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

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Abstract

The Michael reaction of *NH*-1,2,3-triazole (**1**) with α,β -unsaturated ketones was studied. 1*H*-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 2*H*-regioisomers. Together, these two protocols provide direct access to either the *N*1- or *N*2-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** (C₂H₃N₃),² which exists as a rapidly equilibrating mixture of two tautomers in solution, shown in Figure 1.^{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_a = 9.3, pK_b = 1.2),⁵ very high proton conductivity,⁶ and a liquid range spanning nearly 200 degrees (14–205 °C).^{3,7}

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.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.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 α,β -unsaturated ketones in a simple and regioselective manner. Similar transformations have been reported; however, the corresponding adducts were typically isolated in poor yield¹⁰ or as a mixture of regioisomers.¹¹

RESULTS AND DISCUSSION

α,β -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.

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

While these additions can potentially give both *N*1- and *N*2-substituted regioisomers, TLC and LC/MS analyses revealed that one predominant isomer was generated in each case with good to excellent selectivity. Following purification, ¹H- and ¹³C-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 *NH*-1,2,3 triazole was removed via Kugelrohr distillation (0.5 mmHg, T = 100 °C). This yielded the crude adducts and simultaneously permitted excess *NH*-1,2,3-triazole (**1**) to be recovered and reused in further transformations.¹³

Our protocol employing neat *NH*-1,2,3-triazole (**1**) was compatible with a variety of substrates and easily gave access to the corresponding *N*1-substituted adducts. However, we observed post-reaction emergence of the *N*2-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 °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

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 *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 *N*2-isomer was observed when the sample was heated above 80 °C. Heating samples above 120 °C gave the 2*H*-isomer (**4c**) as the major product, with the maximal conversion occurring between 150 °C and 160 °C. This conclusively demonstrated that the *N*1-regioisomer can give rise to the 2*H*-triazolyl ketone **4c** upon extended heating. *N*1- to *N*2-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 *N*1-acylated-1,2,3-triazoles were found to undergo isomerization to the corresponding 2*H*-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 2*H*-isomer via an intermolecular pathway involving retro-Michael/Michael addition. This observation reveals that **3c** is the kinetically favored isomer, while 2*H*-triazolyl ketone **4c** is the thermodynamically more stable product. These assumptions are supported by computational studies, which find that *N*2-substituted-1,2,3-triazoles are typically 4–5 kcal/mol more stable than the corresponding 1*H*-regioisomer.^{4,18}

Given these observations, we sought conditions to facilitate equilibration and hence favor the thermodynamically more stable *N*2-adducts. As expected, basic conditions were effective, with K₂CO₃ giving the best results. Numerous solvents were compatible with this transformation; however, faster conversions and higher yields were obtained when acetonitrile was employed.

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 *N*2-isomer being the major product. We observed that 1,4-conjugate addition and subsequent isomerization to the 2*H*-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 *N*2-regioisomer (Table 2, entry 3 *cf.* entries 4 and 8). Furthermore, we observed that the *N*2-triazolyl ketones (**4c-j**) were consistently more non-polar than their corresponding *N*1-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 *N*1- and *N*2-substituted triazolyl group (Figure 3c).^{19,20} 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 1*H*- and 2*H*-triazolyl ketones by column chromatography.

In conclusion, we have found complementary methods, which provide facile access to either 1*H*- or 2*H*-triazolyl ketones via 1,4-conjugate addition. Using *NH*-1,2,3-triazole (**1**) neat permits the selective formation of the kinetically-favored *N*1-substituted 1,4-adducts from a variety of α,β -unsaturated ketones. Whereas the thermodynamically-favored *N*2-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. ¹H NMR (400 MHz and 500 MHz) and ¹³C NMR (100 MHz, 125 MHz, and 150 MHz) spectra were recorded on Bruker DRX-500, Bruker DRX-600 spectrometers in CDCl₃ unless otherwise noted. Chemical shifts were reported as part per million (ppm) downfield of TMS. The proton signal of residual, non-deuterated solvent (δ 7.26 for CHCl₃, δ 2.50 for DMSO-*d*₆) was used as internal reference for ¹H spectra. ¹³C spectra, chemical shifts were reported relative to the δ 77.0 resonance of CDCl₃. 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 F₂₅₄). 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 1*H*-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 α,β -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-(1*H*-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 (ν [cm⁻¹]) = 3097, 1681, 1454, 1376, 1333, 1213,

1081, 1027, 1001, 962, 751, 716, 690; ^1H NMR (CDCl_3 , 500 MHz): δ 7.97–7.95 (m, 2H), 7.68 (app s, 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): δ 195.8, 139.1, 136.1, 133.8, 133.6, 129.1, 128.7, 128.6, 128.2, 126.8, 124.2, 60.4, 44.3; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{N}_3\text{O}$, 278.1288; found, 278.1285.

