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

An Efficient Synthesis Of 6-Substituted 2-(2H-[1,2,4]Triazol-3-Ylmethyl)-1,2,3,4-Tetrahydro-Isoquinolines

Frank J. Urban [a] & Ralph Breitenbach [a]
[a] Pfizer Inc, Central Research Division Process Research and Development , Eastern Point Rd., Groton, CT, 06340
Published online: 17 Sep 2007.

To cite this article: Frank J. Urban & Ralph Breitenbach (1999) An Efficient Synthesis Of 6-Substituted 2-(2H-[1,2,4]Triazol-3-Ylmethyl)-1,2,3,4-Tetrahydro-Isoquinolines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:4, 645-653, DOI: 10.1080/00397919908085813

To link to this article: http://dx.doi.org/10.1080/00397919908085813

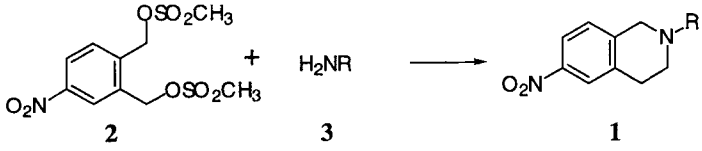
SYNTHETIC COMMUNICATIONS, 29(4), 645-653 (1999)

AN EFFICIENT SYNTHESIS OF 6-SUBSTITUTED 2-(2H-[1,2,4]TRIAZOL-3-YLMETHYL)-1,2,3,4-TETRAHYDRO-ISOQUINOLINES.

Frank J. Urban* and Ralph Breitenbach
Pfizer Inc, Central Research Division
Process Research and Development
Eastern Point Rd., Groton, CT 06340

Abstract: A synthesis of 6-nitro and 6-amino 2-(2H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolines using a bis-alkylation process is described. 5-(Aminomethyl)-1-(p-methoxybenzyl)-triazole was prepared by a regioselective route from 1,2,4-triazole.

Recently, work from these labs described a novel synthesis of tetrahydro-isoquinolines **1** with electron withdrawing groups.[1] The range of substituents on the ring nitrogen was limited to N-allyl or N-benzyl along with the parent compound (R = H). (Scheme 1) In each case, a large excess of the desired amine was used to insure optimal yields. In this paper, the efficient preparation of tetrahydro-isoquinolines substituted with a 3-triazolylmethyl group is described as an example in which the nitrogen substituent is more complex. The required



2 **3** **1**

R = H, allyl, benzyl

Scheme 1

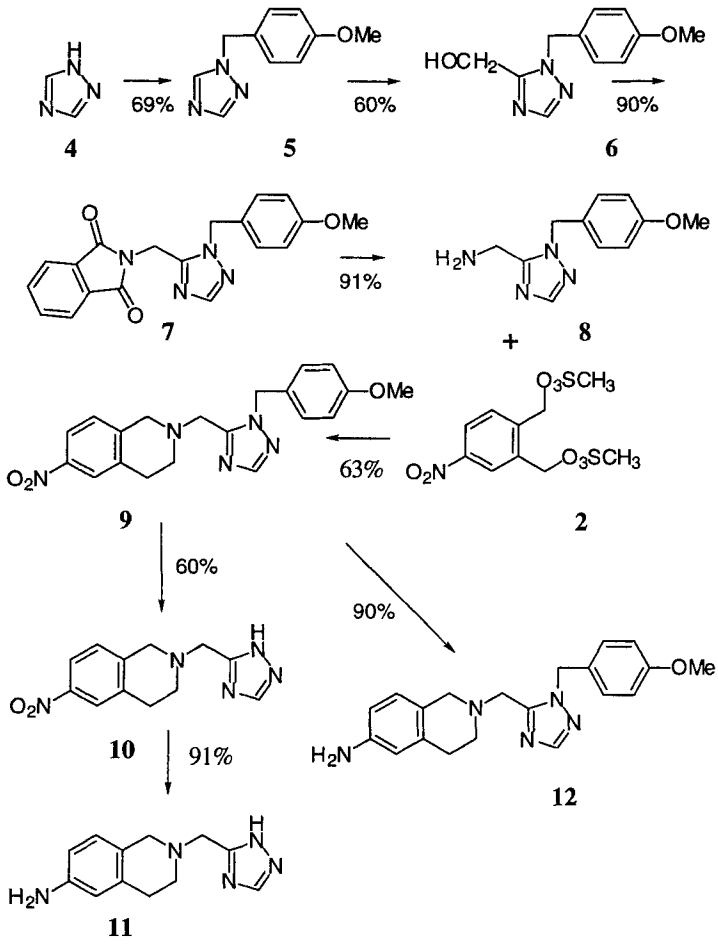
* To whom correspondence should be addressed.

