hz, 1H), 4.90–4.85 (m, 1H), 2.23–2.15 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C nmr: δ 167.9, 146.8, 132.6, 131.5, 128.9, 128.6, 127.7, 126.2, 124.2, 120.2, 109.9, 88.3, 83.5, 31.9, 17.3, 17.1.

HRMS (FAB) Calcd for $C_{18}H_{18}N_4O$ $[M+1]^+$: 307.1559. Found: 307.1557.

General Procedure for Imidazoles **15a-d**.

Amide **12** (2 mmol) was treated with 1.0 equivalent of PCl_5 (0.42g, 2 mmol) in toluene at 70–90 °C for 2–4 hours. The reaction mixture was evaporated *in vacuo* to dryness. The purple residue was dissolved in 20 mL of THF. After the solution was cooled below –40 °C, *t*-BuOK (0.45g, 4 mmol) was added. The mixture was stirred and allowed to warm up to room temperature over 4–6 hours. The reaction mixture was diluted with EtOAc and washed with saturated aqueous NaCl and H_2O. The organic phase was dried over $MgSO_4$. Purification of the crude product by means of column chromatography provided imidazoles **15**.

1-Benzyl-2,4,5-triphenylimidazole (**15a**) [14].

White prisms from hexane (53%), mp 163–164 °C; lit. mp 163–164 °C; ^{1}H nmr: δ 7.77 –7.60 (m, 4H), 7.32– 7.07 (m, 14H), 6.77–6.74 (m, 2H), 5.04 (s, 2H); ^{13}C nmr: δ 147.8, 137.8, 137.3 (2C), 134.3, 130.8, 130.7, 129.8, 128.7, 128.6, 128.5, 128.4, 128.34, 128.3, 127.9, 127.1, 126.5, 126.1, 125.7, 48.0.

1-(4-Methoxybenzyl)-2,5-di(4-methylphenyl)-4-(4-methoxyphenyl)-1*H*-imidazole (**15b**).

White needles from hexane-ethyl acetate (66%), mp 97–98 °C; ^{1}H nmr: δ 7.55 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.12–7.07 (m, 4H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.73 (s, 4H), 3.81 (s, 3H), 3.75 (s, 3H), 2.27 (s, 3H), 2.04 (s, 3H); ^{13}C nmr: δ 159.9, 158.7, 147.6, 138.2, 137.7, 135.6, 131.9, 130.9, 130.3, 129.9, 129.4, 129.3, 128.7, 128.2, 127.2, 126.6, 123.7, 113.9, 113.8, 55.3. 55.2, 47.5, 21.3, 21.1.

Anal. Calcd for $C_{32}H_{30}N_2O_2$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.55; H, 6.83; N, 5.67.

1-(4-Methoxybenzyl)-2,5-di(4-chlorophenyl)-4-(4-methoxyphenyl)-1*H*-imidazole (**15c**).

White needles from hexane-ethyl acetate (71%), mp 171–172 °C; ^{1}H nmr: δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.76–6.68 (m, 4H), 4.99 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C nmr: δ 160.2, 158.9, 148.4, 137.2, 134.8, 132.8, 132.2, 132.1, 130.3, 129.4, 129.2, 129.1, 128.5, 128.3, 128.0, 127.1, 123.0, 114.1, 114.0, 55.3, 55.2, 47.8.

Anal. Calcd for $C_{30}H_{24}Cl_2N_2O_2$: C, 69.91; H, 4.69; N, 5.43. Found: C, 70.00; H, 4.84; N, 5.42.

1-Benzyl-2,5-di(4-chlorophenyl)-4-phenyl-1*H*-imidazole (**15d**).

White prisms from hexane-ethyl acetate (62%), mp 150 °C; ^{1}H nmr: δ 7.63 (brs, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.39–7.37 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.23–7.16 (m, 5H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.80–6.78 (m, 2H), 5.07 (s, 2H); ^{13}C nmr: δ 148.5, 137.5, 137.1 (2C), 134.9 (2C), 132.7, 132.2, 130.5, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 128.0, 127.5, 125.9, 48.4.

Anal. Calcd for $C_{28}H_{20}Cl_2N_2$: C, 73.85; H, 4.43; N, 6.15. Found: C, 73.75; H, 4.38; N, 6.14.

2,3,5,6-Tetraphenylpyrazine (**16a**) [15].

White needles from hexane (20%), mp 250 °C; lit. mp 253–254 °C; ^{1}H nmr: δ 7.66–7.62 (m, 8H), 7.34–7.32 (m, 12H).; ^{13}C nmr: δ 148.4, 138.5, 129.9, 128.6, 128.2.

General Procedure for Amides **12b-d**.

To a solution of the acid chloride (10 mmol) and pyridine (0.9 mL, 11 mmol) in 50 mL of methylene chloride was added dropwise a solution of the amine (10 mmol) in 10 mL of methylene chloride at 0 °C. After the addition, the mixture was stirred at 0 °C to room temperature overnight. After quenching the reaction with water, the organic layer was washed with 5% $NaHCO_3$, water, and dried over $MgSO_4$. Evaporation to remove CH_2Cl_2 gave a white solid, which was recrystallized from hexane-ethyl acetate to give colorless needles in excellent yield.

N-(4-Methoxybenzyl)-4-methylbenzamide (**12b**).

White needles from hexane-ethyl acetate (85%), mp 115–117 °C; ^{1}H nmr: δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.42 (brs, 1H),

4.54 (d, *J* = 5.2 Hz, 2H), 3.79 (s, 3H), 2.38 (s, 3H); ^{13}C nmr; δ 167.2, 159.0, 141.8, 131.5, 130.4, 129.2, 129.1, 126.9, 114.1, 55.2, 43.5, 21.4.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.01; H, 6.92; N, 5.45.

4-Chloro-*N*-(4-methoxybenzyl)benzamide (**12c**).

White needles from hexane-ethyl acetate (90%), mp 138–139 °C; ^{1}H nmr: δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 6.58 (brs, 1H), 4.52 (d, *J* = 5.1 Hz, 2H), 3.78 (s, 3H); ^{13}C nmr: δ 166.2, 159.1, 137.6, 132.7, 129.9, 129.2, 128.7, 128.4, 114.1, 55.2, 43.6.

Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.21; H, 5.16; N, 5.05.

N-Benzyl-4-chlorobenzamide (**12d**) [16].

White needles from hexane-ethyl acetate (92%), mp 162–163 °C; lit. mp 164–165 °C; ^{1}H nmr (DMSO-d_6): δ 9.15 (brs, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 4.4 Hz, 4H), 7.27–7.24 (m, 1H), 4.49 (d, *J* = 5.9 Hz, 2H); ^{13}C nmr (DMSO-d_6): δ 165.3, 139.6, 136.2, 133.2, 129.4, 128.6, 128.5, 127.4, 126.9, 42.8.

Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.19; H, 4.97; N, 5.62.

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