Supporting Information
for DOI: 10.1055/s-0037-1610271
© Georg Thieme Verlag KG Stuttgart · New York 2018
Copper-Catalyzed Synthesis of N-Acylpyrazoles through Cascade Transformation of N-Propargylic Sulfonylhydrazone with Diaryliodonium

Ren-Hao Li, Xin-Yang Fan, Zi-Lin Hu, Zhi-Kai Liu, Ying Yang, Hai-Tao Tang, Yi-Hui Chen, Li Chen and Zhuang-Ping Zhan

Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian, People’s Republic of China.
E-mail: yhchen@xmu.edu.cn

State Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University, Guilin 541004, People’s Republic of China.
# Table of Contents

1. General Information ................................................................................................................... 3

2. General Experimental Procedures for Preparation of $N$-Acylpyrazole 3: ...................... 4

3. Procedures of Control Experiment ........................................................................................... 4

4. Analytical Data of the Products ................................................................................................. 6

5. NMR Spectral of the Products ................................................................................................... 12

6. Mass Spectral of the $\text{3e}^{-18}\text{O}$ .................................................................................... 25
1. General Information

Unless otherwise noted, all reagents and solvents were obtained commercially and used without further purification. N-propargylic sulfonylhydrazones 1 were prepared according to previous work (Y. T. Lee, Y. K. Chung, J. Org. Chem., 2008, 73, 4698-4701). All reaction mixtures were stirred with a magnetic bar in flame-dried glassware.

Chromatography

Thin layer chromatography (TLC) was performed on pre-coated glass-backed TLC plates and visualized by UV lamp (254 nm). Column chromatography on silica gel (300-400 mesh) was carried out using Technical Grade 60-90 °C petroleum ether (distilled prior to use) and analytical Grade EtOAc (without further purification). Concentration under reduced pressure was performed by rotary evaporation. Purified compounds were further addressed under high vacuum (3-5 mmHg). Yields refer to chromatographically purified compounds.

Nuclear magnetic resonance spectra

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 400/100 MHz spectrometer or a Bruker Avance 500/125 MHz spectrometer using CDCl$_3$ as the solvent and TMS as the internal standard. Chemical shifts were reported in ppm. $^1$H-NMR spectra were referenced to CDCl$_3$ (7.26 ppm) and $^{13}$C-NMR spectra were referenced to CDCl$_3$ (77.0 ppm). All $^{13}$C-NMR spectra were measured with complete proton decoupling. Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet and $J$, coupling constant in Hz.

Mass spectroscopy

HRMS spectra were recorded with Micromass QTOF2 Quadrupole/Time-of-Flight Tandem mass spectrometer using electron spray ionization.
2. General Experimental Procedures for Preparation of N-Acylpyrazole 3:

Corresponding N-propargylic sulfonylhydrazones 1 (0.5 mmol), diaryliodonium salts 2 (0.75 mmol) and Cu(OTf)$_2$ (18.1 mg, 0.05 mmol) were added to a 10 mL round-bottom flask followed by the adding of DBE (5 mL), and the reaction mixture was stirred at 80 °C in air. Upon completion (monitored by TLC), the solvent was removed by vacuum and the crude residue was purified by column chromatography on silica gel to afford the corresponding 4-acylpyrazole 3.

