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Copper-Catalyzed Tandem Dehydrocyanation and [3+2] Cycloaddition Reactions of Phenacylmalononitriles: Regioselective Synthesis of Functionalized 4-Benzoyl-5-cyanopyrazoles under Mild Conditions

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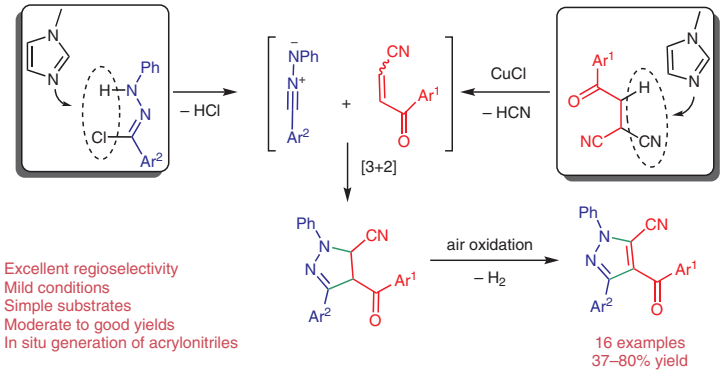

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Abstract A novel copper-catalyzed [3+2] cycloaddition reaction with concomitant in situ generation of benzoylacrylonitriles and nitrile imines from phenacylmalononitriles and hydrazonoyl chlorides, respectively, is reported. The reaction was performed using copper(I) chloride as catalyst and *N*-methylimidazole as a clean complexing agent/weak base to afford the functionalized 4-benzoyl-5-cyanopyrazoles in moderate to good yields and excellent regioselectivity under ambient conditions. This method provides rapid access to a wide range of highly functionalized 4-benzoyl-5-cyanopyrazoles.

Key words 4-benzoyl-5-cyanopyrazoles, copper catalysis, [3+2] cycloaddition, phenacylmalononitrile, hydrazonoyl chloride

The pyrazole structural unit, whether free or fused with other heterocycles, is an active pharmacophore in many biologically important molecules including those possessing antimalarial,[1a] analgesic,[1b] antimicrobial,[1c] anti-inflammatory,[1d] and antidiabetic[1e] properties. Among the commercially available *N*-heterocyclic drugs, celecoxib, sulfaphenazole, lonazolac, mepiprazole, and rimonabant are pyrazole-based compounds. Pyrazole-derived ligands have been employed in transition-metal-catalyzed cross-coupling reactions.[2] Moreover, various substituted pyrazoles have been used as chelating and extracting reagents for many metal ions.[3]

Benzoylpyrazoles, due to their usefulness as pharmaceutical and agrochemical agents,[4] have attracted much attention in recent years (Figure 1). Several patents have reported herbicidal activities of substituted 4-benzoylpyrazoles.[5] The benzoyl moiety can be a useful precursor to a wide range of functional groups such as benzyl alcohols, imines, oximes, and alkenes, thus providing facile access to structurally diverse pyrazoles.[6]

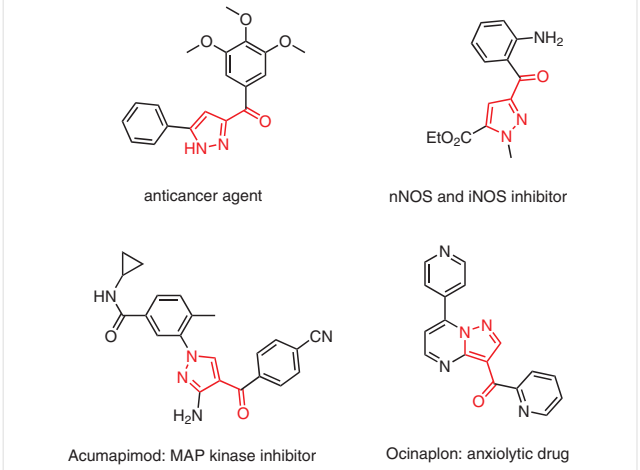

Figure 1 Examples of bioactive benzoylpyrazoles

Among substituted cyanopyrazoles used as pharmaceuticals and agrochemicals[7] are Fipronil, Pyriprole, Pyrafluprole, and Ethiprole as insecticide,[8] Zaleplon as sedative-hypnotic,[9] and Lorlatinib as ALK/ROS1 inhibitor.[10] The cyano group can be converted into acids, ketones, imines, aldehydes, amines, amides, and even triazoles and tetrazoles.[11]

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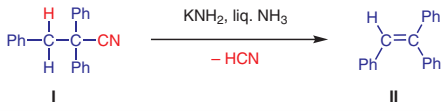
In view of the important applications of pyrazoles, new synthetic strategies for their preparation are currently in demand.

