Synthesis of Pyrazolines by a Site Isolated Resin-Bound Reagents Methodology

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I Various procedures and optimizations ........................................................................................................ 3
  I.1 Optimization of pyrazolines syntheses ................................................................................................... 3
  I.2 Synthesis of enones and aza-Michael product 3b ................................................................................. 4

II NMR spectra ............................................................................................................................................. 6
  II.1 (E)-N'-benzylidene-N-(3-oxo-2,3-diphenylpropyl)acetohydrazide (JMOD) 3b ......................... 6
  II.1 (E)-N'-benzylidene-N-(3-oxo-2,3-diphenylpropyl)acetohydrazide (JMOD) 3b ......................... 6
  II.2 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (JMOD) 4a ......................... 7
  II.2 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (JMOD) 4a ......................... 7
  II.3 1-(3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4b............................... 8
  II.3 1-(3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4b............................... 8
  II.4 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(furan-2-yl)methanone (JMOD) 4c ................. 9
  II.4 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(furan-2-yl)methanone (JMOD) 4c ................. 9
  II.5 benzyl 3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4d ......................... 10
  II.5 benzyl 3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4d ......................... 10
  II.6 N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4e.......................... 12
  II.6 N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4e.......................... 12
  II.7 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (JMOD) 4f ............................................. 13
  II.7 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (JMOD) 4f ............................................. 13
  II.8 1-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4h........... 14
  II.8 1-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4h........... 14
  II.9 3-(4-chlorophenyl)-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4i .... 15
  II.9 3-(4-chlorophenyl)-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4i .... 15
  II.10 benzyl 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4j .... 16
  II.10 benzyl 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4j .... 16
  II.11 1-(3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4k........... 17
  II.11 VI.11 1-(3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4k........... 17
  II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4l .... 18
  II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4l .... 18
II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (13C) 41
......................................................................................................................... 18
II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD)
41 ......................................................................................................................... 19
II.13 1-(3,4-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4m........... 20
II.13 1-(3,4-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4m........ 20
II.14 1-(4-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4n........... 21
II.14 1-(4-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4n........ 21
II.15 N,4-diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4o... 22
II.15 N,4-diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4o...
......................................................................................................................... 22
II.16 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4p...................... 23
II.16 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4p................ 23
II.17 (3-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (1H) 4q..... 24
II.17 (3-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (JMOD) 4q...
......................................................................................................................... 24
II.18 3-isopropyl-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4r............. 25
II.18 3-isopropyl-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4r......... 25
II.19 1-(methylsulfonyl)-3,4-diphenyl-4,5-dihydro-1H-pyrazole (1H) 4s...................... 26
II.19 1-(methylsulfonyl)-3,4-diphenyl-4,5-dihydro-1H-pyrazole (JMOD) 4s................. 26
II.20 N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4t.......... 27
II.20 N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (13C) 4t......... 27
I Various procedures and optimizations

I.1 Optimization of pyrazolines syntheses

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazone 1 $R^1$, $R^2$ (equiv)</th>
<th>Solvent</th>
<th>Temp $(^\circ C)$</th>
<th>PS-TBD (%)</th>
<th>PS-TsOH (%)</th>
<th>Pyrazoline 4b (%)</th>
<th>Enone 2a (%)</th>
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$^a$Yield determined by $^1$H NMR of the crude product by an internal standard. $^b$27% of aza-Michael product 3 was obtained. $^c$59% of aza-Michael product 3 was obtained. $^d$1 equivalent of H$_2$O.

Remark: in optimized conditions the hydrazones could be recovered.
I.2 Synthesis of enones and aza-Michael product 3b

Representative standard procedures for the synthesis of enones (adapted from the literature). Method A – for 1,2-diarylprop-2-en-1-ones synthesis. To a stirred solution of deoxybenzoin (1.96 g, 10 mmol) in MeOH (25 mL) was successively added formaline (3.57 mL: 37% aqueous solution), piperidine (0.128 mL, 1.3 mmol) and AcOH (0.128 mL, 2.2 mmol). The resulting mixture was refluxed for 3 h and concentrated in vacuo. Water was added and the obtained mixture was extracted with CH₂Cl₂. The combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated in vacuo to give 1,2-diphenylprop-2-en-1-one as colorless oil (2.08 g, quantitative crude yield). The rather unstable crude product was used rapidly without further purification. The analytical data are in accordance with literatures.

Method B – for 1- or 2-monoarylprop-2-en-1-ones synthesis. To a stirred solution of propiophenone (1.34 g, 10 mmol) in DMF (25 mL) was successively added paraformaldehyde (1.5 g), piperidine (0.128 mL, 1.3 mmol) and AcOH (0.128 mL, 2.2 mmol). The resulting mixture was heating at 90 °C for 1 h. After cooling, water was added to the residue and the mixture was extracted with Et₂O. The combined organic layers were washed with water, dried over MgSO₄, filtered, and concentrated to give 2-methyl-1-phenylprop-2-en-1-one as colorless oil (1.46 g, quantitative yield). The rather unstable crude product was used rapidly without further purification. The analytical data are in accordance with literatures.