3. Procedures of Control Experiment

N-propargylic sulfonylhydrazones 1e (0.5 mmol), bis(4-chlorophenyl)iodonium trifluoromethanesulfonate (0.75 mmol) and Cu(OTf)$_2$ (18.1 mg, 0.05 mmol) were added to a 10 mL round-bottom flask followed by the adding of DBE (5 mL, dried solvent), and the reaction mixture was stirred 2 h at 80 °C in O$_2$. The yield of 3e was determined < 5% by $^1$H NMR spectroscopy (diethyl phthalate as internal standard).
**N-propargylic sulfonylhydrazones 1e (0.5 mmol), bis(4-chlorophenyl)iodonium trifluoromethanesulfonate (0.75 mmol) and Cu(OTf)$_2$ (18.1 mg, 0.05 mmol) were added to a 10 mL round-bottom flask followed by the adding of DBE (5 mL, dried solvent) and H$_2^{18}$O (1 mL), and the reaction mixture was stirred at 80 °C in O$_2$. Upon completion, the solvent was removed by vacuum and the crude residue was purified by column chromatography on silica gel to afford the corresponding 4-acylpyrazole 3e-$_{18}$O 37% yield.**

\[
\begin{align*}
\text{Ts} & \quad \text{N} \quad \text{N} \\
\text{Cu(OTf)$_2$ (10 mol %)} & \quad \text{DBE without drying} \\
\text{80 °C, in air} & \quad \text{complex}
\end{align*}
\]

**N-propargylic sulfonylhydrazones 1e (0.5 mmol) and Cu(OTf)$_2$ (18.1 mg, 0.05 mmol) were added to a 10 mL round-bottom flask followed by the adding of DBE (5 mL, without drying), and the reaction mixture was stirred 2 h at 80 °C in air. The reaction complex and didn’t detect any pyrazole product.**
4. Analytical Data of the Products

(1,3-diphenyl-1H-pyrazol-4-yl)(phenyl)methanone (3a)

A white solid (mp 117-119 °C), (92 mg, 57% yield), \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.34-7.37 (m, 2H), 7.43 (t, 2H, \(J = 7.7\) Hz), 7.50-7.56 (m, 4H), 7.74-7.77 (m, 2H), 7.80-7.88 (m, 5H), 8.31 (s, 1H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 119.6, 121.2, 127.5, 128.1, 128.3, 128.6, 128.9, 129.4, 129.6, 132.1, 132.2, 132.6, 138.9, 139.2, 154.0, 190.0. \(^\text{HRMS}\) (ESI) \(m/z\) Calculated for C\(_{22}\)H\(_{16}\)N\(_2\)O [M+Na]\(^+\) 347.1155, found: 347.1160.

(3-(4-bromophenyl)-1-(p-tolyl)-1H-pyrazol-4-yl)(phenyl)methanone (3b)

A white solid (mp 139-141 °C), (102 mg, 49% yield), \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 2.43 (s, 3H), 7.30 (d, 2H, \(J = 8.0\) Hz), 7.44-7.52 (m, 4H), 7.58 (t, 1H, \(J = 7.3\) Hz), 7.64-7.72 (m, 4H), 7.86 (d, 2H, \(J = 7.7\) Hz), 8.23 (s, 1H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 21.0, 119.5, 120.8, 122.8, 128.4, 129.4, 130.1, 130.5, 131.1, 131.2, 132.5, 132.6, 136.8, 137.7, 138.9, 152.6, 189.7. \(^\text{HRMS}\) (ESI) \(m/z\) Calculated for C\(_{23}\)H\(_{17}\)BrN\(_2\)O [M+Na]\(^+\) 439.0416 and 441.0396, found: 439.0419 and 441.0399.

(3-(4-bromophenyl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)(phenyl)methanone (3c)
A yellow solid (mp 181-183 °C ), (96 mg, 44% yield), $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44-7.53 (m, 6H), 7.56-7.61 (m, 1H), 7.64-7.68 (m, 2H), 7.71-7.76 (m, 2H), 7.83-7.87 (m, 2H), 8.25 (s, 1H) ; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 120.6, 121.4, 123.1, 128.5, 129.4, 129.7, 130.4, 130.8, 131.3, 132.3, 132.8, 133.3, 137.6, 138.7, 153.0, 189.6. HRMS (ESI) m/z Calculated for C$_{22}$H$_{14}$BrClN$_2$O [M+Na]$^+$ 458.9870 and 460.9850, found: 458.9873 and 460.9853.

