REGIOSELECTIVE SYNTHESIS OF EITHER 1H- OR 2H-1,2,3-TRIAZOLES VIA MICHAEL ADDITION TO α,β-UNSATURATED KETONES

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th Birthday

Abstract – The Michael reaction of NH-1,2,3-triazole (1) with α,β-unsaturated ketones was studied. 1H-1,2,3-triazolyl-ketones were selectively generated when 1 was combined neat with a variety of enones. The use of aprotic solvents with catalytic base gave the corresponding 2H-regioisomers. Together, these two protocols provide direct access to either the N1- or N2-substituted 1,3-triazolyl ketone regioisomers.

INTRODUCTION
The regioselective synthesis of substituted-1,2,3-triazoles has become synonymous with the rapid assembly of modular molecular architectures.1 Our focus on this robust and under-appreciated azole class led us back to the simple parent core 1 (C\textsubscript{2}H\textsubscript{3}N\textsubscript{3}),\textsuperscript{2} which exists as a rapidly equilibrating mixture of two tautomers in solution, shown in Figure 1.\textsuperscript{3,4} The physical properties of 1 struck us as highly unusual and in fact very like those of water. These include its weak acid/base character (pK\textsubscript{a} = 9.3, pK\textsubscript{b} = 1.2),\textsuperscript{5} very high proton conductivity,\textsuperscript{6} and a liquid range spanning nearly 200 degrees (14–205 °C).\textsuperscript{3,7}

![Figure 1. 1H- and 2H-tautomers of NH-1,2,3-triazole (1)](image)

A small molecule with three contiguous nitrogens contributing to approximately 60% of its total weight naturally evokes safety concerns. Indeed, there has been some debate regarding its stability.\textsuperscript{8} However, exhaustive and precise tests by Malow et. al. have now established that NH-1,2,3-triazole is insensitive to impact, friction, rapid heating, and even detonation.\textsuperscript{9}
Our recent studies have found that 1 engages in and supports a number of useful addition and displacement reactions, especially when employed in the absence of any exogenous solvent. This first report is confined to Michael additions of NH-1,2,3-triazole (1) with \( \alpha,\beta \)-unsaturated ketones in a simple and regioselective manner. Similar transformations have been reported; however, the corresponding adducts were typically isolated in poor yield\(^\text{10}\) or as a mixture of regioisomers.\(^\text{11}\)

**RESULTS AND DISCUSSION**

\( \alpha,\beta \)- Unsaturated ketones were simply added to neat NH-1,2,3-triazole (1) (Table 1). In all cases 1 was employed in excess (5–15 equiv.) and served as a solvent for the enones. Upon warming the corresponding 1,4-conjugate addition adducts were obtained.

**Table 1.** Michael additions of 1 to \( \alpha,\beta \)-unsaturated ketones under neat conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time</th>
<th>Yield(^a)</th>
<th>Entry</th>
<th>Product</th>
<th>Time</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Diagram" /></td>
<td>2.0 h</td>
<td>73%(^b)</td>
<td>5</td>
<td><img src="image2" alt="Diagram" /></td>
<td>2.0 h</td>
<td>67%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Diagram" /></td>
<td>2.0 h</td>
<td>89%</td>
<td>6</td>
<td><img src="image4" alt="Diagram" /></td>
<td>2.0 h</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Diagram" /></td>
<td>1.5 h</td>
<td>84%(^c)</td>
<td>7</td>
<td><img src="image6" alt="Diagram" /></td>
<td>1.0 h</td>
<td>65% (1.3%(^c))</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Diagram" /></td>
<td>6.0 h</td>
<td>73%</td>
<td>8</td>
<td><img src="image8" alt="Diagram" /></td>
<td>2.0 h</td>
<td>73% (17%)(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after crystallization or column chromatography.\(^b\) Products isolated as a 2:1 mixture of diastereomers.\(^c\) Isolated yield of N2-regioisomer.
While these additions can potentially give both \( \text{N1} \)- and \( \text{N2} \)-substituted regioisomers, TLC and LC/MS analyses revealed that one predominant isomer was generated in each case with good to excellent selectivity. Following purification, \(^1\)H- and \(^{13}\)C-NMR analysis identified these adducts as the corresponding 1\(H\)-triazolyl ketones (3a-h).\(^{12}\) In addition to giving very high regioselectivity, performing the reaction in the absence of exogenous solvent or catalyst facilitated rapid isolation and purification of the 1\(H\)-triazolyl ketones. Once the reaction had gone to completion, as determined by TLC or LC/MS analysis, excess \( \text{NH}\)-1,2,3 triazole was removed via Kugelrhor distillation (0.5 mmHg, \( T = 100 \text{ °C} \)). This yielded the crude adducts and simultaneously permitted excess \( \text{NH}\)-1,2,3-triazole (1) to be recovered and reused in further transformations.\(^{13}\)

Our protocol employing neat \( \text{NH}\)-1,2,3-triazole (1) was compatible with a variety of substrates and easily gave access to the corresponding \( \text{N1} \)-substituted adducts. However, we observed post-reaction emergence of the \( \text{N2} \)-substituted triazolyl isomer in two cases (Table 1, entries 7 and 8). In these examples, the reaction mixture prior to workup by distillative concentration did not indicate significant erosion of regioselectivity. Monitoring the product distribution prior to and during distillation revealed that the appearance of the 2\(H\)-isomer in significant quantities occurred only upon heating the sample above 100 \( \text{ °C} \). In addition, we noted that prolonged reaction time at higher temperatures led to a drastic change in the product distribution in the case of cyclopenten-2-one (2g).\(^{14}\)