On the pallet of organic reactions that are used in heterocyclic synthesis, dipolar cycloadditions possess a prominent position, since they are efficient methods for creating new five-membered heterocycles with control of stereochemistry.[12] The 1,3-dipolar cycloaddition, also referred as the Huisgen cycloaddition, is a classical and fundamental organic reaction, which consists of the reactions of dipoles (e.g., nitrile imines) with olefinic dipolarophiles, resulting in formation of various highly substituted pyrazoles and pyrazolines in a regio- and stereoselective manner.[13] However, there have been only a few cases of performing the substituted pyrazole synthesis with the dipolarophile generated in situ.[14]

Unsaturated cyanocarbonyl compounds provide an attractive entry into electron-deficient dienophiles employed in Diels–Alder cycloadditions.[15] To prepare these valuable substrates, several synthetic methodologies have been reported, including Wittig type olefination of glyoxal derivatives, palladium-catalyzed four-step procedure from alkenals, dehydrohalogenation of suitable substituted precursors, or five-step chemical modification of *trans*-styrylacetic acid.[16] These approaches are frequently long and cumbersome. To our knowledge, there is no report regarding either in situ generation of benzoylacrylonitriles, or describing their use as a dipolarophile in 1,3-dipolar cycloaddition reactions.

Dehydrocyanation of substituted nitriles was first introduced by Hauser and Brasen, wherein 2,2,3-triphenylpropionitrile (**I**) undergoes β-elimination to form triphenylethylene (**II**) (Scheme 1).[17]

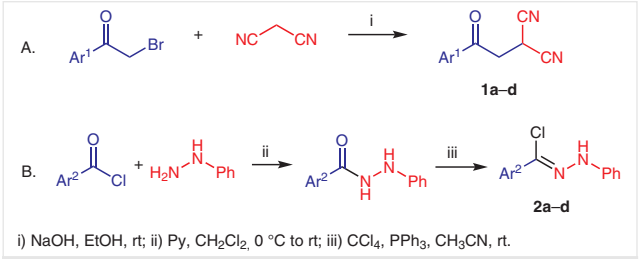


Scheme 1 The first reported dehydrocyanation of nitriles

As can be inferred from Scheme 1, strong alkaline conditions are required for the dehydrocyanation process when leading to an olefinic target. This type of reaction might be more facile if a more stable aromatic product is formed.[18] Since the use of a strong, or even a moderate base such as Et_3N in the methodology investigated causes side reactions, we previously conceived that a weak base (e.g., *N*-methylimidazole in the presence of a catalytic amount of copper mono halides as Lewis acid) might lead to the desired outcome.

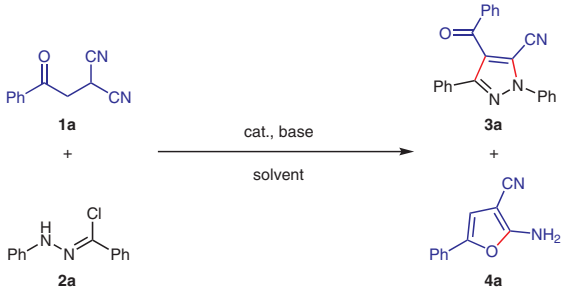
In line with the studies conducted in our research group focused on the synthesis of different substituted pyrazoles,[19] we decided to carry out the synthesis of multiply substituted pyrazoles with the concomitant in situ generation of both the dipole and the dipolarophile.

The starting materials (i.e., phenacylmalononitriles **1a–d**) were prepared according to a reported procedure (Scheme 2A).[20] Hydrazonoyl chlorides **2a–d** were also obtained from commercially available benzoyl chlorides and phenylhydrazine according to standard reported procedures (Scheme 2B).[21]



Scheme 2 Synthesis of the starting materials

Table 1 Optimization of Reaction Conditions for the Synthesis of Pyrazole **3a**[a]



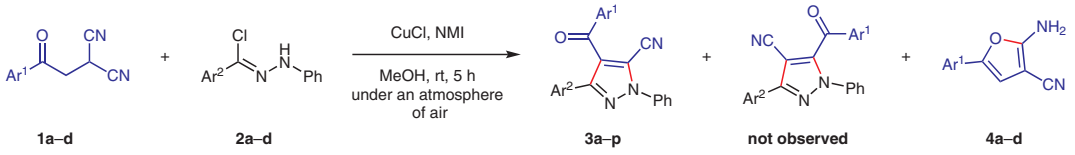
Entry	Catalyst	Base	Solvent	**3a** (%)[b]	**3a**/**4a**[c]
1	none	imidazole	EtOH	trace	1:1
2	CuCl	imidazole	EtOH	37	6:1
3	CuCl	NMI[d]	EtOH	53	13:1
4[e]	CuCl	NMI	MeOH	61	15:1
5	CuCl	NMI	MeOH	69	18:1
6[f]	CuCl	NMI	MeOH	56	8:1
7	CuCl	NMI	MeCN	21	1:1.5
8	CuCl	Et_3N	MeCN	ND[g]	1:19<
9	CuBr	NMI	MeOH	47	9:1
10	CuI	NMI	MeOH	36	5:1
11[h]	$CuCl_2$	NMI	MeOH	ND	–
12	$Cu(OAc)_2$	NMI	MeOH	ND	–