precursor, 5-(aminomethyl)-1-(4-methoxybenzyl)-triazole **8**, was prepared from 1,2,4-triazole by introduction of a p-methoxybenzyl group and hydroxymethylation regioselectively.

2-(Aminomethyl)-triazole has been prepared by several routes. Ainsworth used thiosemicarbazide intermediates to synthesize both the phthalimidomethyl derivative and the unprotected compound.[2] Westermann utilized acylhydrazines with imidates to prepare the same compounds.[3] Since the desired N-triazolylmethyl isoquinolines as well as 2-aminomethyl triazole itself had exhibited poor solubility characteristics, it was decided to introduce the moiety with the triazole ring nitrogen protected.

The overall process is shown in Scheme 2. 1,2,4-Triazole **4** was reacted with 4-methoxybenzyl chloride in dimethylformamide solution with potassium hydroxide to provide the N1 protected **5**.[4] Triazole **5** was hydroxymethylated by heating in formalin solution for four days following the precedent of Jones for the corresponding N-benzyl-triazole.[5] The regiochemistry of the groups in triazole **6** was confirmed by single crystal X-ray analysis. The Mitsunobu reaction[6] of **6** with phthalimide in tetrahydrofuran provided compound **7** directly from the reaction mixture after the addition of hexanes to complete its precipitation. Finally, the phthalimide group was removed by hydrazinolysis in methanol. (Aminomethyl)-triazole **8** was reacted with one equivalent of bis-mesylate **2** in tetrahydrofuran in the presence of excess triethylamine to provide the desired isoquinoline **9**.

With isoquinoline **9** in hand, the selective reactions of the nitro group and the p-methoxybenzyl group were explored. Treatment of compound **9** with neat trifluoroacetic acid cleanly removed the p-methoxybenzyl group yielding compound **10**.[7] The reduction of the nitro group in **10** with hydrogen over palladium on carbon provided 6-amino-tetrahydroisoquinoline **11**. The same



Scheme 2

hydrogenation conditions on intermediate **9** reduced the nitro group without removing the p-methoxybenzyl protecting group. In further work, amides of compound **12** have been deprotected by treatment with trifluoroacetic acid in good yields.

In summary, an efficient synthesis of 6-nitro and 6-amino 2-(2H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolines using a bis-alkylation process was

described. The use of a p-methoxybenzyl protecting group on the triazole moiety allowed the flexibility to remove the protection at different stages of the synthesis.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on a Brucker WM 300 (300 MHz) spectrometer in deuteriochloroform or dimethylsulfoxide-d_6. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

1-(4-Methoxybenzyl)-1,2,4-triazole 5:

1,2,4-Triazole **4** (7.5 g, 0.109 mol) was dissolved in dimethylformamide (50 ml) and stirred under a nitrogen atmosphere in an ice bath at 10°C while partially ground pellets of sodium hydroxide (17.5 g, 0.438 mol) were added in one portion which resulted in an exotherm to ca. 25°C. A solution of 4-methoxybenzyl chloride (15 ml, 0.111 mol) in DMF was added dropwise over five minutes at 25°C. After stirring at room temperature for four hours, ethyl acetate and water were added. The layers were separated and the aqueous was extracted with ethyl acetate. The combined organics were washed with water (4X), with brine (1X), and were dried over magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo afforded product **5** as an oil in 69% yield; 14.15 g; ^{1}HMR (deuteriochloroform) δ 8.00 (s, 1), 7.93 (s, 1), 7.19 (d, 2), 6.88 (d, 2), 5.23 (s, 2), 3.78 (s, 3). mass spectrum: *m/z* 109 (M + 1).