**Figure 2.** Thermal \( \text{N1–N2} \) isomerization of 1,4-conjugate addition adduct 3c

These observations prompted us to test the thermal stability of our products over a range of temperatures (Figure 2). 1\(H\)-Triazolyl ketone 3c was re-dissolved in \( \text{NH}\)-1,2,3-triazole and heated using microwave irradiation for a period of one hour. After each experiment, the product distribution was determined by LC/MS.\(^{15}\) While no change occurred at lower temperatures, conversion to the \( \text{N2} \)-isomer was observed
when the sample was heated above 80 °C. Heating samples above 120 °C gave the 2H-isomer (4c) as the major product, with the maximal conversion occurring between 150 °C and 160 °C. This conclusively demonstrated that the N1-regioisomer can give rise to the 2H-triazolyl ketone 4c upon extended heating. N1- to N2-isomerism of N-substituted-1,2,3-triazoles is not unprecedented.\(^{16}\) One particularly outstanding example of this phenomenon was reported in a detailed study by Birkofer and Wegner, where N1-acylated-1,2,3-triazoles were found to undergo isomerization to the corresponding 2H-isomer upon heating above 120 °C.\(^{17}\) In our system the conversion from 3c to 4c is best rationalized by assuming that the 1,4-conjugate addition is reversible under these conditions, giving rise to the 2H-isomer via an intermolecular pathway involving retro-Michael/Michael addition. This observation reveals that 3c is the kinetically favored isomer, while 2H-triazolyl ketone 4c is the thermodynamically more stable product. These assumptions are supported by computational studies, which find that N2-substituted-1,2,3-triazoles are typically 4–5 kcal/mol more stable than the corresponding 1H-regioisomer.\(^{4,18}\)

Given these observations, we sought conditions to facilitate equilibration and hence favor the thermodynamically more stable N2-adducts. As expected, basic conditions were effective, with K\(_2\)CO\(_3\) giving the best results. Numerous solvents were compatible with this transformation; however, faster conversions and higher yields were obtained when acetonitrile was employed.

**Table 2.** Michael additions of 1 to α,β-unsaturated ketones using base catalysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>N1 (%)(^{a})</th>
<th>N2 (%)(^{a})</th>
<th>Entry</th>
<th>Enone</th>
<th>N1 (%)(^{a})</th>
<th>N2 (%)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2c</td>
<td>3c (15%)</td>
<td>4c (61%)</td>
<td>5</td>
<td>3g</td>
<td>3g (11%)</td>
<td>4g (83%)</td>
</tr>
<tr>
<td>2</td>
<td>2d</td>
<td>3d (16%)</td>
<td>4d (63%)</td>
<td>6</td>
<td>2h</td>
<td>3h (8%)</td>
<td>4h (80%)</td>
</tr>
<tr>
<td>3</td>
<td>2e</td>
<td>3e (10%)</td>
<td>4e (61%)</td>
<td>7</td>
<td>2i</td>
<td>3i (13%)</td>
<td>4i (65%)</td>
</tr>
<tr>
<td>4</td>
<td>2f</td>
<td>3f (13%)</td>
<td>4f (68%)</td>
<td>8</td>
<td>2j</td>
<td>3j (18%)(^{b})</td>
<td>4j (54%)(^{b})</td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated yield after column chromatography. \(^{b}\) Product isolated as a 1:1 mixture of diastereomers.
The scope of this base-catalyzed process was briefly explored (Table 2). Both cyclic and acyclic enones reacted with 1 to afford a mixture of regioisomers with the N2-isomer being the major product. We observed that 1,4-conjugate addition and subsequent isomerization to the 2H-triazolyl ketone proceeded much more rapidly with cyclic systems than in the acyclic counterparts. Within the acyclic series, we noted that the presence of an electron-withdrawing group at the α-carbon facilitated the conversion to the N2-regioisomer (Table 2, entry 3 cf. entries 4 and 8). Furthermore, we observed that the N2-triazolyl ketones (4c-j) were consistently more non-polar than their corresponding N1-adducts (Figure 3a,b). The dissimilar polarity of these two regioisomers can be attributed to the large difference in both the orientation and magnitude of the dipole moment for the N1- and N2-substituted triazolyl group (Figure 3c). This difference in polarity not only allowed the reaction progress to be readily monitored by TLC analysis, but also greatly facilitated the separation of the 1H- and 2H-triazolyl ketones by column chromatography.

**Figure 3.** Comparative analysis of 1H- and 2H-isomers by thin layer chromatography.

In conclusion, we have found complementary methods, which provide facile access to either 1H- or 2H-triazolyl ketones via 1,4-conjugate addition. Using NH-1,2,3-triazole (1) neat permits the selective formation of the kinetically-favored N1-substituted 1,4-adducts from a variety of α,β-unsaturated ketones. Whereas the thermodynamically-favored N2-regioisomers become the major products when catalytic base is employed. Studies to extend the utility of this and related processes will be presented in due course.