Representative example for reactions employing Kugelrohr distillation: 1-

Phenyl-3-(1*H*-1,2,3-triazol-1-yl)butan-1-one (3e)—*NH*-1,2,3-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%; R_f = 0.16 (50% EtOAc/hexanes); mp 76.5–78.0 °C; IR ($\nu[\text{cm}^{-1}]$) = 3130, 3111, 2977, 2933, 1683, 1449, 1367, 1213, 1077, 1000, 953, 795, 761, 688; ^1H NMR (CDCl_3 , 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 (dq, 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); ^{13}C NMR (CDCl_3 , 125 MHz): δ 196.4, 136.2, 133.7, 133.2, 128.7, 128.0, 123.3, 52.8, 45.1, 21.5; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}$, 216.1131; found, 216.1129.

2-(2-(1*H*-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 ($\nu[\text{cm}^{-1}]$) = 3120, 2954, 1709, 1456, 1369, 1298, 1221, 1123, 1070, 1015, 783. Major diastereomer: ^1H NMR (CDCl_3 , 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 (ddd, 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); ^{13}C NMR (CDCl_3 , 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 (CDCl_3 , 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 (ddd, 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): δ 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): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{N}_3\text{O}$, 222.1601; found, 222.1605.

1,4-Diphenyl-2-(1*H*-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 ($\nu[\text{cm}^{-1}]$) = 3121, 3101, 2970, 2911, 1695, 1670, 1594, 1448, 1406, 1294, 1186, 1080, 1008, 830, 798, 764, 729, 686; ^1H NMR ($\text{DMSO}-d_6$, 500 MHz): δ 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, $J = 18.1, 6.9$, 1H), 4.01 (dd, $J = 18.1, 6.2$, 1H); ^{13}C NMR (DMSO- d_6 , 150 MHz): δ 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): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_2$, 306.1237; found, 306.1236.

4-Phenyl-4-(1*H*-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 (ν [cm^{-1}]) = 3089, 1714, 1493, 1455, 1362, 1218, 1169, 1120, 1088, 1028, 816, 753, 719, 694; ^1H NMR (CDCl_3 , 500 MHz): δ 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): δ 204.3, 138.8, 138.9, 129.1, 128.6, 126.6, 124.1, 60.1, 48.5, 30.3; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}$, 216.1131; found, 216.1130.

4-Methyl-4-(1*H*-1,2,3-triazol-1-yl)pentan-2-one (3f)—Prepared using method A, mesityl oxide (**2f**) (572 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 (50–85% EtOAc/hexanes) to afford **3f** as a pale yellow oil (0.69 g, 83%): IR (ν [cm^{-1}]) = 3129, 2983, 2937, 1715, 1435, 1367, 1290, 1220, 1146, 1071, 1018, 952, 784; ^1H NMR (CDCl_3 , 500 MHz): δ 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): δ 205.0, 133.0, 121.2, 59.7, 53.4, 31.2, 28.2; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{14}\text{N}_3\text{O}$, 168.1131; found, 168.1129.

3-(1*H*-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 (ν [cm^{-1}]) = 3126, 3102, 2980, 2925, 1732, 1483, 1452, 1291, 1210, 1159, 1085, 902, 815, 616; ^1H NMR (CDCl_3 , 400 MHz): δ 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); ^{13}C NMR (CDCl_3 , 100 MHz): δ 213.5, 133.6, 122.6, 57.3, 44.4, 36.2, 30.0; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{10}\text{N}_3\text{O}$, 152.0818; found, 152.0817.

3-(1*H*-1,2,3-Triazol-1-yl)cyclohexanone (3h)—Prepared using method A, cyclohex-2-enone (**2h**) (486 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 (80–90% EtOAc/hexanes) to afford **3h** as a white solid (0.60 g, 73%): mp 59.0–60.0 °C; IR (ν [cm^{-1}]) = 3128, 3093, 2961, 2876, 1706, 1453, 1324, 1213, 1116, 1094, 1020, 826, 750, 705; ^1H NMR (CDCl_3 , 500 MHz): δ 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): δ 206.4, 133.6, 121.9, 58.6, 47.3, 40.4, 31.7, 21.6; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{12}\text{N}_3\text{O}$, 166.0975; found, 166.0979.

Method B: General procedure for the synthesis of 2*H*-triazolyl-ketones using base catalysis

α,β -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_2CO_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 2*H*-triazoles: 3-

(2*H*-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 K₂CO₃ (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 (ν[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-(2*H*-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** (0.21g, 15%) as the minor product.