5-(Hydroxymethyl)-1-(4-methoxybenzyl)-1,2,4-triazole 6:

1-(4-Methoxybenzyl)-1,2,4-triazole **5** (7.6 g, 40 mmol) was dissolved in 37% formalin solution (25 ml) and heated in a 130°C oil bath for four days. The course

of the hydroxymethylation was monitored by tlc on silica gel with 3:1, ethyl acetate: chloroform as eluant. The reaction mixture was cooled to room temperature, poured into water and extracted twice with ethyl acetate. The combined organic layers were washed with 1N NaOH, water, and brine. After drying the solution over magnesium sulfate, evaporation afforded crude product which was slurried in hexanes with a small amount of 2-propanol to give 4.9 g, 56% yield; mp 95–100°C. ^{1}HMR (deuteriochloroform) δ 7.72 (s, 1), 7.21 (d, 2), 6.85 (d, 2), 5.70 (bs, 1, OH), 5.32 (s, 2), 4.69 (s, 2), 3.78 (s, 3). ^{13}CMR (deuteriochloroform) δ 159.6, 149.8, 145.6, 129.2, 127.0, 114.3, 55.3, 54.9, 52.0. IR (KBr) 1610, 1585, 1512 cm^{-1}. mass spectrum: *m/z* 220 (M + 1).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.30; H, 6.16; N, 19.66.

The structure was confirmed by single crystal X-ray analysis.

5-(Phthalimidomethyl)-1-(4-methoxybenzyl)-1,2,4-triazole 7:

5-(Hydroxymethyl)-1-(4-methoxybenzyl)-1,2,4-triazole **6** (8.5 g, 38.8 mmol), triphenylphosphine (11.2 g, 42.7 mmol) and phthalimide (6.3 g, 42.7 mmol) were dissolved in tetrahydrofuran (125 ml) at room temperature with only a slight haze remaining out of solution. A solution of diisopropyl azodicarboxylate (8.4 ml, 42.7 mmol) in tetrahydrofuran (40 ml) was added dropwise over 40 minutes with the temperature held at ca. 15°C with an ice water bath. During the addition the product began to precipitate as a white solid. The reaction was stirred at room temperature overnight and then was diluted with hexanes (125 ml). After stirring for thirty minutes, the white solid was collected, washed with hexanes and dried in vacuo; 12.2 g, 91% yield; mp 167–72°C. ^{1}HMR (deuteriochloroform) δ 7.85 (s, 1), 7.81 (m, 2), 7.69 (m, 2), 7.09 (d, 2), 6.77 (d, 2), 5.43 (s, 2), 4.89 (s, 2), 3.72 (s, 3). ^{13}CMR (deuteriochloroform) δ 150.9, 145.6, 134.2, 131.8, 128.3, 127.0,

123.6, 114.3, 112.9, 112.1, 55.2, 52.0, 32.8. IR (KBr) 1772, 1720, 1689, 1612, 1586, 1519 cm^{-1}. mass spectrum: *m/z* 349 (M + 1).

Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.50; H, 4.63; N, 16.08. Found: C, 65.35; H, 4.80; N, 16.18.

5-(Aminomethyl)-1-(4-methoxybenzyl)-1,2,4-triazole 8:

5-(Phthalimidomethyl)-1-(4-methoxybenzyl)-1,2,4-triazole **7** (5 g, 14.4 mmol) was suspended in methanol (50 ml) and hydrazine hydrate (1.6 ml, 32 mmol) was added with stirring. After several minutes a clear solution was obtained and the reaction was stirred at room temperature overnight during which time phthalhydrazide precipitated. Methylene chloride (50 ml) was added to the slurry of white solid. This was stirred for 45 minutes, filtered and the solids washed with methylene chloride. The filtrate was evaporated in vacuo and the residue was dissolved in methylene chloride and 1N NaOH. The aqueous layer was pH 12. The layers were separated, the aqueous layer was extracted with methylene chloride and the organics were combined. After washing the organic layers with brine and drying over magnesium sulfate, the product was recovered as a colorless oil by evaporation of the solvent in vacuo; 3 g, 97% yield. ^{1}HMR (deuteriochloroform) δ 7.79 (s, 1), 7.12 (d, 2), 6.81 (d, 2), 5.27 (s, 2), 3.88 (s, 2), 3.74 (s, 3), 1.59 (bs, 2, $N\underline{H}_2$). ^{13}CMR (deuteriochloroform) δ 150.3, 145.6, 130.4, 129.0, 128.8, 127.3, 114.3, 55.3, 51.7, 37.7.