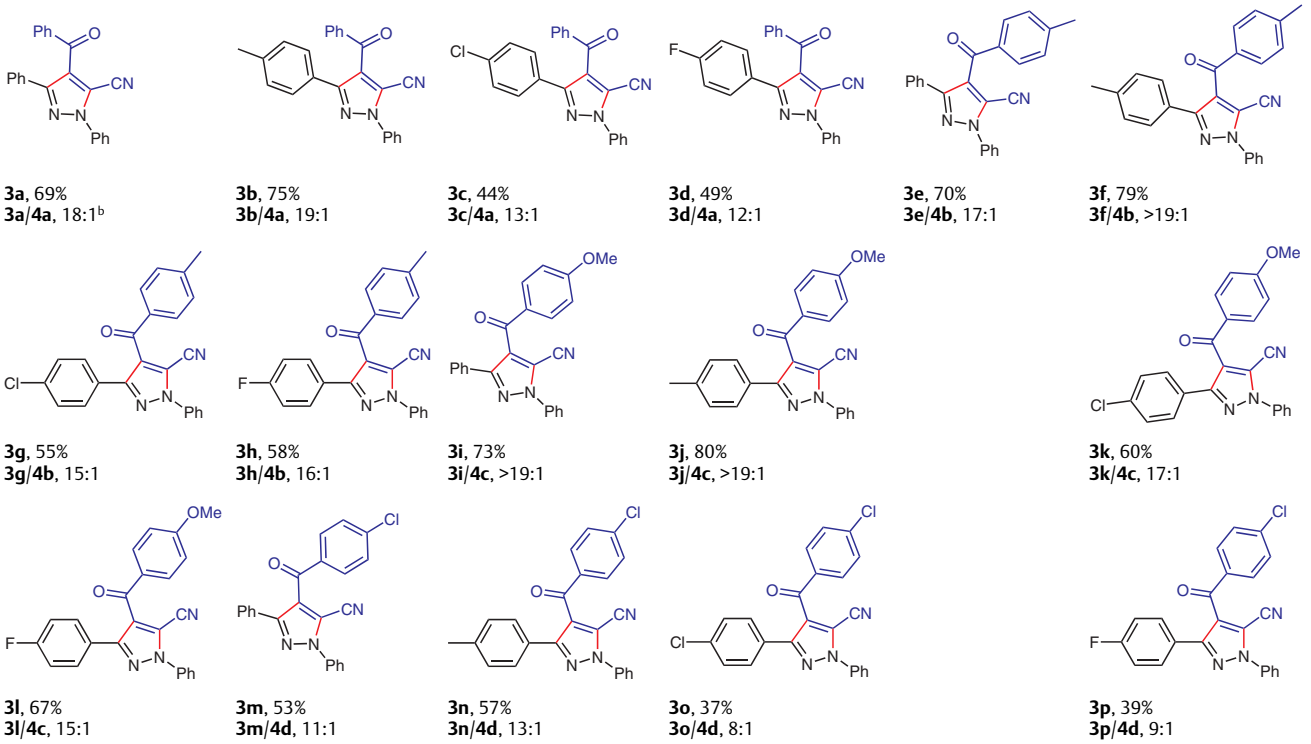
[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), catalyst (10 mol%), base (2.5 equiv), solvent (1 mL), r.t., under an atmosphere of air.
[b] Yield of isolated product.
[c] The selectivity for **3a**/**4a** was determined by ^{1}H NMR spectroscopic analysis of the reaction mixtures.
[d] *N*-Methylimidazole.
[e] CuCl (5 mol%) was used.
[f] The reaction was allowed stirred for 24 h.
[g] Not detected.
[h] A complex mixture was obtained.

Initially we chose phenacylmalononitrile (**1a**), and hydrazonoyl chloride **2a**, as model substrates to optimize the conditions for the [3+2] cycloaddition reaction. Initially, the reaction was carried out in EtOH at room temperature in the presence of imidazole as base, as Garve et al. used in their work with hydrazonoyl chlorides,[22] resulting a trace amount of both **3a** and the by-product **4a** (Table 1, entry 1). Upon further examination, it was found that in the presence of a catalytic amount of a copper compound, the efficiency of the reaction increased (entry 2). Additionally, *N*-methylimidazole (NMI) was found to be more effective than imidazole (entry 3). A change of solvent to MeOH was shown to be effective (entry 4), wherein CuCl (10 mol%) proved to be the best catalyst, resulting in a 69% yield of the cycloadduct (entry 5). Increasing the reaction time resulted in a considerable decrease in the yield of **3a** (entry 6). Running the reaction in MeCN showed that product **1a** tends to undergo intramolecular cyclization to form the by-product 2-amino-5-phenylfuran-3-carbonitrile (**4a**) especially in aprotic solvents (entry 7). When using Et_3N, the reported base of choice to generate nitrile imines,[23] compound **4a** was dominant while **3a** was not detected (entry 8). Running the reaction with a catalytic amount of other copper mono halides (CuBr and CuI) decreased the amount of product **3a** formed (entries 9 and 10). When using $CuCl_2$ or $Cu(OAc)_2$ as catalyst, a complex mixture was obtained (entries 11 and 12).

