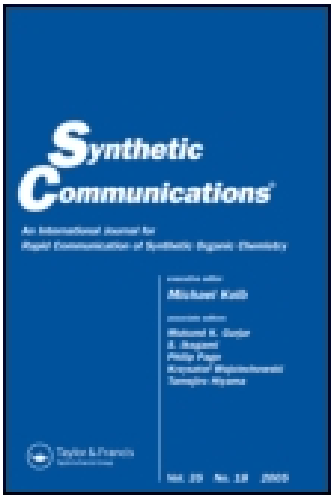

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 15 Feb 2008.

To cite this article: John L. Belletire , Robert A. Bills & Scott A. Shackelford (2008) Practical Methylation Procedure for (1H)-1,2,4-Triazole, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:5, 738-745, DOI: 10.1080/00397910701820319

To link to this article: http://dx.doi.org/10.1080/00397910701820319

Synthetic Communications®, 38: 738–745, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701820319

Practical Methylation Procedure for (1H)-1,2,4-Triazole

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Abstract: Conversion of (1H)-1,2,4-triazole to its sodium salt with methanolic sodium methoxide is followed by reaction with iodomethane. A scalable approach that overcomes problems associated with water-soluble starting material and water-soluble product combined continuous extraction (chloroform/water) with a final short-path distillation under a controlled vacuum to obtain spectroscopically pure 1-methyl-1,2,4-triazole in 63% yield. Adaptation to microwave synthesis conditions, while providing a faster reaction time, offers no product yield or purification advantages over the conventional approach described. Conversions of this product to related derivatives such as 1,4-dimethyl-1,2,4-triazolium iodide and 1-methyl-1,2,4-triazolium hydrochloride are readily achieved.

Keywords: 1-methyl-1,2,4-triazole, regioselective alkylation, sequential continuous extraction, short-path distillation, 1,2,4-triazole sodium salt

INTRODUCTION

A large body of published chemistry has emerged pertaining to heterocycles containing multiple nitrogen atoms within the ring system.[1] The alkylation of amide-anions derived from such heterocycles with various alkyl halides

Received in the USA September 14, 2007
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provides useful methodology for the preparation of valuable reaction products from relatively inexpensive starting materials. Illustrating this approach, and made more significant by their utility in numerous agrichemical and medicinal applications,[2] alkylations of 1,2,4-triazoles have been widely examined. Past reports using a direct methylation process[3–5] or an alternative deamination strategy[6] provided promising background methodology. Although previous investigations often concentrated on alkylations with higher-molecular-weight electrophiles rather than on synthesizing the methyl homolog, the simple reaction to obtain the monomethyl derivative, 1-methyl-1,2,4-triazole from (1H)-1,2,4-triazole presents experimental problems for which a focused solution has not been addressed. A procedural approach is herein provided that partially achieves these goods:

1. counters the appreciable water solubility of both the starting material and the desired reaction product,
2. reduces regiochemical scrambling in the alkylation product,
3. minimizes overalkylation (i.e., quaternization), and
4. overcomes similar vapor pressure properties of both the 1-methyl-1,2,4-triazole product and the (1H)-1,2,4-triazole reactant.

Because these challenges are common to the methylation of other low-molecular-weight heterocycle substrates, our process should have considerable generality.