2-[2-(4-Methoxybenzyl)-2H-[1,2,4]triazol-3-ylmethyl]-6-nitro-1,2,3,4-tetrahydro-isoquinoline 9:

2-(2-Hydroxyethyl)-5-nitrobenzyl alcohol[1] (6.38 g, 32.4 mmol) and triethylamine (11.3 ml, 81 mmol were suspended in methylene chloride (100 ml) under nitrogen and cooled to –30°C with stirring. A solution of methanesulfonyl chloride (5.5 ml, 71.2 mmol) in methylene chloride (32 ml) was added dropwise over fifteen minutes. After thirty minutes, the cooling bath was removed and 1N HCl (130 ml)

was added. This was stirred for ten minutes and the layers were separated. The organic layer was washed with water, sat. sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate, filtered and evaporated in vacuo to a yellow solid which was used without further purification; 10.7 g, 94% yield. ^{1}HMR (deuteriochloroform) δ 8.17 (m, 2), 7.66 (d, 1), 5.39 (s, 2), 4.50 (t, 2), 3.28 (t, 2), 3.10 (s, 3), 3.00 (s, 3).

5-(Aminomethyl)-1-(4-methoxybenzyl)-1,2,4-triazole **8** (1.1 g, 5 mmol) and triethylamine (1.8 ml, 12.7 mmol) were dissolved in tetrahydrofuran (15 ml) under a nitrogen atmosphere and treated dropwise with a solution of bis-mesylate **2** (1.75 g, 5 mmol) in tetrahydrofuran (10 ml). The solution was stirred at room temperature for two hours and at reflux overnight. The reaction was cooled and methylene chloride and 1N NaOH were added. The layers were separated and the aqueous was extracted with additional methylene chloride. The combined organics were washed with water and with brine and were dried over magnesium sulfate. The crude product was recovered from the methylene chloride and purified by chromatography over silica gel with 30% ethyl acetate in chloroform; 1.2 g, 63% yield as a yellow oil which slowly solidified. ^{1}H M R (deuteriochloroform) δ 7.98 (m, 2), 7.88 (s, 1), 7.10 (m, 3), 6.76 (d, 2), 5.40 (s, 2), 3.81 (s, 2), 3.73 (s, 3), 3.63 (s, 2), 2.95 (t, 2), 2.80 (t, 2). ^{13}CMR (deuteriochloroform) δ 159.4, 151.4, 150.4, 145.6, 141.5, 135.6, 129.0, 127.4, 123.7, 123.7, 120.8, 114.1, 112.1, 55.5, 55.2, 53.1, 52.1, 50.1, 29.0. IR (KBr) 1610, 1584, 1517 cm^{-1}. mass spectrum: *m/z* 380 (M + 1).

2-(2H-[1,2,4]triazol-3-ylmethyl)-6-nitro-1,2,3,4-tetrahydro-isoquinoline 10:

2-[2-(4-Methoxybenzyl)-2H-[1,2,4]triazol-3-ylmethyl]-6-nitro-1,2,3,4-tetrahydro-isoquinoline **9** (8.8 g, 23.2 mmol) was dissolved in trifluoroacetic acid (88 ml) and stirred at room temperature overnight. The reaction mixture was evaporated in vacuo to an oil which was dissolved in methylene chloride. The organic solution

was extracted 2 times with 1N HCl solution and the combined acidic extracts were washed one time with methylene chloride. The acidic extract was layered with fresh methylene chloride and the pH adjusted to 10 with sodium carbonate to precipitate the desired material which was collected and washed with water and methylene chloride; 3.99 g, 66% yield; mp 163 – 6°C. ^{1}HMR (dimethylsulfoxide-d_6) δ 8.20 (s, 1), 7.97 (d, 1), 7.92 (dd, 1), 7.30 (s, 1), 3.82 (s, 2), 3.73 (s, 2), 2.92 (t, 2), 2.76 (t, 2). ^{13}CMR (dimethylsulfoxide-d_6) δ 147.8, 146.2, 143.2, 136.5, 128.2, 123.8, 120.8, 55.1, 53.4, 49.6, 28.9. mass spectrum: *m/z* 260 (M + 1).