With the optimal conditions in hand, a range of hydrazonoyl chlorides and phenacylmalononitriles were examined. In particular, a number of *N*′-arylbenzohydrazonoyl chlorides with various substituents on the aryl fragments were tested, and most afforded moderate to good yields of **3** (Table 2). The method worked well especially for methyl and methoxy derivatives, and moderate yields were obtained for 4-chloro- and 4-fluoro-*N*-phenylbenzohydrazonoyl chlorides. An electron-releasing functional group at the *para*-position of phenacylmalononitrile (e.g., 4-methoxy-, and 4-methyl-) showed higher efficiency compared

Table 2 Scope of the Reaction with Respect to 4-Benzoyl-5-cyanopyrazoles[a]





3a, 69%
3a/**4a**, 18:1[b]

3b, 75%
3b/**4a**, 19:1

3c, 44%
3c/**4a**, 13:1

3d, 49%
3d/**4a**, 12:1

3e, 70%
3e/**4b**, 17:1

3f, 79%
3f/**4b**, >19:1

3g, 55%
3g/**4b**, 15:1

3h, 58%
3h/**4b**, 16:1

3i, 73%
3i/**4c**, >19:1

3j, 80%
3j/**4c**, >19:1

3k, 60%
3k/**4c**, 17:1

3l, 67%
3l/**4c**, 15:1

3m, 53%
3m/**4d**, 11:1

3n, 57%
3n/**4d**, 13:1

3o, 37%
3o/**4d**, 8:1

3p, 39%
3p/**4d**, 9:1

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), CuCl (0.05 mmol, 10 mol%), *N*-methylimidazole (1.25 mmol, 2.5 equiv), MeOH (3 mL), r.t., under an atmosphere of air, 5 h.
[b] The selectivity for **3**/**4** was determined by ^1H NMR spectroscopic analysis of the reaction mixtures.

to 4-chloro-phenacylmalononitrile. The highest yield of 80%, was achieved for 4-(4-methoxybenzoyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole-5-carbonitrile, having electron-donating groups at the *para*-positions of both aryl moieties of the initial materials. In contrast, 4-(4-chlorobenzoyl)-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile was obtained only in 37% yield. In addition to the low reactivity of 4-halo-*N*-phenylbenzohydrazonoyl chlorides in this 1,3-dipolar cycloaddition reaction, the higher tendency of 4-chloro-phenacylmalononitrile to partake in the side reaction resulting the by-product **4**, could presumably be a reason for these observations (Scheme 3). It is noteworthy that 10–25% of the hydrazonoyl chloride substrates always remained unreacted, whereas in all reactions the phenacylmalononitrile substrates **1a–d** were completely consumed.

The structures of compounds **3a–p** were assigned on the basis of their IR, mass, ^{1}H NMR, and ^{13}C NMR spectroscopic analyses. IR spectra showed a medium absorption at 2230–2250 cm^{-1} together with a strong absorption at 1630–1655 cm^{-1} corresponding to the cyano and carbonyl functional groups, respectively. The mass spectra of products **3** displayed molecular ion peaks at appropriate *m*/*z* values. Unequivocal evidence for the regioselective formation of 3-(4-chlorophenyl)-4-(4-methoxybenzoyl)-1-phenyl-1*H*-pyrazole–5-carbonitrile (**3k**) was obtained from single-crystal X-ray analysis (Figure 2).[24] The same structures were assumed for the other derivatives on the basis of their NMR spectroscopic similarities.

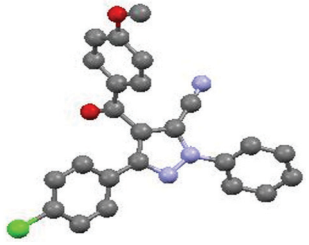
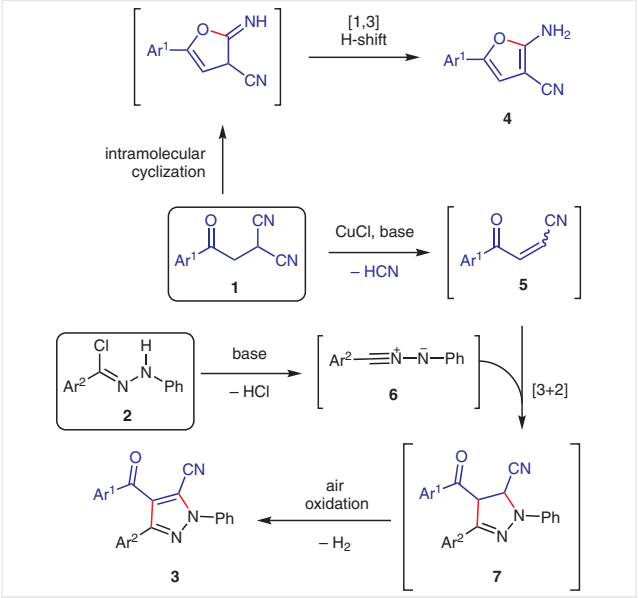


Figure 2 X-ray crystal structure of compound **3k**. Nitrogen atoms are shown in blue, oxygen atoms in red, chlorine atom in green. Hydrogen atoms are omitted for clarity.

These observations, together with reported evidence, led us to propose the mechanism shown in Scheme 3.[25] The phenacylmalononitrile substrate **1** undergoes a dehydrocyanation reaction triggered by CuCl as a Lewis acid to generate the acrylonitrile intermediate **5**, the olefinic dipolarophile. Deprotonation of hydrazonoyl chloride and concomitant loss of HCl leads to nitrile imine **6** with a 1,3-dipolar structure. Then, a regioselective [3+2] cycloaddition between the dipole **6**, and the dipolarophile **5**, leads to intermediate **7**, which subsequently affords the pyrazole product as a result of an air oxidation.