**EXPERIMENTAL**

Melting points were recorded on either a Barnstead Electrothermal digital melting point apparatus (Model IA9300) or on Thomas-Hoover capillary melting apparatus and are uncorrected. IR spectra were recorded on pure undiluted samples using a ThermoNicolet Avatar 370 FT-IR with a Smart MIRacle™ single reflection HATR attachment. High-resolution mass spectra (HRMS) were recorded at the mass
spectrometry facility at The Scripps Research Institute, La Jolla, CA, USA. Analytical HPLC was performed on an Agilent HP 1100 series LC/MS with a variable wavelength diode array detector. $^1$H NMR (400 MHz and 500 MHz) and $^{13}$C NMR (100 MHz, 125 MHz, and 150 MHz) spectra were recorded on Bruker DRX-500, Bruker DRX-600 spectrometers in CDCl$_3$ unless otherwise noted. Chemical shifts were reported as part per million (ppm) downfield of TMS. The proton signal of residual, non-deuterated solvent ($\delta$ 7.26 for CHCl$_3$, $\delta$ 2.50 for DMSO-$d_6$) was used as internal reference for $^1$H spectra. $^{13}$C spectra, chemical shifts were reported relative to the $\delta$ 77.0 resonance of CDCl$_3$. Coupling constants ($J$) are reported in Hertz (Hz). Flash column chromatography was performed using Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical TLC was performed on precoated glass plates (Merck Kieselgel 60 F$_{254}$). All chemicals purchased from vendors were used as received without further purification. $NH$-$1,2,3$-triazole (1) was purchased from AK scientific. Recovered $NH$-$1,2,3$-triazole (see Method A) was re-purified prior to reuse by vacuum distillation (0.5 mmHg) at 65°C over a short path apparatus and stored in Nalgene bottle at 4°C.

**Method A: General procedure for the synthesis of $1H$-triazolyl-ketones using neat $NH$-$1,2,3$-triazole.**

$NH$-$1,2,3$-Triazole (1, 5–15 equivalents, amount adjusted to obtain a homogeneous solution) was added to $\alpha,\beta$-unsaturated ketone. The reaction mixture was heated (50–80°C) for 2–6 h and monitored by TLC or LC/MS. Upon complete consumption of starting material, excess triazole was removed by Kugelrohr distillation (0.5 mmHg, T = 100°C). The residue was purified by column chromatography over silica gel. In situations where the product solidified or precipitated from the reaction mixture, product was triturated (MeOH or EtOAc/hexanes) and collected by vacuum filtration.

**Representative example for reactions employing trituration:**

$1,3$-Diphenyl-$3$-($1H$-$1,2,3$-triazol-$1$-yl)$propan$-$1$-one (3c)

$NH$-$1,2,3$-Triazole (1) (24.8 mL, 480 mmol) was added to chalcone (2c) (10.00 g, 48.00 mmol). The reaction was warmed to 80°C in an open Erlenmeyer flask and stirred vigorously. Progress was monitored by TLC (30% EtOAc/hexanes) and LC/MS. After 1.5 h conversion was complete and the flask was cooled to room temperature. The product precipitated from the mixture and was triturated with small amount of MeOH and collected by filtration to afford 3c as a white solid (11.12 g, 84%): $R_f = 0.1$ (30% EtOAc/hexanes); mp 107.0–109.0°C; IR (\nu [cm$^{-1}$]) = 3097, 1681, 1454, 1376, 1333, 1213, 1081, 1027, 1001, 962, 751, 716, 690; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.97–7.95 (m, 2H), 7.68 (app s, 1H), 7.59–7.55 (m, 1H), 7.47–7.44 (m, 2H), 7.37–7.31 (m, 5H), 6.32 (dd, $J = 8.5$, 5.0, 1H), 7.60 (app s, 1H), 7.59–7.55 (m, 1H), 7.47–7.44 (m, 2H), 7.37–7.31 (m, 5H), 6.32 (dd, $J = 8.5$, 5.0, 1H), 4.66 (dd, $J = 178$, 8.8, 1H), 3.74 (dd, $J = 18.0$, 5.0, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 195.8, 139.1, 136.1, 133.8, 133.6,
Representative example for reactions employing Kugelrohr distillation:

1-Phenyl-3-(1H-1,2,3-triazol-1-yl)butan-1-one (3e)


\[
\text{NH}-1,2,3-\text{Triazole (1) (3.7 mL, 64 mmol) was added to 1-phenylbut-2-en-1-one (2e) (1.88 g, 12.9 mmol) in a screw-top scintillation vial. The vial was capped and then warmed to 80 °C and stirred vigorously. Progress was monitored by TLC (30% EtOAc/hexanes) and LC/MS. After 2 h the reaction was complete and was cooled to room temperature. The reaction mixture was transferred to a Kugelrohr apparatus and all volatile material was removed by distillation (0.5 mmHg, T = 100 °C, 20–25 min). After cooling to room temperature, the residue was taken up in EtOAc (5 mL) and then a large excess of hexanes (100–150 mL) was added. A precipitate formed and was collected by filtration to give 3e as a white powder (1.54 g, 56%). The filtrate was concentrated under vacuum and again diluted with EtOAc (5 mL). Precipitation with a second washing of hexanes (100 mL) gave a precipitate which was isolated by filtration to give a second crop of 3e (0.17 g, 6%), total isolated yield of the two fractions = 1.71 g, 62%: Rf = 0.16 (50% EtOAc/hexanes); mp 76.5–78.0 °C; IR (υ[cm⁻¹]) = 3130, 3111, 2977, 2933, 1683, 1449, 1367, 1213, 1077, 1000, 953, 795, 761, 688; ¹H NMR (CDCl₃, 500 MHz): δ 7.93–7.91 (m, 2H), 7.67 (br s, 1H), 7.66 (br s, 1H), 7.59–7.56 (m, 1H), 7.47–7.44 (m, 2H), 5.34 (dqd, J = 7.3, 6.5, 5.8, 1H), 3.92 (dd, J = 17.8, 7.3, 1H), 3.46 (dd, J = 18.2, 5.8, 1H), 1.74 (d, J = 6.5, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 196.4, 136.2, 133.7, 133.2, 128.7, 123.3, 52.8, 45.1, 21.5; HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₂H₁₄N₃O, 216.1131; found, 216.1129.