Anal. Calcd. for $C_{12}H_{13}N_5O_2$ (0.15 CH_2Cl_2): C, 53.65; H, 4.93; N, 25.98. Found: C, 53.65; H, 4.93; N, 25.75.

6-Amino-2-(2H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinoline 11:

2-(2H-[1,2,4]triazol-3-ylmethyl)-6-nitro-1,2,3,4-tetrahydro-isoquinoline **10** (4.46 g, 17.4 mmol) was dissolved in methanol (220 ml) and hydrogenated over 10% palladium on carbon (2.23 g) at 50 psi for four hours. The catalyst was removed by filtration through celite and the methanol was evaporated in vacuo to provide the product as a white solid, 3.56 g, 91% yield. mp 191–3°C. ^{1}HMR (dimethylsulfoxide-d_6) δ 6.65 (d, 1), 6.32 (dd, 1), 6.28 (d, 1), 4.79 (s, 2), 3.71 (s, 2), 3.41 (s, 2), 3.34 (s, 2). ^{13}CMR (dimethylsulfoxide-d_6) δ 155.9, 147.0, 134.5, 127.1, 122.4, 113.8, 112.7, 55.4, 53.9, 50.9, 29.2. IR (KBr) 1633, 1612, 1584, 1513 cm^{-1}. mass spectrum: *m/z* 230 (M + 1).

Anal. Calcd. for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.55. Found: C, 62.49; H, 6.39; N, 30.45.

6-Amino-2-(2-(4-Methoxybenzyl)-2H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinoline 12:

2-[2-(4-Methoxybenzyl)-2H-[1,2,4]triazol-3-ylmethyl]-6-nitro-1,2,3,4-tetrahydro-isoquinoline **9** (0.5 g, 1.3 mmol) was hydrogenated in methanol (25 ml) with 10% Pd/C (0.25 g) at 50 psi for three hours. The reaction mixture was filtered and the

solvent was evaporated in vacuo. Ethyl acetate and water were added and the pH was adjusted with sodium carbonate. The layers were separated and the aqueous layer extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo to an oil; 0.4 g, 87% yield. ^{1}HMR (deuteriochloroform) δ 7.86 (s, 1), 7.18 (d, 2), 6.79 (m, 3), 6.48 (m, 2), 5.42 (s, 2), 3.76 (s, 3), 3.73 (s, 2), 3.50 (s, 2), 2.80 (m, 2), 2.69 (m, 2). IR (KBr) 1613, 1587, 1513 cm^{-1}. Mass spectrum: *m/z*: 348 ($M^+ - 1$).

References and Notes:

1. Quallich, G. J.; Makowski, T. W.; Sanders, A. F.; Urban, F. J. and Vazquez, E. *J. Org. Chem.*, **1998**, *63*, 4116.

2. Ainsworth, C. and Jones, R. G., *J. Am. Chem. Soc.* **1954**, *76*, 5651.

3. Westermann, P.; Paul, H. and Hilgetag, G. *Chem. Ber.*, **1964**, *97*, 528.

4. Katritzky, A. R.; Kuzmierkiewicz, W. and Greenhill, J. V., *Recl. Trav. Chim. Pays-Bas*, **1991**, *110*, 369.

5. Jones, R. G. and Ainsworth, C. J. *Am. Chem. Soc.*, **1955**, *77*, 1528.

6. Mitsunobu, O., *Synthesis*, **1981**, 1.

7. Buckle, D. R. and Rockwell, C. J. M., *J. Chem. Soc. Perkin* I, **1982**, 627.

(Received in the USA 13 July 1998)