(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3d)

A yellow solid (mp 164-166 °C ), (131 mg, 65% yield), $^1$H NMR (500 MHz, CDCl$_3$) δ 7.37-7.42 (m, 1H), 7.46 (t, 2H, $J = 7.8$ Hz), 7.49-7.54 (m, 4H), 7.57-7.61 (m, 1H), 7.68-7.72 (m, 2H), 7.77-7.81 (m, 2H), 7.85-7.89 (m, 2H), 8.28 (s, 1H) ; $^{13}$C NMR (125 MHz, CDCl$_3$) δ 119.6, 121.0, 122.9, 127.6, 128.5, 129.4, 129.6, 130.5, 131.0, 131.3, 132.5, 132.7, 138.9, 139.1, 152.8, 189.7. HRMS (ESI) m/z Calculated for C$_{22}$H$_{15}$BrN$_2$O [M+Na]$^+$ 425.0260 and 427.0240, found: 425.0262 and 427.0242.

(1-(4-chlorophenyl)-3-(p-tolyl)-1H-pyrazol-4-yl)(phenyl)methanone (3e)

A yellow solid (mp 184-186 °C ), (110 mg, 59% yield), $^1$H NMR (500 MHz, CDCl$_3$) δ 2.37 (s,
3H), 7.17 (d, 2H, J = 7.9 Hz), 7.41-7.49 (m, 4H), 7.53-7.58 (m, 1H), 7.61-7.65 (m, 2H),
7.73-7.77 (m, 2H), 7.84-7.88 (m, 2H), 8.25 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 21.3,
120.6, 121.4, 128.4, 128.7, 128.9, 128.9, 129.4, 129.7, 129.7, 130.2, 132.6, 132.9, 137.8, 138.6,
138.8, 154.2, 189.9. HRMS (ESI) m/z Calculated for C$_{23}$H$_{17}$N$_2$ClO [M+Na]$^+$ 395.0922, found:
395.0925. $^{3}$e-$^{18}$O HRMS (ESI) m/z calcd for C$_{23}$H$_{17}$ClN$_2$$^{18}$O [M+Na]$^+$ 397.0964, found:
397.0973.

(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3f)

A white solid (mp 133-135 °C ), (98 mg, 55% yield), $^1$H NMR (400 MHz, CDCl$_3$) δ
7.33-7.37 (m, 2H), 7.39-7.42 (m, 1H), 7.44-7.49 (m,2H), 7.49-7. 54 (m, 2H), 7.56-7.61 (m,
1H), 7.73-7.77 (m, 2H), 7.77-7.81 (m, 2H), 7.85-7.88 (m, 2H), 8.29 (s, 1H); $^{13}$C NMR (100
MHz, CDCl$_3$) δ 119.5, 121.0, 127.6, 128.3, 128.4, 129.4, 129.6, 130.2, 130.5, 132.6, 132.7,
134.6, 138.8, 139.0, 152.8, 189.8. HRMS (ESI) m/z Calculated for C$_{22}$H$_{15}$N$_2$ClO [M+Na]$^+$
381.0765, found: 381.0769.

(3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3g)

A yellow solid (mp 127-129 °C ), (95 mg, 47% yield), $^1$H NMR (400 MHz, CDCl$_3$) δ 7.22 (t,
1H, J = 7.9 Hz), 7.37-7.42 (m, 1H), 7.43-7.54 (m, 5H), 7.55-7.60 (m, 1H), 7.67-7.71 (m, 1H),
7.77-7.82 (m, 2H), 7.83-7.88 (m, 2H), 7.96-8.00 (m, 1H), 8.29 (s, 1H); $^{13}$C NMR (100 MHz,
CDCl$_3$) δ 119.5, 121.1, 122.1, 127.6, 127.7, 128.4, 129.3, 129.5, 129.6, 131.5, 131.6, 132.5,
132.7, 134.0, 138.7, 139.0, 152.4, 189.7. HRMS (ESI) m/z Calculated for C$_{22}$H$_{15}$BrN$_2$O