(**4c**): mp 95.5–97.5 °C; IR (ν[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-(2*H*-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 (ν[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), 2.19 (s, 3H); 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-(2*H*-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*-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 (ν[cm⁻¹]) = 3062, 2986, 1685, 1597, 1448, 1369, 1217, 1147, 1001, 962, 817, 755, 689; ¹H NMR (CDCl₃, 500 MHz): δ 7.97–7.94 (m, 2H), 7.58–7.55 (m, 3H), 7.47–7.44 (m, 2H), 5.46 (dq, *J* = 7.0, 6.8, 6.5, 1H), 3.87 (dd, *J* = 17.5, 6.5, 1H), 3.45 (dd, *J* = 17.5, 7.0, 1H), 1.66 (d, *J* = 6.8, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 196.5, 136.5, 133.8, 133.4, 128.6, 128.1,

57.0, 44.4, 21.0; HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{12}H_{14}N_3O$, 216.1131; found, 216.1130.

4-Methyl-4-(2H-1,2,3-triazol-2-yl)pentan-2-one (4f)—Prepared using method B, mesityl oxide (**2f**) (572 μ L, 5 mmol), *NH*-1,2,3-triazole (304 μ L, 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 (ν [cm^{-1}]) = 3124, 2988, 2939, 1718, 2421, 1365, 1325, 1179, 1140, 962, 817; 1H NMR ($CDCl_3$, 500 MHz): δ 7.59 (s, 2H), 3.15 (s, 2H), 1.98 (s, 3H), 1.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.4, 133.5, 63.5, 53.5, 31.1, 27.6; HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_8H_{14}N_3O$, 168.1131; found, 168.1127.

3-(2H-1,2,3-Triazol-2-yl)cyclopentanone (4g)—Prepared using method B, cyclopent-2-enone (**2g**) (419 μ L, 5 mmol), *NH*-1,2,3-triazole (304 μ L, 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 the **3g** (0.08 g, 11%) as the minor product.

(**4g**): IR (ν [cm^{-1}]) = 3126, 3009, 1743, 1418, 1351, 1154, 1117, 963, 902, 819, 752; 1H NMR ($CDCl_3$, 500 MHz): δ 7.58 (s, 2H), 5.36–5.31 (m, 1H), 2.91–2.87 (br dd, J = 18.5, 4.5, 1H), 2.74 (br dd, J = 18.8, 7.6, 1H), 2.57–2.46 (m, 3H), 2.36–2.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 214.7, 134.2, 61.5, 44.2, 36.1, 29.7; HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_7H_{10}N_3O$, 152.0818; found, 152.0817.

3-(2H-1,2,3-Triazol-2-yl)cycloheptanone (4i)—Prepared using method B, cyclohept-2-enone (**2i**) (223 μ L, 2 mmol), *NH*-1,2,3-triazole (139 μ L, 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 (ν [cm^{-1}]) = 3131, 2935, 2863, 1699, 1448, 1418, 1342, 1162, 1130, 961, 818, 736; 1H NMR ($CDCl_3$, 500 MHz): δ 7.50 (s, 2H), 4.86–4.81 (m, 1H), 3.26 (dd, J = 15.1, 10.5, 1H), 2.86 (app dd, J = 15.2, 2.7, 1H), 2.57–2.43 (m, 2H), 2.20–2.16 (m, 2H), 1.88–1.81 (m, 2H), 1.73–1.65 (m, 1H), 1.60–1.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 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 $C_9H_{14}N_3O$, 180.1131; found, 180.1129.

(**3i**): IR (ν [cm^{-1}]) = 3122, 2926, 2862, 1699, 1447, 1220, 1112, 1072, 1027, 791, 757, 730; 1H NMR ($CDCl_3$, 500 MHz): δ 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): δ 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 $C_9H_{14}N_3O$, 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*-1,2,3-triazole (304 μ L, 5.25 mmol), 65 °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 (ν [cm^{-1}]) = 3123, 2986, 2940, 1712, 1452, 1420, 1339, 1152, 1081, 961, 818; Diastereomer A: 1H NMR ($CDCl_3$, 500 MHz): δ 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): δ 209.6, 133.8, 61.8, 51.3, 28.8, 17.5,

13.2; Diastereomer B: ^1H NMR (CDCl_3 , 500 MHz): δ 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): δ 209.5, 133.7, 62.5, 53.0, 29.7, 19.2, 14.0; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{14}\text{N}_3\text{O}$, 168.1131; found, 168.1126.

(**3j**) (isolated as a 1:1 mixture of diastereomers): IR ($\nu[\text{cm}^{-1}]$) = 3128, 2983, 2941, 1709, 1453, 1360, 1224, 1115, 1077, 953, 792; Diastereomer A: ^1H NMR (CDCl_3 , 500 MHz): δ 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): δ 209.8, 133.3, 123.1, 57.8, 51.7, 29.2, 18.3, 13.8; Diastereomer B: ^1H NMR (CDCl_3 , 500 MHz): δ 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): δ 209.5, 133.1, 123.5, 58.1, 52.7, 29.7, 19.7, 14.0; HRMS (ESI-TOF) (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{14}\text{N}_3\text{O}$, 168.1131; found, 168.1128.