Compound **1**, can undergo an intramolecular cyclization reaction under alkaline conditions, followed by a 1,3-hydrogen shift to yield the by-product **4**. As noted above,



Scheme 3 Proposed mechanism for the formation of product **3** and byproduct **4**

when using a weak base in a protic solvent, the amount of the side product is negligible (optimal conditions, Table 1, entry 5).

In conclusion, we have described an unprecedented copper-catalyzed regioselective synthesis of 4-arylcarboxo-1-phenyl-3-aryl-1*H*-pyrazole-5-carbonitriles via a [3+2] cycloaddition reaction between phenacylmalononitriles and hydrazonoyl chlorides. In situ generation of the dipole and the dipolarophile, nitrile imine and acrylonitrile, respectively, the mild copper-catalyzed/weak base mediated formation of two new C–C and C–N bonds, excellent regioselectivity, and the retention of the benzoyl group, are the advantages of this one-pot method. The reaction works well with a wide range of of hydrazonoyl chloride and phenacylmalononitrile substrates. The methodology reported here may serve as a simple strategy to synthesize a wide variety of highly functionalized 4-benzoyl-5-cyanopyrazoles.

All purchased solvents and chemicals were of analytical grade and used without further purification. Phenacylmalononitriles **1a–d**, and hydrazonoyl chlorides **2a–d**, were prepared by reported procedures.[20,21] The physical properties of the known compound **4a** corresponds to the reported data.[26] Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were recorded with a Shimadzu-IR 460 spectrophotometer (ύ in cm^{-1}). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker DRX-500 Avance instrument using $CDCl_3$ as solvent at 500.1, 125.7, and 471 MHz, respectively (δ in ppm, *J* in Hz). Mass spectra were recorded with a Finnigan-MAT-8430MS spectrometer at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed with a Heraeus CHN-O-Rapid analyzer. X-ray crystal structure data were collected with a Marresearch 345 dtb diffractometer using Mo Kα radiation (0.71073 Å) at

295 K. The structure was solved by direct methods using SHELXS-97 and the obtained model was refined with SHELXL-97. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were added at ideal positions and refined using a riding model.

4-Benzoyl-5-cyanopyrazoles; General Procedure

A mixture of **1** (0.6 mmol), **2** (0.5 mmol), CuCl (5 mg, 10 mol%), and *N*-methylimidazole (103 mg, 2.5 equiv) in MeOH (3 mL) was stirred for 5 h at r.t. under an atmosphere of air. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the product was purified by silica gel (Merck 230–400 mesh) column chromatography (*n*-hexane/EtOAc, 8:1).

4-Benzoyl-1,3-diphenyl-1*H*-pyrazole-5-carbonitrile (3a)

Yield: 121 mg (69%); colorless solid; mp 127–129 °C.

IR (KBr): 3058, 2239, 1650, 1595, 1498, 1453, 1418, 906, 763, 694 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.98–7.75 (m, 4 H), 7.75–7.45 (m, 6 H), 7.40 (t, *J* = 7.3 Hz, 2 H), 7.36–7.28 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.9, 152.6, 138.2, 136.6, 134.1, 130.4, 130.1, 129.9, 129.8, 129.3, 128.7, 128.6, 127.5, 125.6, 123.4, 116.4, 109.8.

MS: *m*/*z* (%) = 349 (100), 332 (24), 320 (43), 272 (74), 105 (25), 77 (15), 77 (83), 51 (23).

Anal. Calcd for $C_{23}H_{15}N_3O$ (349.39): C, 79.07; H, 4.33; N, 12.03. Found: C, 79.36; H, 4.35; N, 12.06.

4-Benzoyl-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole-5-carbonitrile (3b)

Yield: 136 mg (75%); colorless solid; mp 143–145 °C.

IR (KBr): 3062, 2923, 2232, 1650, 1617, 1515, 1498, 1449, 1422, 918, 768, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.79 (m, 4 H), 7.66–7.51 (m, 4 H), 7.48 (d, *J* = 7.4 Hz, 2 H), 7.44–7.35 (m, 2 H), 7.11 (d, *J* = 7.3 Hz, 2 H), 2.33 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.9, 151.5, 138.3, 137.0, 135.0, 133.0, 128.9, 128.7, 128.6, 128.2, 127.6, 127.3, 126.4, 126.2, 122.3, 115.1, 108.8, 20.3.

MS: *m*/*z* (%) = 368 (100), 346 (17), 334 (26), 286 (49), 105 (20), 77 (69), 51 (14).

Anal. Calcd for $C_{24}H_{17}N_3O$ (363.42): C, 79.32; H, 4.72; N, 11.56. Found: C, 79.65; H, 4.70; N, 11.61.

4-Benzoyl-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3c)

Yield: 84 mg (44%); colorless solid; mp 168–170 °C.

IR (KBr): 3062, 2924, 2231, 1649, 1593, 1500, 1448, 1285, 1198, 1093, 1014, 917, 692 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.76 (m, 4 H), 7.65–7.49 (m, 6 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.7, 151.5, 138.0, 136.6, 135.6, 134.4, 130.0, 130.0, 129.9, 129.9, 129.8, 128.9, 128.9, 127.3, 123.4, 116.6, 109.6.