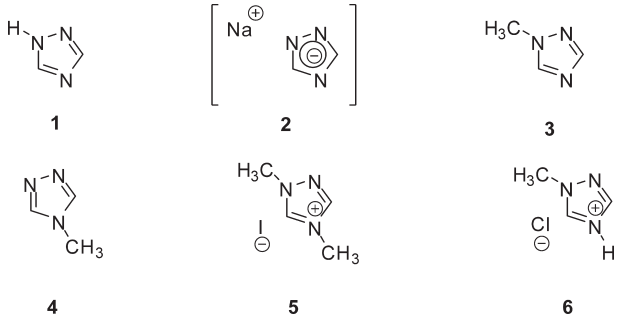
RESULTS AND DISCUSSION

By effectively solubilizing the reactants, intermediates, and products, methanol serves as a polar protic solvent well suited for alkylation of (1H)-1,2,4-triazole **1**. Screening of possible bases for removal of the acidic proton prior to alkylation revealed that triethylamine was too weak to effectively deprotonate the triazole, instead affording an intractable postalkylation mixture largely consisting of (1H)-1,2,4-triazole, recovered triethylamine, and triethylmethylammonium iodide. In contrast, an equivalent of sodium methoxide, introduced as a 25% w:w solution in methanol, led to efficient deprotonation[3–5] when the reaction mixture was warmed (56°C) for 2 h. Although the sodium salt **2** of (1H)-1,2,4-triazole is commercially available, in situ preparation of the anion is a trivial operation that allows the less expensive triazole free base to be employed as starting material. Methylation involves the dropwise addition of iodomethane to a precooled solution of the sodio-intermediate, while maintaining the temperature using both an external cooling bath and the electrophile's rate of addition to control the considerable exotherm. The reaction mixture is then allowed to stir for 19 h with gentle heating at reflux. In range-finding experiments, heating the iodomethane/triazole mixture for 6 h at reflux led to ~10% recovered unreacted starting

material, whereas heating the iodomethane/sodio-triazole reaction mixture for 72 h at 45°C gave a crude reaction mixture essentially identical to the 19-h variant. A simple atmospheric distillation to concentrate the reaction mixture to a viscous residue is performed using a short-path column. Although this operation minimizes codistillation of the somewhat volatile alkylation product, an actual test comparison using a rotary evaporator under a modest vacuum (75 mbar) with a rt water bath afforded only a modest (4%) decrease in yield. Upon isolation of the concentrated residue, ^{1}H NMR of the crude syrup demonstrated that the organic components included the desired final product 1-methyl-1,2,4-triazole **3** (93%), ~2% of starting material **1**, ~2% of the undesired regioisomer **4**, and ~2% of the quaternary bis-alkylation salt **5**.

Structures

Efficient workup and purification of the reaction mixture encompassed a sequence of simple operations. The reaction residue is diluted with a minimum volume of water (in practice, 33 mL of water per 10 g of the starting material) to remove the inorganic salts as well as small amounts of very water-soluble by-products. Using a small continuous extraction apparatus, the water solution is extracted with 170–200 mL of chloroform with heating at reflux maintained for 22.5 h. Cooling of the system, separation and drying of the chloroform layer, filtration, and careful removal of the chloroform can be achieved on a rotary evaporator equipped with a rt water bath and operating at a modest vacuum (75 mbar). Alternatively, and for best yields, distillation of the chloroform through a Vigreaux column at atmospheric pressure affords a mobile oil whose proton NMR exhibits essentially complete absence of starting material **1**, regioisomer **4**, and quaternization product **5** (see structures shown in Scheme 1). The presence of several very small baseline peaklets in the proton NMR of the



Scheme 1.

residue as well as a pale yellow color are evidence for trace amounts of polymer. Final purification is accomplished when the residual oil is subjected to a short-path distillation at constant moderate vacuum (70 mbar) with external oil-bath heating and isolation of the center cut. A practical source of constant reduced pressure involves simply disconnecting the original flexible tubing connection between the Bűchi vacuum controller assembly and the actual Bűchi rotary evaporator apparatus and then reconnecting that flexible tubing to the vacuum takeoff of the all-glass distillation system. Trapping of the distilled product in an ice–salt water bath causes the distillate to freeze into a snow-white solid. Thawing provides an approximate melting point of 3–5°C for this sample. By reference to a standard pressure/temperature (P/T) nomagraph, the published boiling point of 1-methyl-1,2,4-triazole, 177–178°C at 755 mm Hg,[3] and our observed boiling-point parameters at moderate pressure, 74–78°C at 70 mbar, are in agreement. Distillation at oil pump vacuum (0.1–0.3 mm Hg), both by reference to the P/T nomagraph and by actual trial, occurs inconveniently at temperatures colder than rt. Replication consistency is illustrated by two consecutive methylations at a scale of 10 g of (1H)-1,2,4-triazole starting material that gave 62.5% and 63.1% overall yields of distilled, spectroscopically pure **3**.