Analysis data of unknown enone 2

1,2-bis(4-methoxyphenyl)prop-2-en-1-one (Table 3, entry 13). Pale yellow oil; δ_H (300 MHz; CDCl₃) 7.94-7.89 (2 H, m), 7.36-7.32 (2 H, m), 6.91-6.84 (4 H, m), 5.89 (1 H, s), 5.44 (1 H, s), 3.84 (3 H, s), 3.79 (3 H, s); δ_C (75.4 MHz; CDCl₃) 196.7 (C), 163.7 (C), 159.8 (C), 147.9 (C), 132.5 (CH), 129.9 (C), 129.7 (C), 128.1 (CH), 117.1 (CH₂), 114.1 (CH), 113.7 (CH), 55.5 (CH₃), 55.3 (CH₃); MS (EI) m/z : 268, 240, 225, 209, 165, 135, 118, 107, 92, 77.

4-methyl-2-phenylpent-1-en-3-one (Table 3, entries 17-18). Colorless oil; δ_H (300 MHz; CDCl₃) 7.27-7.18 (5 H, m), 5.89 (1 H, s), 5.75 (1 H, s), 3.20-3.06 (1 H, m), 1.05 (3 H, d, J 6.9); δ_C (75.4 MHz; CDCl₃) 207.0 (C), 149.1 (C), 137.5 (C), 128.3 (CH), 128.2 (CH), 128.1 (CH), 122.7 (CH₂), 36.8 (CH), 18.8 (CH₃); MS (EI) m/z : 174, 159, 131, 115, 103, 91, 77.

Analysis data for aza-Michael product (Table 1, entry 8).

(E)-N²-benzylidene-N-(3-oxo-2,3-diphenylpropyl)acetohydrazide (3b). White solid (150.0 mg, 81 %); R_f = 0.46 (Petroleum ether/EtOAc: 2/1); mp 126-128 °C; IR (KBr) ν_max/cm⁻¹ 1672, 1612, 1596, 1578, 1493, 1440, 1408, 1359, 1215, 1146, 1036, 975, 749.

702; $\delta_H$(300 MHz; CDCl$_3$) 7.94-7.91 (2 H, m), 7.56-7.17 (14 H, m), 5.16 (1 H, t, $J$ 7.7), 4.61 (1 H, dd, $J$ 14.5 and $J$ 6.2), 4.38 (1 H, dd, $J$ 14.5 and $J$ 7.9), 2.42 (3 H, s); $\delta_C$(75.4 MHz; CDCl$_3$) 198.6 (C), 173.7 (C), 139.6 (CH), 137.1 (C), 136.1 (C), 134.7 (C), 133.3 (CH), 129.7 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.0 (CH), 51.0 (CH), 44.2 (CH$_2$), 22.1 (CH$_3$); HRMS (ESI+): Calcd for C$_{24}$H$_{23}$N$_2$O$_2$ [M+H]$^+$: 371.1760; Found: 371.1767.
II NMR spectra

II.1 (E)-N' -benzylidene-N- (3-oxo-2,3-diphenylpropyl)acetohydrazide (1H) 3b

II.1 (E)-N' -benzylidene-N- (3-oxo-2,3-diphenylpropyl)acetohydrazide (JMOD) 3b
II.2 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (1H) 4a

II.2 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (JMOD) 4a
II.3 1-(3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (IH) 4b

II.3 1-(3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4b
II.4 (3,4-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)(furan-2-yl)methanone (1H) 4c
II.5 benzyl 3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (1H) 4d

Remark: the peak corresponding to carbon 3 (CH) appeared as a small broad signal due to relaxation issue in pyrazoline-NCbz series.
II.5 benzyl 3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4d
II.6 N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4e

![N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4e](image1.png)

II.6 N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4e

![N,3,4-triphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4e](image2.png)
II.7 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (1H) 4f

![NMR Spectrum of 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (1H) 4f](image)

II.7 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (JMOD) 4f

![NMR Spectrum of 3,4-diphenyl-1-tosyl-4,5-dihydro-1H-pyrazole (JMOD) 4f](image)
II.8 1-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4h

II.8 1-(3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4h
II.9 3-(4-chlorophenyl)-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4i
II.10 benzyl 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (1H) 4j

Remark: the peak corresponding to carbon 3 (CH) appeared as a small broad signal due to relaxation issue in pyrazoline-NCbz series.
II.11 1-(3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4k

II.11 VI.11 1-(3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4k
II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (1H) 4l

II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (13C) 4l
Remark: the peak corresponding to carbon 3 (CH) appeared as a small broad signal due to relaxation issue in pyrazoline-NCbz series.

II.12 benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxylate (JMOD) 4l
II.13 1-(3,4-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H)

4m

II.13 1-(3,4-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4m
II.14 1-(4-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4n
II.15 N,4-diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4o

II.15 N,4-diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (JMOD) 4o
II.16 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4p

![NMR spectrum of 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (1H) 4p](image)

II.16 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4p

![NMR spectrum of 1-(4-methyl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (JMOD) 4p](image)
II.17 (3-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (1H) 4q

II.17 (3-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (JMOD) 4q
II.18 3-isopropyl-N,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4r
II.19 1-(methylsulfonyl)-3,4-diphenyl-4,5-dihydro-1H-pyrazole (1H) 4s

II.19 1-(methylsulfonyl)-3,4-diphenyl-4,5-dihydro-1H-pyrazole (JMOD) 4s
II.20 **N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4t**

![N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1H) 4t](image1)

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II.20 **N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (13C) 4t**

![N-cyclohexyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (13C) 4t](image2)