2-(2-(1H-1,2,3-Triazol-1-yl)propan-2-yl)-5-methylcyclohexanone (3a)

Prepared using method A, R-(-)-pulegone (2a) (812 µL, 5 mmol), NH-1,2,3-triazole (1) (1.45 mL, 25 mmol), 80 °C. NH-1,2,3-Triazole was removed via Kugelrohr distillation. The oily residue was purified by column chromatography (50–80% EtOAc/hexanes) to afford 3a (mixture of diastereomers ~ 2:1) as a yellow oil (0.80 g, 73%): IR (υ[cm⁻¹]) = 3120, 2954, 1709, 1456, 1369, 1298, 1221, 1123, 1070, 1015, 783. Major diastereomer: ¹H NMR (CDCl₃, 500 MHz): δ 7.66 (d, J = 1.0, 1H), 7.63 (d, J = 1.0, 1H), 3.43–3.30 (m, 1H), 2.28 (dd, J = 12.8, 4.0, 2.3, 1H), 2.09–2.03 (m, 1H), 1.92–1.78 (m, 2H), 1.78 (s, 3H), 1.72 (s, 3H), 1.63–1.53 (m, 1H), 1.46 (qd, J = 13.0, 3.0, 1H), 1.39–1.30 (m, 1H), 0.99 (d, J = 6.0, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 209.2, 132.52, 121.64, 62.57, 58.2, 51.7, 36.0, 33.9, 28.3, 26.3, 24.16, 22.1. Minor diastereomer: ¹H NMR (CDCl₃, 500 MHz): δ 7.66 (d, J = 1.0, 1H), 7.63 (d, J = 1.0, 1H), 3.43–3.30 (m, 1H), 2.63 (dd, J = 13.0, 6.0, 0.5, 1H), 2.44–2.36 (m, 1H), 2.09–2.03 (m, 1H), 1.92–1.78 (m, 1H), 1.79
(s, 3H), 1.73 (s, 3H), 1.63–1.53 (m, 1H), 1.50–1.44 (m, 1H), 0.90 (d, J = 7.5, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 209.7, 132.54, 121.67, 62.60, 58.6, 49.7, 31.9, 30.7, 26.2, 24.23, 23.9, 18.4; HRMS (ESI-TOF) ($m/z$): [M + H]$^+$ calcd for C$_{12}$H$_{20}$N$_3$O, 222.1601; found, 222.1605.

1,4-Diphenyl-2-(1H-1,2,3-triazol-1-yl)butane-1,4-dione (3b)
Prepared using method A, 1,4-diphenylbut-2-ene-1,4-dione (2b) (0.70 g, 2.96 mmol), NH-1,2,3-triazole (1) (2.6 mL, 44.4 mmol) 65 °C. After 0.5 h, a white solid precipitated from the reaction mixture and was pulverized. Reaction mixture was heated for an additional 1.5 h. After this time MeOH was added to the flask and the suspension was stirred vigorously for 20 min. The precipitate was then collected by filtration to afford 3b as a white solid (0.81 g, 89%): mp 180.0–182.0 °C; IR ($\nu$[cm$^{-1}$]) = 3121, 3101, 2970, 2911, 1695, 1670, 1594, 1448, 1406, 1294, 1186, 1080, 1008, 830, 798, 764, 729, 686; $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 8.42 (d, $J$ = 0.7, 1H), 8.05–7.99 (m, 4H), 7.76 (br s, 1H), 7.69–7.65 (m, 2H), 7.56–7.52 (m, 4H), 6.96 (dd, $J$ = 6.5, 6.9, 1H), 4.26 (dd, $J$ = 18.1, 6.2, 1H), 4.01 (dd, $J$ = 18.1, 6.2, 1H); $^{13}$C NMR (DMSO-d$_6$, 150 MHz): $\delta$ 197.3, 194.3, 137.0, 136.5, 135.6, 135.4, 135.0, 130.3, 130.1, 129.9, 129.4, 126.6, 60.1, 41.6; HRMS (ESI-TOF) ($m/z$): [M + H]$^+$ calcd for C$_{18}$H$_{16}$N$_3$O$_2$, 306.1237; found, 306.1236.