Microwave experiments conducted using a Biotage/Personal Chemistry™ Initiator apparatus sought to optimize the alkylation procedural parameters. It was found that deprotonation of a 14.5-mmol sample of the starting material could be accomplished using an equivalent of the 25% w/w methanolic sodium methoxide solution with heating to 65°C for 5 min in a 5-mL sealed microwave reaction vessel within the microwave apparatus. After cooling the reaction mixture in an ice bath to 0–3°C, uncrimping the reaction assembly, layering of the requisite neat iodomethane, and recrimping the 5-mL reaction vessel, the reaction vessel was reinserted into the microwave apparatus. The reaction mixture was then subjected to a second microwave heating at a set point of 90°C for a total overall heating cycle of 8 min. In this cycle, an initial very rapid (~15 s in duration) exotherm to 114°C was followed by re-equilibration to 90°C within 200 s. After cooling to rt, removal of the methanol on a rotary evaporator afforded a viscous gelatinous residue, which was then subjected to extraction with six 5-mL portions of reagent-grade chloroform. The combined chloroform washes were filtered through a bed of Celite® and evaporated at reduced pressure to a solvent-free residue with a recovery of 0.78 g. This residue is essentially identical in composition to that obtained by the aforementioned conventional reaction procedure. Thus, by ^{1}H NMR integration, the microwave-derived crude product contains an amount equal to, or greater than, 93% of the desired 1-Me-1,2,4-triazole **3** along with 1.5–2.7% each of the starting (1H)-1,2,4-triazole **1**, the 4-Me-1,2,4-triazole regioisomer **4**, and the quarternary 1,4-di-Me-1,2,4-triazolium iodide **5**. Final purification of the crude isolate could then be accomplished

as described previously. Although the microwave runs permit a much faster reaction than the previous pot-boiler approach, we observed no advantage with respect to the impurity profile, nor are the microwave runs easily scalable to the 10-g level.

With convenient access to multigram samples of pure 1-methyl-1,2,4-triazole, our own synthetic work required that this material be transformed into several additional compounds. Two examples are given that afford the ionic solids **5** and **6**. Product **5** is obtained by reaction of the 1-methyl-1,2,4-triazole with an excess of iodomethane. Because the light-sensitive, highly crystalline 1,4-dimethyl-1,2,4-triazolium iodide **5** rapidly darkens from white to grayish-green under fluorescent illumination, during all stages of **5**'s preparation, workup, and storage, the apparatus should be protected from direct light by wrapping with aluminium foil. However, it is found that somewhat darkened samples of **5** are still suitable for use as a chemical intermediate. Reaction of **3** with 12M aqueous hydrochloric acid in methanol at rt conveniently provides, after removal of volatiles, the crystalline, but hygroscopic, 1-methyl-1,2,4-triazolium hydrochloride **6**.

EXPERIMENTAL

Equipment was generally dried in a glassware oven at 100°C for several hours before use. All solvents were Sigma-Aldrich reagent grade. Starting materials were purchased from Sigma-Aldrich and from Spectrum. NMR spectra were taken on a Bruker 400-MHz spectrometer. IR spectra were taken on a Nicolet 6700 FTIR equipped with an HATR optical system.

1-Methyl-1,2,4-triazole (3)