MS: *m*/*z* (%) = 383 (100), 368 (13), 354 (19), 306 (49), 129 (25), 105 (73), 77 (63), 51 (5).

Anal. Calcd for $C_{23}H_{14}ClN_3O$ (383.84): C, 79.97; H, 3.68; N, 10.95. Found: C, 80.39; H, 3.70; N, 11.00.

4-Benzoyl-3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3d)

Yield: 90 mg (49%); colorless solid; mp 101–103 °C.

IR (KBr): 3069, 2238, 1653, 1597, 1496, 1452, 1280, 1180, 1099, 917, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.90–7.79 (m, 4 H), 7.67–7.50 (m, 6 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.00 (t, *J* = 8.4 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.7, 162.3 (d, $^1J_{CF}$ = 249.6 Hz), 150.6, 136.9, 135.4, 133.2, 129.4 (d, $^3J_{CF}$ = 8.5 Hz), 128.9, 128.8, 127.7, 126.0, 125.5 (d, $^4J_{CF}$ = 3.0 Hz), 123.3, 122.3, 115.5, 114.6 (d, $^2J_{CF}$ = 21.7 Hz), 108.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –106.4.

MS: *m*/*z* (%) = 367 (100), 338 (13), 290 (19), 129 (6), 105 (16), 77 (55), 51 (13).

Anal. Calcd for $C_{23}H_{14}FN_3O$ (367.38): C, 75.19; H, 3.84; N, 11.44. Found: C, 75.56; H, 3.82; N, 11.49.

4-(4-Methylbenzoyl)-1,3-diphenyl-1*H*-pyrazole-5-carbonitrile (3e)

Yield: 127 mg (70%); colorless solid; mp 118–120 °C.

IR (KBr): 3068, 2922, 2242, 1636, 1605, 1494, 1425, 1290, 1177, 923, 772, 688 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.2 Hz, 2 H), 7.78 (d, *J* = 7.3 Hz, 2 H), 7.67–7.46 (m, 5 H), 7.38–7.28 (m, 3 H), 7.21 (d, *J* = 7.2 Hz, 2 H), 2.40 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.5, 152.4, 145.4, 138.2, 134.1, 130.5, 130.3, 129.9, 129.7, 129.5, 129.3, 128.7, 128.5, 127.8, 123.4, 116.1, 109.9, 21.9.

MS: *m*/*z* (%) = 363 (100), 347 (81), 334 (25), 271 (28), 119 (23), 91 (34), 77 (41), 51 (14).

Anal. Calcd for $C_{24}H_{17}N_3O$ (363.42): C, 79.32; H, 4.72; N, 11.56. Found: C, 79.03; H, 4.71; N, 11.60.

4-(4-Methylbenzoyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole-5-carbonitrile (3f)

Yield: 149 mg (79%); colorless solid; mp 129–131 °C.

IR (KBr): 3059, 2951, 2922, 2232, 1647, 1616, 1609, 1497, 1457, 1175, 919, 764, 624 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.1 Hz, 2 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 7.67–7.45 (m, 5 H), 7.23 (d, *J* = 7.4 Hz, 2 H), 7.13 (d, *J* = 7.3 Hz, 2 H), 2.41 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.5, 151.3, 144.2, 138.2, 137.1, 133.0, 129.1, 128.9, 128.7, 128.5, 128.4, 128.3, 127.2, 126.4, 122.2, 114.8, 108.8, 20.8, 20.3.

MS: *m*/*z* (%) = 377 (100), 362 (70), 348 (22), 286 (21), 119 (23), 91 (38), 77 (33), 65 (5), 51 (8).

Anal. Calcd for $C_{25}H_{19}N_3O$ (377.45): C, 79.55; H, 5.07; N, 11.13. Found: C, 79.96; H, 5.09; N, 11.17.

3-(4-Chlorophenyl)-4-(4-methylbenzoyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3g)

Yield: 109 mg (55%); colorless solid; mp 159–161 °C.

IR (KBr): 3062, 2958, 2927, 2235, 1649, 1607, 1499, 1176, 1097, 920, 768 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.1 Hz, 2 H), 7.78 (d, *J* = 7.3 Hz, 2 H), 7.68–7.48 (m, 5 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 7.25 (d, *J* = 7.2 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.2, 150.1, 144.6, 136.9, 134.3, 132.9, 129.1, 128.7, 128.7, 128.7, 128.6, 128.5, 127.8, 126.4, 122.2, 115.1, 108.6, 20.8.

MS: *m*/*z* (%) = 397 (100), 382 (86), 368 (18), 306 (33), 119 (54), 91 (58), 77 (60), 65 (22), 51 (15).

Anal. Calcd for $C_{24}H_{16}ClN_3O$ (397.86): C, 72.45; H, 4.05; N, 10.56. Found: C, 72.86; H, 4.06; N, 10.61.

3-(4-Fluorophenyl)-4-(4-methylbenzoyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3h)

Yield: 103 mg (58%); colorless solid; mp 102–104 °C.