4-Phenyl-4-(1H-1,2,3-triazol-1-yl)butan-2-one (3d)
Prepared using method A, 4-phenylbut-3-en-2-one (2d) (0.73 g, 5 mmol), NH-1,2,3-triazole (1) (1.45 mL, 25 mmol), 80 °C. NH-1,2,3-Triazole was removed via Kugelrohr distillation. Solid residue was re-dissolved in small amount of EtOAc and then hexanes was added slowly to give a fine precipitate. This solid was triturated to afford 3d as a white solid (0.78 g, 72%): mp 110.0–113.0 °C; IR ($\nu$[cm$^{-1}$]) = 3089, 1714, 1493, 1455, 1362, 1218, 1169, 1120, 1088, 1028, 816, 753, 719, 694; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.65 (d, $J$ = 0.5, 1H), 7.49 (d, $J$ = 1.0, 1H), 7.35–7.28 (m, 3H), 7.26–7.24 (m, 2H), 6.05 (dd, J = 9.3, 4.8, 1H), 4.07 (dd, $J$ = 17.5, 9.5, 1H), 3.15 (dd, $J$ = 17.8, 4.8, 1H), 2.20 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 204.3, 133.0, 138.8, 138.9, 129.1, 128.6, 126.6, 124.1, 60.1, 48.5, 30.3; HRMS (ESI-TOF) ($m/z$): [M + H]$^+$ calcd for C$_{12}$H$_{14}$N$_3$O, 216.1131; found, 216.1130.

4-Methyl-4-(1H-1,2,3-triazol-1-yl)pentan-2-one (3f)
Prepared using method A, mesityl oxide (2f) (572 $\mu$L, 5 mmol), NH-1,2,3-triazole (1) (1.45 mL, 25 mmol), 80 °C. NH-1,2,3-Triazole was removed via Kugelrohr distillation. The oily residue was purified by column chromatography (50–85% EtOAc/hexanes) to afford 3f as a pale yellow oil (0.69 g, 83%): IR ($\nu$[cm$^{-1}$]) = 3129, 2983, 2937, 1715, 1435, 1367, 1290, 1220, 1146, 1071, 1018, 952, 784; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.66–7.65 (m, 2H), 3.20 (s, 2H), 2.00 (s, 3H), 1.77 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 205.0, 133.0,
121.2, 59.7, 53.4, 31.2, 28.2; HRMS (ESI-TOF) \((\text{m/z})\): \([M + H]^+\) calcd for C8H14N3O, 168.1131; found, 168.1129.

3-(1H-1,2,3-Triazol-1-yl)cyclopentanone (3g)
Prepared using method A, cyclopent-2-enone (2g) (2.07 g, 25 mmol), NH-1,2,3-triazole (1) (7.3 mL, 126 mmol), 50 °C, 1 h. NH-1,2,3-Triazole was removed via Kugelrohr distillation. The oily residue was purified by column chromatography using (50% EtOAc/hexanes – 100% EtOAc) to afford 3g as a beige solid (2.48 g, 65%): mp 62.5–64.0 °C; IR (\(\upsilon\) [cm\(^{-1}\)]) = 3126, 3102, 2980, 2925, 1732, 1483, 1452, 1291, 1210, 1159, 1085, 902, 815, 616; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.65 (s, 1H), 7.60 (s, 1H), 5.23–5.17 (m, 1H), 2.82–2.70 (m, 2H), 2.60–2.24 (m, 4H); 13C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 213.5, 133.6, 122.6, 57.3, 44.4, 36.2, 30.0; HRMS (ESI-TOF) \((\text{m/z})\): \([M + H]^+\) calcd for C7H10N3O, 152.0818; found, 152.0817.

3-(1H-1,2,3-Triazol-1-yl)cyclohexanone (3h)
Prepared using method A, cyclohex-2-enone (2h) (486 \(\mu\)L, 5 mmol), NH-1,2,3-triazole (1) (1.45 mL, 25 mmol), 80 °C. NH-1,2,3-Triazole was removed via Kugelrohr distillation. The oily residue was purified by column chromatography (80–90% EtOAc/hexanes) to afford 3h as a white solid (0.60 g, 73%): mp 59.0–60.0 °C; IR (\(\upsilon\) [cm\(^{-1}\)]) = 3128, 3093, 2961, 2876, 1706, 1453, 1324, 1213, 1116, 1094, 1020, 826, 750, 705; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.69 (d, \(J = 1.0\), 1H), 7.58 (d, \(J = 1.0\), 1H), 4.86 (dddd, \(J = 10.0\), 10.0, 5.0, 4.0, 1H), 2.97 (ddd, \(J = 14.5\), 5.3, 1.3, 1H), 2.92 (dddd, \(J = 14.5\), 5.5, 1.5, 1.5, 1H) 2.52–2.26 (m 4H), 2.11–2.04 (m, 1H), 1.83–1.74 (m, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 206.4, 133.6, 121.9, 58.6, 47.3, 40.4, 31.7, 21.6; HRMS (ESI-TOF) \((\text{m/z})\): \([M + H]^+\) calcd for C\(_8\)H\(_{12}\)N\(_3\)O, 166.0975; found, 166.0979.

Method B: General procedure for the synthesis of 2H-triazolyl-ketones using base catalysis.
\(\alpha,\beta\)-Unsaturated ketone and NH-1,2,3-triazole (1, 1.05–1.20 equiv.) were dissolved in MeCN (0.5–1 M) and treated with K\(_2\)CO\(_3\), (0.1 equiv.). The reaction was heated (55–80 °C) and monitored by TLC or LC/MS. When no further change in the \(N1/N2\) ratio was observed, the solvent was removed under reduced pressure and the products were purified by column chromatography over silica gel. Note: In every case, the \(N2\)-product elutes long before the more polar \(N1\)-isomer.