To a 250-mL, three-necked round-bottom reaction flask (RBRF) equipped with a 1-inch Teflon®-clad magnetic stirring bar, a rubber septum, a 50-mL constant pressure addition funnel, a reflux condenser, and a nitrogen inlet, were added methanol (Sigma-Aldrich, reagent grade, 75 mL) and (1H)-1,2,4-triazole **1** (Spectrum, MW 69.04, 10.00 g, 144.84 mmol). [Spectral data of starting material: ^{1}H (400.13 MHz, DMSO-d6, DMSO = 2.500 ppm); 13.800 (br s, 1H), 8.299 (s, 2H)]. With ice-bath cooling and under a gentle nitrogen purge, a commercial solution of sodium methoxide in methanol [Sigma-Aldrich, 25% w:w (den. = 0.943 g/mL), 33.1 mL (31.21 g of solution = 7.803 g of actual NaOMe); MW 54.02; 144.45 mmol (thus, the limiting reagent)] was added dropwise. Using an oil bath, the reaction mixture was heated (internal T = 56°C) for 2 h. The flask was then cooled with an external ice bath. Under gentle nitrogen purge and with continued ice-bath cooling of the reaction flask, neat iodomethane [Sigma-Aldrich, MW 141.94, 10.1 mL (den. = 2.28 g/mL), 23.03 g, 162.24 mmol, (handle with care: toxic

and volatile)] was added dropwise over 1 h. The ice bath was removed and was replaced with an oil bath. The reaction mixture was heated at gentle reflux under a nitrogen atmosphere for 19 h and then cooled to room temperature. Upon substituting a glass stopper for the Liebig condenser and replacement of the addition funnel by a short-path distillation apparatus, the methanol was distilled using oil-bath heating and atmospheric pressure. To the resulting thick semisolid residue (predominantly NaI) remaining in the flask, deionized water (33 mL) was added, and the mixture was swirled to produce a homogeneous solution. This was then loaded into a 250-mL continuous extraction apparatus (Sigma-Aldrich, Z126926) and 190 mL of chloroform (Sigma-Aldrich, reagent grade) was added. Under nitrogen, the immiscible solutions were subjected to continuous extraction with refluxing chloroform for 22.5 h. After the two-phase mixture had cooled to room temperature, the layers were separated. The original yellow color of the water layer had now completely disappeared, and the chloroform layer had acquired a faint yellow tint. The chloroform layer was dried over $MgSO_4$, filtered, and, using the short-path distillation apparatus, the chloroform layer was distilled in portions at atmospheric pressure from a 200-mL, one-neck, round-bottom reaction flask. The residue (11.11 g, 92.6% crude yield) was then transferred to a 50-mL, one-neck, round-bottom flask equipped with a 0.5-inch Teflon®-clad magnetic stir bar and a short-path distillation apparatus. A tared receiver was used as the initial recovery flask. The distillation apparatus was connected to a vacuum system consisting of a Büchi Vac 500 diaphragm pump and a Büchi V805 pressure controller. The vacuum was adjusted to a pressure of 87 mbar, and the oil bath was kept at 65°C. Over 2 h, only a trace of material (0.1 g) consisting of a mixture of chloroform, water, and 1-methyl-1,2,4-triazole could be condensed. The recovery flask was replaced with a tared fresh one-neck 25-mL receiver. The vacuum was decreased to 70 mbar, and the oil bath was warmed to 131°C (subsequently, the oil bath gradually was warmed to 140°C). At 131°C oil-bath temperature, the product now began to distill into the clean receiver and did so over a bp range of 74–78°C. (Because of the on-and-off cycling of the diaphragm pump, the internal pressure of the system showed approximately a 10% fluctuation around 70 mbar, and the actual overall temperature range for the distillation was 71–94°C, but almost all the material distilled between 74 and 78°C.) During the distillation, the recovery flask was cooled in a ice/salt/water bath kept at approx. −8°C, thereby allowing the distillate to crystallize into a snow-white solid, which, in turn, remelted at approximately 3–5°C on warming. Upon thawing, the distillate is a colorless mobile liquid that weighed 7.57 g (63.1% yield), No extraneous peaks are visible in the ^{1}H or ^{13}C NMR; spectral data: ^{1}H (400.13 MHz, DMSO-*d6*, DMSO = 2.500 ppm) $\delta = 8.454$ (s, 1H), 7.943 (s, 1H), 3.863 (s, 3H); ^{13}C (100.61 MHz, proton decoupled, DMSO-*d6*, DMSO-C = 39.510) $\delta = 151.362$, 144.445, 35.679; IR partial listing: 3113.3, 3015.2, 2945.7, 1585.0, 1515.6, 1437.9, 1413.4, 1339.8, 1266.3, 1205.0, 1143.7. 1070.1 cm^{-1}.