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References

1. Ball P. Chemistry World 2007;4:46. Wu P, Fokin VV. Aldrichimica Acta 2007;40:7. Moses JE, Moorhouse AD. Chem Soc Rev 2007;36:1249. [PubMed: 17619685]
2. *NH*-1,2,3-triazole is commercially available on kilogram scale from several suppliers.
3. Tomé, AC. Science of Synthesis: 1,2,3-Triazoles. Storr, RC.; Gilchrist, TL., editors. Vol. 13. Thieme; New York: 2004. p. 415
4. Davarski KA, Khalachev NK, Yankova RZ, Raikov S. Chem Heterocycl Compd 1998;34:568.
5. Catalan J, Abboud J-LM, Elguero J. Adv Heterocycl Chem 1987;41:187.
6. Zhou Z, Liu R, Wang J, Li S, Liu M, Bredas J-L. J Phys Chem A 2006;110:2322. [PubMed: 16480289]
7. An early report cited the melting point as 23 °C; Catino A. Ann Chim (Rome, Italy) 1968;58:1507. Goddard R, Heinemann O, Kruger C. Acta Crystallogr Sect C: Cryst Struct Commun 1997;C53:1846.
8. Prashad M, Liu Y, Har D, Repic O, Blacklock TJ. Tetrahedron Lett 2005;46:5455. Katritzky AR, Wang Z, Tsikolia M, Hall CD, Carman M. Tetrahedron Lett 2006;47:7653.
9. Malow M, Wehrstedt KD, Neuenfeld S. Tetrahedron Lett 2007;48:1233.
10. Wiley RH, Smith NR, Johnson DM, Moffat J. J Am Chem Soc 1954;76:4933.
11. Dinér P, Nielsen M, Marigo M, Jørgensen KA. Angew Chem Int Ed 2007;46:1983.
12. The *N*1-substituted triazolyl group displays two distinct signals in both the ^1H and ^{13}C spectra, while only one is observed for the *N*2-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 *N*1- (36%) and *N*2- (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.
16. Kamijo S, Jin T, Huo Z, Yamamoto Y. J Org Chem 2004;69:2386. [PubMed: 15049635] Komeda S, Lutz M, Spek AL, Yamanaka Y, Sato T, Chikuma M, Reedijk J. J Am Chem Soc 2002;124:4738. [PubMed: 11971723] Polak M, Vercsek B. Synth Commun 2000;30:2863. Hassner A, Stern M, Gottlieb HE, Frolov F. J Org Chem 1990;55:2304.

17. Birkofer L, Wegner P. Chem Ber 1967;100:3485.
18. Nagy PI, Tejada FR, Messer WS Jr. J Phys Chem B 2005;109:22588. [PubMed: 16853941]Foces-Foces C, Saiz ALL, Elguero J. Heterocyc Commun 1999;5:137.
19. Jug K, Chiodo S, Calaminici P, Avramopoulos A, Papadopoulos MG. J Phys Chem A 2003;107:4172.Kassimi NE-B, Doerksen RJ, Thakkar AJJ. Phys Chem 1995;99:12790.
20. Abboud J-LM, Foces-Foces C, Notario R, Trifonov RE, Volovodenko AP, Ostrovskii VA, Alkorta I, Elguero J. Eur J Org Chem 2001:3013.

Figure 1.
1*H*- and 2*H*-tautomers of *NH*-1,2,3-triazole (**1**)

Figure 2.
Thermal *N*1–*N*2 isomerization of 1,4-conjugate addition adduct **3c**

Figure 3. Comparative analysis of 1*H*- and 2*H*-isomers by thin layer chromatography.^a ref. 19. ^b ref. 20.

Table 1Michael additions of **1** to α,β -unsaturated ketones under neat conditions.

Entry	Product	Time
1	3a	2.0 h
2	3b	2.0 h

Entry	Product	Time
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3

1.5 h

Entry	Product	Time
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4

6.0 h

Entry	Product	Time
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5		2.0 h
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6		2.0 h
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7		1.0 h
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Entry	Product	Time
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8

2.0 h

^a Isolated yield after crystallization or column chromatography.

^b Products isolated as a 2:1 mixture of diastereomers.

^c Isolated yield of *N*2-regioisomer.

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

Entry	Enone	<i>N1</i> (%) ^a
1	2c	3c (15%)
2	2d	3d (16%)
3	2e	3e (10%)
4	2f	3f (13%)
5	2g	3g (11%)
6	2h	3h (8%)
7	2i	3i (13%)

Entry

Enone

N1 (%)^a

8

3j (18%)^b ^a Isolated yield after column chromatography.^b Product isolated as a 1:1 mixture of diastereomers.