Representative example for base-catalyzed synthesis of 2H-triazoles:
3-(2H-1,2,3-Triazol-2-yl)cyclohexanone (4h)
Cyclohex-2-enone (2h) (2.30 g, 24.0 mmol) and NH-1,2,3-triazole (1.46 mL, 25 mmol) were dissolved in MeCN (48 mL) in a round bottom flask and treated with K\(_2\)CO\(_3\), (0.33 g, 2.4 mmol, 0.1 equiv.). The
reaction was then capped and heated to 55 °C for 13.5 h, and monitored by TLC (80% EtOAc/hexanes) and LC/MS. When no further change in the product distribution was observed the reaction was cooled to room temperature and concentrated under vacuum. The crude residue was purified by column chromatography (40% EtOAc/hexanes – 100% EtOAc) to afford 4h as a pale yellow oil (3.15 g, 80%) along with 3h (0.33 g, 8.3%) as the minor product.

(4h): IR (υ [cm⁻¹]) = 3155, 2956, 2874, 1713, 1418, 1343, 1223, 1107, 1015, 962, 818, 753; ¹H NMR (CDCl₃, 500 MHz): δ 7.54 (s, 2H), 4.96 – 4.91 (m, 1H), 2.99 (dd, J = 14.8, 9.3, 1H), 2.80 (dd, J = 14.8, 5.3, 1H), 2.40–2.37 (dd, J = 8.0, 6.0, 2H), 2.27–2.16 (m, 2H), 1.95–1.88 (m, 1H), 1.75–1.67 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 207.1, 133.9, 62.2, 46.2, 30.3, 30.8, 21.1; HRMS (ESI-TOF) (m/z): [M + H]^+ calcd for C₈H₁₂N₃O, 166.0975; found, 166.0969.

1,3-Diphenyl-3-(2H-1,2,3-triazol-1-yl)propan-1-one (4c)
Prepared using method B, chalcone (2c) (1.04 g, 5 mmol), NH⁻1,2,3-triazole (304 μL, 5.25 mmol), 70 °C. Purified by column chromatography (20–50% EtOAc/hexanes) to afford the 4c as an off-white solid (0.84 g, 61%) along with 3c (0.21 g, 15%) as the minor product.

(4c): mp 95.5–97.5 °C; IR (υ [cm⁻¹]) = 3133, 3066, 1682, 1422, 1370, 1333, 1210, 1144, 962, 832, 749, 722, 687; ¹H NMR (CDCl₃, 500 MHz): δ 8.00–7.98 (m, 2H), 7.60 (s, 2H), 7.60–7.56 (m, 1H), 7.48–7.45 (m, 1H), 7.36–7.27 (m, 5H), 6.51 (dd, J = 9.0, 5.5, 1H), 5.52 (dd, J = 17.5, 9.0, 1H), 3.73 (dd, J = 17.8, 5.3, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 195.7, 139.4, 136.4, 134.1, 133.4, 128.8, 128.7, 128.3, 128.2, 126.7, 64.0, 44.0; HRMS (ESI-TOF) (m/z): [M + H]^+ calcd for C₁₇H₁₆N₃O, 278.1288; found, 278.1291.

4-Phenyl-4-(2H-1,2,3-triazol-2-yl)butan-2-one (4d)
Prepared using method B, 4-phenylbut-3-en-2-one (2d) (731 mg, 5 mmol), NH⁻1,2,3-triazole (304 μL, 5.25 mmol), 65 °C. Purified by column chromatography (25% EtOAc/hexanes to 100% EtOAc) to afford 4d as a pale yellow oil (0.68 g, 63%) along with 3d (0.17 g, 16%) as the minor product.

(4d): IR (υ [cm⁻¹]) = 3129, 3062, 2958, 1719, 1455, 1417, 1353, 1165, 1142, 1024, 961, 818, 753, 698; ¹H NMR (CDCl₃, 500 MHz): δ 7.60 (s, 2H), 7.33–7.24 (m, 5H), 6.25 (dd, J = 9.5, 5.0, 1H), 3.94 (dd, J = 17.5, 9.5, 1H), 3.18 (dd, J = 17.8, 5.3, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 204.3, 139.1, 134.1, 128.8, 128.3, 126.5, 63.9, 48.4, 30.3; HRMS (ESI-TOF) (m/z): [M + H]^+ calcd for C₁₂H₁₄N₃O, 216.1131; found, 216.1130.

1-Phenyl-3-(2H-1,2,3-triazol-2-yl)butan-1-one (4e)
Prepared using method B, 1-phenylbut-2-en-1-one (2e) (710 μL, 5 mmol), \( NH\text{-1,2,3-triazole} \) (304 μL, 5.25 mmol), 65 °C. Purified by column chromatography (15% EtOAc/hexanes to 100% EtOAc) to afford 4e as a pale yellow oil (0.65 g, 61%) along with 3e (0.11 g, 10%) as the minor product.