1,4-Dimethyl-1,2,4-triazolium Iodide (5)

To a 100-mL, one-neck RBRF equipped with a rubber septum, 1-methyl-1,2,4-triazole (MW 83.09, 2.6133 g, 31.45 mmol), methanol (Sigma-Aldrich, reagent grade, 5.0 mL), and iodomethane [Sigma-Aldrich, MW 141.94, density = 2.28 g/mL, 9.804 g (4.30 mL), 69.07 mmol (significant excess, handle with care: toxic and volatile)] were added. The reaction flask was flushed with nitrogen, the apparatus was wrapped with alunimium foil, and the clear homogeneous liquid was allowed to stand for 96 h at rt, whereupon the solution had become very faintly green in color. Volatiles were removed on a rotary evaporator with the last traces of solvent taken off on a high-vacuum system (0.01 torr for several hours), whereupon the resulting viscous syrup gradually crystallized to a light yellow solid. Trituration with anhydrous diethyl ether afforded off-white granular crystals 6.5770 g (82.0%). Because the crystals turn from white to light grayish-green after 1–2 days of exposure to laboratory-level fluorescent lighting, they should be stored in an amber bottle or in a flask protected from laboratory light by a layer of aluminum foil. Spectral data: ^{1}H (400.13 MHz, DMSO-*d6*, DMSO = 2.500 ppm) $\delta = 10.052$ (s, 1H), 9.149 (s, 1H), 4.064 (s, 3H), 3.902 (s, 3H); ^{13}C (100.62 MHz, proton decoupled, DMSO-*d6*, DMSO-C = 39.510) $\delta = 145.106$, 143.206, 38.787, 34.235; IR partial listing: 3019.3, 2974.3, 2945.7, 1585.0, 1540.1, 1442.0, 1417.5, 1364.4, 1286.7, 1237.7, 1164.1, 1066.1, 984.3 cm^{-1}.

1-Methyl-1,2,4-triazolium Hydrochloride (6)

To a 100-mL one-neck RBRF equipped with a rubber septum, 1-methyl-1,2,4-triazole (MW 83.09, 1.2443 g, 14.975 mmol), methanol (Sigma-Aldrich, reagent grade, 5.0 mL), and conc. aqueous HCl (J. T. Baker, 12 M, 1.25 mL, 15 mol) were added. The reaction flask was flushed with nitrogen, and the clear homogeneous liquid was allowed to stand for 96 h at rt to afford a colorless reaction mixture. Volatiles were removed on a rotary evaporator, and the resulting semisolid was pumped for several hours on a vacuum line (0.03 torr). Trituration with anhydrous diethyl ether afforded moderately hygroscopic white granular crystals. After rapid filtration on a Buchner funnel under a flooding dry nitrogen atmosphere (provided by an inverted plastic funnel), the crystals can be obtained solvent-free (1.5082 g, 84.2%) by pumping on a high vacuum line (final P = 0.01 torr). Spectral data: ^{1}H (400.13 MHz, DMSO-*d6*, DMSO = 2.500 ppm) $\delta = 14.602$ (br s, 1H), 9.845 (s, 1H), 8.879 (s, 1H), 4.006 (s, 3H); ^{13}C (100.62 MHz, proton decoupled, DMSO-*d6*, DMSO-C = 39.510) $\delta = 145.140$, 142.366, 37.714; IR partial listing: 3383.0, 3150.1, 3113.3, 2986.3, 2925.3, 2884.4, 1564.6, 1527.8, 1429.7, 1364.4, 1262.2, 1151.9, 984.3, 939.4, 865.8 cm^{-1}.

ACKNOWLEDGMENTS

The authors acknowledge the Office of Naval Research (ONR, Project Number N0001406MP20093) and the Air Force Research Laboratory (AFRL/RZSP, Edwards AFB, CA) for their generous financial support.

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