IR (KBr): 3097, 2927, 2247, 1654, 1607, 1498, 1447, 1226, 1160, 909, 766 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.5 Hz, 2 H), 7.77 (d, *J* = 7.5 Hz, 2 H), 7.69–7.51 (m, 5 H), 7.24 (d, *J* = 7.5 Hz, 2 H), 7.02 (t, *J* = 8.2 Hz, 2 H), 2.42 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.4, 163.4 (d, $^1J_{CF}$ = 249.4 Hz), 151.5, 145.6, 138.1, 134.1, 130.4 (d, $^3J_{CF}$ = 8.4), 130.3, 129.9, 129.8, 129.6, 127.5, 126.7 (d, $^4J_{CF}$ = 3.2 Hz), 123.4, 116.3, 115.8 (d, $^2J_{CF}$ = 21.6 Hz), 109.8, 21.9.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –106.5.

MS: *m*/*z* (%) = 381 (100), 366 (85), 352 (19), 290 (38), 119 (39), 91 (40), 77 (43), 65 (15), 51 (11).

Anal. Calcd for $C_{24}H_{16}FN_3O$ (381.41): C, 75.58; H, 4.23; N, 11.02. Found: C, 75.87; H, 4.25; N, 11.07.

4-(4-Methoxybenzoyl)-1,3-diphenyl-1*H*-pyrazole-5-carbonitrile (3i)

Yield: 138 mg (73%); colorless solid; mp 163–165 °C.

IR (KBr): 3068, 2965, 2934, 2241, 1641, 1596, 1573, 1501, 1263, 1168, 908, 759, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91–7.81 (m, 4 H), 7.66–7.57 (m, 4 H), 7.55 (t, *J* = 6.65, 1 H), 7.37–7.29 (m, 3 H), 6.89 (d, *J* = 7.95 Hz, 2 H), 3.87 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 186.2, 163.4, 151.0, 137.1, 131.5, 129.4, 128.7, 128.5, 128.4, 128.2, 127.6, 127.3, 126.7, 122.2, 114.8, 113.0, 108.8, 54.5.

MS: *m*/*z* (%) = 379 (100), 362 (23), 348 (62), 336 (6), 272 (17), 190 (8), 135 (40), 92 (15), 77 (59), 64 (8), 51 (12).

Anal. Calcd for $C_{24}H_{17}N_3O_2$ (379.42): C, 75.98; H, 4.52; N, 11.08. Found: C, 76.29; H, 4.51; N, 11.12.

4-(4-Methoxybenzoyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole-5-carbonitrile (3j)

Yield: 157 mg (80%); colorless solid; mp 156–158 °C.

IR (KBr): 3058, 2979, 2917, 2232, 1649, 1616, 1596, 1572, 1501, 1259, 1168, 906, 762 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92–7.76 (m, 4 H), 7.64–7.56 (m, 2 H), 7.56–7.47 (m, 3 H), 7.13 (d, *J* = 7.1 Hz, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 3.87 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.5, 164.6, 152.2, 139.3, 138.3, 132.6, 129.8, 129.7, 129.6, 129.4, 128.3, 127.8, 127.7, 123.3, 115.8, 114.1, 110.0, 55.7, 21.4.

MS: *m*/*z* (%) = 393 (100), 376 (20), 362 (51), 135 (33), 92 (13), 77 (51), 51 (8).

Anal. Calcd for $C_{25}H_{19}N_3O_2$ (393.45): C, 76.32; H, 4.87; N, 10.68. Found: C, 76.01; H, 4.89; N, 10.70.

3-(4-Chlorophenyl)-4-(4-methoxybenzoyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3k)

Yield: 124 mg (60%); colorless solid; mp 159–161 °C.

IR (KBr): 3073, 2974, 2937, 2237, 1642, 1608, 1577, 1498, 1268, 1170, 845, 773 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98–7.79 (m, 4 H), 7.71–7.51 (m, 5 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.3 Hz, 2 H), 3.89 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 186.0, 163.4, 149.9, 136.9, 134.3, 131.5, 128.7, 128.7, 128.5, 128.3, 127.9, 127.8, 126.6, 122.2, 114.9, 113.1, 108.6, 54.6.

MS: *m*/*z* (%) = 413 (100), 396 (19), 382 (57), 135 (27), 91 (29), 77 (44).

Anal. Calcd for $C_{24}H_{16}ClN_3O_2$ (413.86): C, 69.65; H, 3.90; N, 10.15. Found: C, 69.98; H, 3.94; N, 10.28.

3-(4-Fluorophenyl)-4-(4-methoxybenzoyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3l)

Yield: 133 mg (67%); colorless solid; mp 125–127 °C.

IR (KBr): 3077, 2932, 2235, 1649, 1596, 1499, 1260, 1165, 909, 842, 762 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90–7.79 (m, 4 H), 7.67–7.58 (m, 4 H), 7.55 (t, *J* = 6.9 Hz, 1 H), 7.03 (t, *J* = 8.2 Hz, 2 H), 6.90 (d, *J* = 8.2 Hz, 2 H), 3.88 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.2, 164.7, 163.4 (d, $^1J_{CF}$ = 249.5 Hz), 151.3, 138.1, 132.6, 130.4 (d, $^3J_{CF}$ = 8.4 Hz), 129.9, 129.8, 129.7, 129.0, 127.6, 126.7 (d, $^4J_{CF}$ = 3.0 Hz), 123.4, 115.8 (d, $^2J_{CF}$ = 21.8 Hz), 114.2, 109.9, 55.7.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –106.5.