\((4e)\): IR \((\nu [\text{cm}^{-1}]) = 3062, 2986, 1685, 1597, 1448, 1369, 1217, 1147, 1001, 962, 817, 755, 689; {^1}\text{H NMR} \) (CDCl\(_3\), 500 MHz): \( \delta 7.97−7.94 \text{ (m, 2H)}, 7.58−7.55 \text{ (m, 3H)}, 7.47−7.44 \text{ (m, 2H)}, 5.46 \text{ (dqd, } J = 7.0, 6.8, 6.5, 1\text{H}), 3.87 \text{ (dd, } J = 17.5, 6.5, 1\text{H}), 3.45 \text{ (dd, } J = 17.5, 7.0, 1\text{H}), 1.66 \text{ (d, } J = 6.8, 3\text{H}); {^{13}}\text{C NMR} \) (CDCl\(_3\), 125 MHz): \( \delta 196.5, 136.5, 133.8, 133.4, 128.6, 128.1, 57.0, 44.4, 21.0; \text{HRMS (ESI-TOF) } (m/z): [M + H]^+ \text{ calcd for C}_{12}\text{H}_{14}\text{N}_3\text{O, 216.1131; found, 216.1130.}\)

4-Methyl-4-(2\(H\)-1,2,3-triazol-2-yl)pentan-2-one (4f)

Prepared using method B, mesityl oxide (2f) (572 μL, 5 mmol), \( NH\text{-1,2,3-triazole} \) (304 μL, 5.25 mmol), 65 °C. Purified by column chromatography (50% EtOAc/hexanes to 100% EtOAc) to afford 4f as a pale yellow oil (0.57 g, 68%) along with 3f (0.11 g, 13%) as the minor product.

\((4f)\): IR \((\nu [\text{cm}^{-1}]) = 3124, 2988, 2939, 1718, 2421, 1365, 1325, 1179, 1140, 962, 819; {^1}\text{H NMR} \) (CDCl\(_3\), 500 MHz): \( \delta 7.59 \text{ (s, 2H)}, 3.15 \text{ (s, 2H)}, 1.98 \text{ (s, 3H)}, 1.75 \text{ (s, 6H); } {^{13}}\text{C NMR} \) (CDCl\(_3\), 125 MHz): \( \delta 205.4, 133.5, 63.5, 53.5, 31.1, 27.6; \text{HRMS (ESI-TOF) } (m/z): [M + H]^+ \text{ calcd for C}_{8}\text{H}_{14}\text{N}_3\text{O, 168.1131; found, 168.1127.}\)

3-(2\(H\)-1,2,3-Triazol-2-yl)cyclopentanone (4g)

Prepared using method B, cyclopent-2-enone (2g) (419 μL, 5 mmol), \( NH\text{-1,2,3-triazole} \) (304 μL, 5.25 mmol), 65 °C. Purified by column chromatography (70% EtOAc/hexanes to 100% EtOAc) to afford 4g as a pale yellow oil (0.63 g, 83%) along with 3g (0.08 g, 11%) as the minor product.

\((4g)\): IR \((\nu [\text{cm}^{-1}]) = 3126, 2988, 2939, 1718, 2421, 1365, 1325, 1179, 1140, 962, 819, 752; {^1}\text{H NMR} \) (CDCl\(_3\), 500 MHz): \( \delta 7.58 \text{ (s, 2H)}, 5.36-5.31 \text{ (m, 1H)}, 2.91-2.87 \text{ (br dd, } J = 18.5, 4.5, 1\text{H)}, 2.74 \text{ (br dd, } J = 18.8, 7.6, 1\text{H), 2.57-2.46 \text{ (m, 3H), 2.36-2.26 \text{ (m, 1H); } {^{13}}\text{C NMR} \}) \) (CDCl\(_3\), 125 MHz): \( \delta 214.7, 134.2, 61.5, 44.2, 36.1, 29.7; \text{HRMS (ESI-TOF) } (m/z): [M + H]^+ \text{ calcd for C}_{7}\text{H}_{10}\text{N}_3\text{O, 152.0818; found, 152.0817.}\)

3-(2\(H\)-1,2,3-Triazol-2-yl)cycloheptanone (4i)

Prepared using method B, cyclohept-2-enone (2i) (223 μL, 2 mmol), \( NH\text{-1,2,3-triazole} \) (139 μL, 2.4 mmol), 70 °C. Purified by column chromatography (50%−90% EtOAc/hexanes) to afford 4i as a colorless oil (0.23 g, 65%) along with 3i (0.045 g, 13%) as the minor product.

\((4i)\): IR \((\nu [\text{cm}^{-1}]) = 3131, 2985, 2863, 1699, 1448, 1418, 1342, 1162, 1130, 961, 818, 736; {^1}\text{H NMR} \) (CDCl\(_3\), 500 MHz): \( \delta 7.50 \text{ (s, 2H)}, 4.86-4.81 \text{ (m, 1H)}, 3.26 \text{ (dd, } J = 15.1, 10.5, 1\text{H)}, 2.86 \text{ (app dd, } J = 15.2, 2.7, 1\text{H), 2.57-2.43 \text{ (m, 2H), 2.20-2.16 \text{ (m, 2H), 1.88-1.81 \text{ (m, 2H), 1.73-1.65 \text{ (m, 1H), 1.60-1.52 \text{ (m, 1H); } {^{13}}\text{C}} \) (CDCl\(_3\), 125 MHz): \( \delta 214.7, 134.2, 61.5, 44.2, 36.1, 29.7; \text{HRMS (ESI-TOF) } (m/z): [M + H]^+ \text{ calcd for C}_{7}\text{H}_{16}\text{N}_3\text{O, 152.0818; found, 152.0817.}\)
NMR (CDCl$_3$, 125 MHz): $\delta$ 209.6, 133.7, 61.2, 48.8, 43.9, 36.7, 26.1, 23.5; HRMS (ESI-TOF) ($m/z$): [M + H]$^+$ calcd for C$_9$H$_{14}$N$_3$O, 180.1131; found, 180.1129.