(3-(naphthalen-1-yl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3h)

A yellow solid (mp 158-160 °C), (93 mg, 50% yield), $^1$H NMR (500 MHz, CDCl$_3$) δ 7.18-7.22 (m, 2H), 7.35-7.38 (m, 1H), 7.41-7.43 (m, 1H), 7.43-7.48 (m, 3H), 7.52-7.56 (m, 2H), 7.58-7.61 (m, 1H), 7.66-7.70 (m, 2H), 7.83 (d, 2H, $J = 8.3$ Hz), 7.86-7.89 (m, 2H), 8.02-8.05 (m, 1H), 8.54 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 119.6, 123.4, 124.9, 125.5, 125.7, 126.3, 127.6, 127.9, 128.2, 128.5, 128.9, 129.0, 129.6, 130.0, 131.5, 131.9, 132.1, 133.5, 138.5, 139.3, 153.1, 189.7. HRMS (ESI) m/z Calculated for C$_{26}$H$_{18}$N$_2$O [M+Na]$^+$ 397.1311, found: 397.1314.

(1,3-diphenyl-1H-pyrazol-4-yl)(4-fluorophenyl)methanone (3i)

A yellow solid (mp 154-156 °C), (91 mg, 53% yield), $^1$H NMR (500 MHz, CDCl$_3$) δ 7.05-7.09 (m, 2H), 7.33-7.37 (m, 3H), 7.38-7.42 (m, 1H), 7.53 (t, 2H, $J = 7.5$ Hz), 7.68-7.71 (m, 2H), 7.80-7.83 (m, 2H), 7.85-7.89 (m, 2H), 8.32 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 115.4 (d, $J = 21.9$ Hz), 119.6, 121.2, 127.6, 128.2, 128.6, 128.9, 129.6, 131.9, 132.0 (d, $J = 9.2$ Hz), 132.1, 135.0, 139.2, 153.8, 165.4 (d, $J = 254.5$ Hz) 188.6. HRMS (ESI) m/z Calculated for C$_{22}$H$_{15}$FN$_2$O [M+Na]$^+$ 365.1061, found: 365.1065.

(4-bromophenyl)(1,3-diphenyl-1H-pyrazol-4-yl)methanone (3j)
A yellow solid (mp 173-175 °C ), (115 mg, 57% yield), **1H NMR** (500 MHz, CDCl₃) δ 7.34-7.38 (m, 3H), 7.39-7.42 (m, 1H), 7.51-7.56 (m, 4H), 7.69-7.73 (m, 4H), 7.79-7.83 (m, 2H), 8.31 (s, 1H); **13C NMR** (125 MHz, CDCl₃) δ 119.5, 120.9, 127.6, 128.2, 128.7, 128.9, 129.6, 130.9, 131.6, 131.9, 132.1, 137.5, 139.1, 153.9, 188.9. **HRMS** (ESI) m/z Calculated for C₂₂H₁₅BrN₂O [M+Na]⁺ 425.0260 and 427.0240, found: 425.0262 and 427.0242.

(4-bromophenyl)(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methanone (3k)

A yellow solid (mp 201-203 °C ), (154 mg, 64% yield), **1H NMR** (500 MHz, CDCl₃) δ 7.41 (t, 1H, J = 7.4 Hz), 7.50-7.54 (m, 4H), 7.58-7.62 (m, 2H), 7.66-.769 (m, 2H), 7.71-7.75 (m, 2H), 7.77-7.80 (m, 2H), 8.26 (s, 1H) ; **13C NMR** (125 MHz, CDCl₃) δ 119.6, 120.7, 123.1, 127.8, 127.8, 129.7, 130.5, 130.9, 131.4, 131.8, 132.4, 137.6, 139.0, 152.8, 188.6. **HRMS** (ESI) m/z Calculated for C₂₂H₁₄Br₂N₂O [M+Na]⁺ 504.9345, found: 504.9351.