MS: *m*/*z* (%) = 397 (100), 380 (21), 366 (65), 290 (21), 198 (8), 135 (50), 92 (15), 77 (49), 51 (8).

Anal. Calcd for $C_{24}H_{16}FN_3O_2$ (397.41): C, 72.54; H, 4.06; N, 10.57. Found: C, 72.13; H, 4.04; N, 10.60.

4-(4-Chlorobenzoyl)-1,3-diphenyl-1*H*-pyrazole-5-carbonitrile (3m)

Yield: 101 mg (53%); colorless solid; mp 147–149 °C.

IR (KBr): 3080, 3055, 2242, 1652, 1584, 1494, 1418, 1278, 1088, 905, 762, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.35 Hz, 2 H), 7.78 (d, *J* = 8.1 Hz, 2 H), 7.65–7.43 (m, 5 H), 7.40–7.26 (m, 5 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 186.4, 151.4, 139.6, 136.9, 133.7, 130.2, 129.1, 128.8, 128.4, 127.9, 127.6, 127.5, 125.9, 123.3, 122.3, 115.4, 108.6.

MS: *m*/*z* (%) = 383 (100), 366 (11), 347 (62), 272 (42), 139 (19), 111 (23), 77 (39), 51 (11).

Anal. Calcd for $C_{23}H_{14}ClN_3O$ (383.84): C, 71.97; H, 3.68; N, 10.95. Found: C, 72.36; H, 3.70; N, 11.98.

4-(4-Chlorobenzoyl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole-5-carbonitrile (3n)

Yield: 113 mg (57%); colorless solid; mp 160–162 °C.

IR (KBr): 3071, 2926, 2243, 1640, 1618, 1591, 1500, 1274, 921, 623 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.6 Hz, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H), 7.61 (t, *J* = 7.2 Hz, 2 H), 7.56 (t, *J* = 7.0 Hz, 1 H), 7.44 (d, *J* = 7.7 Hz, 2 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 7.12 (d, *J* = 7.6 Hz, 2 H), 2.35 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.7, 152.6, 140.7, 139.7, 138.1, 134.9, 131.4, 129.9, 129.8, 129.5, 129.1, 128.5, 127.4, 124.5, 123.4, 116.4, 109.8, 21.4.

MS: *m*/*z* (%) = 397 (100), 382 (13), 362 (42), 286 (31), 139 (23), 111 (28), 77 (45), 51 (11).

Anal. Calcd for $C_{24}H_{16}ClN_3O$ (397.86): C, 72.45; H, 4.05; N, 10.56. Found: C, 72.83; H, 4.06; N, 10.59.

4-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3o)

Yield: 77 mg (37%); colorless solid; mp 153–155 °C.

IR (KBr): 3092, 2246, 1653, 1498, 1448, 1089, 1015, 907 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.6 Hz, 2 H), 7.80 (d, *J* = 8.2 Hz, 2 H), 7.65–7.55 (m, 2 H), 7.53 (d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 186.3, 162, 150.3, 139.9, 136.8, 134.6, 133.6, 130.2, 128.9, 128.8, 128.7, 128.2, 127.9, 127.6, 122.2, 115.4, 108.4.

MS: *m*/*z* (%) = 417 (100), 400 (9), 382 (61), 306 (50), 139 (39), 111 (44), 77 (56), 51 (16).

Anal. Calcd for $C_{23}H_{13}Cl_2N_3O$ (418.28): C, 66.05; H, 3.13; N, 10.05. Found: C, 66.43; H, 3.15; N, 10.09.

4-(4-Chlorobenzoyl)-3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-5-carbonitrile (3p)

Yield: 78 mg (39%); colorless solid; mp 161–163 °C.

IR (KBr): 3079, 2241, 1652, 1589, 1500, 1450, 1224, 1089, 920, 851, 764 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.9 Hz, 2 H), 7.79 (d, *J* = 7.5 Hz, 2 H), 7.67–7.48 (m, 5 H), 7.40 (d, *J* = 7.6 Hz, 2 H), 7.03 (t, *J* = 7.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.5, 163.5 (d, $^1J_{CF}$ = 250.2 Hz), 151.6, 141.0, 138.0, 134.9, 131.4, 130.6 (d, $^3J_{CF}$ = 8.5 Hz), 129.9, 129.6, 129.2, 126.7, 126.5 (d, $^4J_{CF}$ = 2.9 Hz), 124.4, 123.4, 115.9 (d, $^2J_{CF}$ = 21.9 Hz), 109.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –105.9.

MS: *m*/*z* (%) = 401 (100), 384 (11), 366 (66), 290 (62), 139 (40), 111 (41), 77 (62), 51 (16).

Anal. Calcd for $C_{23}H_{13}ClFN_3O$ (401.83): C, 68.75; H, 3.26; N, 10.46. Found: C, 69.18; H, 3.28; N, 10.48.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691591.

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