(3i): IR ($\nu$ [cm$^{-1}$]) = 3122, 2926, 2862, 1699, 1447, 1220, 1112, 1027, 791, 757, 730; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.67 (s, 1H), 7.56 (s, 1H), 4.83 (tt, $J = 10.8, 3.3$, 1H), 3.28 (dd, $J = 14.5, 11.0$, 1H), 2.92 (ddd, $J = 14.8, 2.5, 2.0$, 1H), 2.66–2.61 (m, 1H), 2.53 (ddd, $J = 16.0, 11.3, 4.0$, 1H), 2.30–2.26 (m, 1H), 2.18 (tdd, $J = 14.0, 11.3, 2.8$, 1H), 2.07–1.96 (m, 2H), 1.80–1.72 (m, 1H), 1.64–1.56 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 209.0, 133.7, 121.5, 57.6, 49.8, 43.9, 37.7, 26.4, 23.5; HRMS (ESI-TOF) ($m/z$): [M + H]$^+$ calcd for C$_9$H$_{14}$N$_3$O, 180.1131; found, 180.1128.

3-Methyl-4-(2H-1,2,3-triazol-2-yl)pentan-2-one (4j)

Prepared using method B, 3-methylpent-3-en-2-one (2j) (491 mg, 5 mmol), NH$_2$-1,2,3-triazole (304 $\mu$L, 5.25 mmol), 65 $^\circ$C. Purified by column chromatography (50% EtOAc/hexanes to 100% EtOAc) to afford 4j as a colorless oil (0.45 g, 54%) and 3j (0.15 g, 18%) as the minor product:

(4j) (isolated as a 1:1 mixture of diastereomers): IR ($\nu$ [cm$^{-1}$]) = 3123, 2986, 2940, 1712, 1452, 1420, 1339, 1152, 1081, 961, 818; Diastereomer A: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.60 (s, 1H), 5.01 (dq, $J = 8.5, 6.8$, 1H), 3.35 (dq, $J = 8.5, 7.5$, 1H), 2.08 (s, 3H), 1.55 (d, $J = 6.5$, 3H), 1.18 (d, $J = 7.0$, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 209.6, 133.8, 61.8, 51.3, 28.8, 17.5, 13.2; Diastereomer B: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.56 (s, 1H), 4.96 (dq, $J = 9.3, 6.8$, 1H), 3.20 (dq, $J = 9.3, 7.3$, 1H), 2.22 (s, 3H), 1.53 (d, $J = 6.5$, 3H), 0.81 (d, $J = 7.0$, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 209.5, 133.7, 62.5, 53.0, 29.7, 19.2, 14.0; HRMS (ESI-TOF) ($m/z$): [M + H]$^+$ calcd for C$_8$H$_{14}$N$_3$O, 168.1131; found, 168.1126.

(3j) (isolated as a 1:1 mixture of diastereomers): IR ($\nu$ [cm$^{-1}$]) = 3128, 2983, 2941, 1709, 1453, 1360, 1224, 1115, 1077, 953, 792; Diastereomer A: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.69 (d, $J = 1.0$, 1H), 7.55 (d, $J = 1.0$, 1H), 4.88–4.82 (m, 1H), 3.29 (dq, $J = 8.8, 7.3$, 1H), 2.04 (s, 3H), 1.58 (d, $J = 7.0$, 3H), 1.21 (d, $J = 7.0$, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 209.8, 133.3, 123.1, 57.8, 51.7, 29.2, 18.3, 13.8; Diastereomer B: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.63 (d, $J = 1.0$, 1H), 7.53 (d, $J = 1.0$, 1H), 4.88–4.82 (m, 1H), 3.18 (dq, $J = 8.8, 7.3$, 1H), 2.22 (s, 3H), 1.57 (d, $J = 6.5$, 3H), 0.88 (d, $J = 7.0$, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 209.5, 133.1, 123.5, 58.1, 52.7, 29.7, 19.7, 14.0; HRMS (ESI-TOF) ($m/z$): [M + H]$^+$ calcd for C$_8$H$_{14}$N$_3$O, 168.1131; found, 168.1128.

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REFERENCES AND NOTES


2. NH-1,2,3-triazole is commercially available on kilogram scale from several suppliers.


12. The N1-substituted triazolyl group displays two distinct signals in both the 1H and 13C spectra, while only one is observed for the N2-isomer due to symmetry of the ring.

13. In our hands, distillation and manipulation of NH-1,2,3-triazole in the presence of a variety of organic reagents has never proven to be hazardous. Even so, caution should be exercised. NH-1,2,3-Triazole does undergo pyrolysis when heated above 300 °C (decomposition energy = 42 kcal/mol, see ref. 11).

14. Reaction of 2h at 80 °C for 6 h gave a mixture of N1- (36%) and N2- (14%) isomers. Improved yield was observed at 50 °C (see experimental section).

15. Product ratio determined by integration of UV absorbance at (254 nm) from LC chromatogram.