(1,3-diphenyl-1H-pyrazol-4-yl)(4-methoxyphenyl)methanone (3l)
A yellow solid (mp 138-140 °C ), (104 mg, 59% yield), \textbf{^1H NMR} (500 MHz, CDCl$_3$) δ 3.87 (s, 3H), 6.88-6.91 (m, 2H), 7.34-7.40 (m, 4H), 7.50-7.54 (m, 2H), 7.73-7.76 (m, 2H), 7.80-7.83 (m, 2H), 7.86-7.89 (m, 2H), 8.29 (s, 1H); \textbf{^13C NMR} (125 MHz, CDCl$_3$) δ 55.4, 113.6, 119.5, 121.4, 127.3, 128.2, 128.4, 128.7, 129.6, 131.4, 131.5, 131.9, 132.2, 139.3, 153.5, 163.3, 188.8. \textbf{HRMS (ESI)} m/z Calculated for C$_{23}$H$_{18}$N$_2$O$_2$ [M+Na]$^+$ 377.1260, found: 377.1262.

(3-(4-bromophenyl)-1-(p-tolyl)-1H-pyrazol-4-yl)(phenyl)methanone (3m)

![Chemical Structure Image]

A yellow solid (mp 199-200 °C ), (89 mg, 41% yield), \textbf{^1H NMR} (500 MHz, CDCl$_3$) δ 7.30-7.36 (m, 3H), 7.41-7.48 (m, 3H), 7.54-7.59 (m, 2H), 7.68-7.74 (m, 3H), 7.77-7.81 (m, 2H), 7.89-7.92 (m, 1H), 7.95-7.98 (m, 1H), 8.17 (s, 1H), 8.33-8.38 (m, 1H); \textbf{^13C NMR} (125 MHz, CDCl$_3$) δ 120.6, 123.5, 124.2, 125.5, 126.5, 127.5, 127.9, 128.0, 128.3, 128.8, 128.9, 129.7, 130.6, 131.7, 131.7, 133.2, 133.3, 133.7, 137.3, 137.6, 154.6, 190.8. \textbf{HRMS (ESI)} m/z Calculated for C$_{26}$H$_{17}$ClN$_2$O [M+Na]$^+$ 431.0922, found: 431.0926.
5. NMR Spectral of the Products

(1,3-diphenyl-1H-pyrazol-4-yl)(phenyl)methanone (3a)
(3-(4-bromophenyl)-1-(p-tolyl)-1H-pyrazol-4-yl)(phenyl)methanone (3b)
(3-(4-bromophenyl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)(phenyl)methane (3c)
(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3d)
(1-(4-chlorophenyl)-3-(p-tolyl)-1H-pyrazol-4-yl)(phenyl)methanone (3e)
(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3f)
(3-(3-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3g)
(3-(naphthalen-1-yl)-1-phenyl-1H-pyrazol-4-yl)(phenyl)methanone (3h)
(1,3-diphenyl-1H-pyrazol-4-yl)(4-fluorophenyl)methanone (3i)
(4-bromophenyl)(1,3-diphenyl-1H-pyrazol-4-yl)methanone (3j)
(4-bromophenyl)(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methanone (3k)
(1,3-diphenyl-1H-pyrazol-4-yl)(4-methoxyphenyl)methanone (3l)
(1-(4-chlorophenyl)-3-phenyl-1H-pyrazol-4-yl)(naphthalen-1-yl)methanone (3m)
6. Mass Spectral of the $3e^{-18}O$
3e-$^{18}$O HRMS (ESI) m/z calcld for C$_{23}$H$_{17}$ClN$_2$$^{18}$O [M+Na]$^+$ 397.0964, found: 397.0973.