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Nonchromatographic Isolation of 2-Alkyl-2*H*-1,2,3-Triazoles in the Synthesis of NK3 Receptor Antagonists

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Abstract:

A nonchromatographic isolation of a 2-alkyl-2*H*-triazole from a 1:1 mixture with the corresponding 1-alkyl-1*H* isomer was developed in a scalable synthesis of a synthetic intermediate for NK3 receptor antagonists. Based on the fundamental nucleophilicity difference in the isomeric triazoles, this method could be used as a general tactic in the isolation of 2*H*-triazoles.

Introduction

1,2,3-Triazole derivatives are an important class of compounds due to their wide application in medicinal chemistry as biologically active systems, as well as in the fine chemical industry as dyestuffs, fluorescent whiteners, corrosion inhibitors, and photostabilizers.[1] N-1-Substituted 1*H*-1,2,3-triazoles can usually be synthesized via 1,3-dipolar cycloaddition reactions,[2] whereas a general and scalable method for the synthesis of N-2-substituted 2*H*-1,2,3-triazoles is still unavailable. There have been reported selective syntheses of 2-substituted 2*H*-1,2,3-triazoles; however, the substituent on N-2 is limited to aryl,[3] allyl,[4] or hydroxymethyl.[5]

One of the most convenient ways of preparing 2-substituted 2*H*-1,2,3-triazole is by alkylation of N*H*-1,2,3-triazole. A significant drawback of this method, however, is that a mixture of regioisomeric 1*H* and 2*H* products is produced, and the product distribution is often unfavorable for the 2*H* isomer in the cases of simple alkyls.[6,7] This is especially cumbersome in the context of process development, as it entails undesirable chromatographic separation to obtain the pure 2*H* product. Herein we wish to report a simple yet potentially general, nonchromatographic method for the isolation of a 2-alkyl 2*H*-1,2,3-triazole.

Results and Discussion

In our synthesis of a group of neurokinin 3 (NK3) receptor antagonists of general structure **1**,[8] easy access to the common intermediate ester **2** was required. The triazole moiety in the target structure could be conveniently introduced by an S_N2 displacement of benzyl bromide **3**[8,9] with the triazole anion (Scheme 1). However, despite considerable effort, a 1:1 mixture of 1*H* and 2*H* isomers (**5** and **2**, respectively) was produced in this alkylation reaction (Table 1). Different solvents (entries 1−6), bases (entries 7−12), or reaction temperature (entry 13) proved ineffective in further improving the selectivity. Although separation of the two isomers was achieved by chromatography, a nonchromatographic isolation of the target 2*H* product **2** was deemed more desirable.

It is known that 2-alkyl-2*H*-1,2,3-triazole and 1-alkyl-1*H*-1,2,3-triazole have marked difference in their pK_a's, with N-3 in 1-alkyl-1*H*-1,2,3-triazole being by far the most basic (Figure 1).[10] It was therefore envisioned that after protonation of the quinoline, protonation of a mixture of **2** and **5** would occur selectively on N-3 of the 1*H* isomer **5**, thus enabling the separation of the two isomers by selective salt formation (Scheme 2).

A number of strong acids, including HCl, H_2SO_4, MsOH, TsOH, and TfOH were tried in different solvents, and selective salt formation indeed was observed. However, in most of the cases the corresponding salt **6** formed as an oil. The only excep-

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Scheme 1

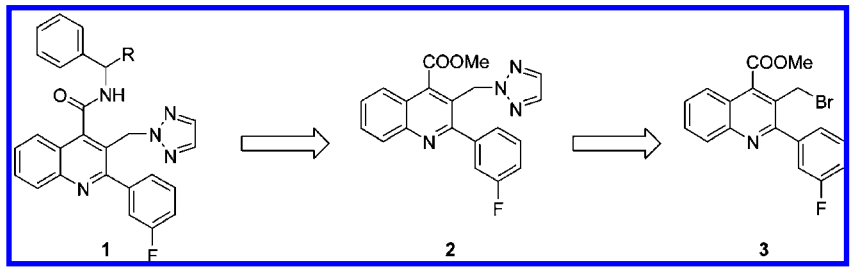
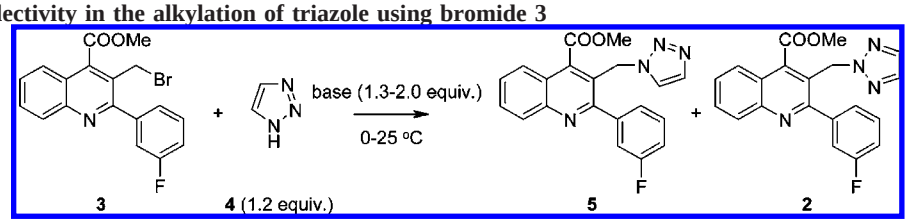


Table 1. **N-1/N-2 selectivity in the alkylation of triazole using bromide 3**



entry	solvent	base	time/min	conversion/%	**5**/**2**[a]
1	DMF	NaH	60	100	1.1
2	DMSO	NaH	60	100	1.2
3	THF	NaH	60	96	11.3
4	MeCN	NaH	60	100	1.8
5	toluene	NaH	120	60	1.1
6	Me_2CO_3	NaH	60	87	2.1
7	DMF	K_2CO_3	40	100	1.0
8	DMF	Na_2CO_3	30	50	1.0
9	DMF	Et_3N	30	38	11.3
10	DMF	NaHMDS	15	99	1.0
11	DMF	LiHMDS	15	100	1.0
12	DMF	KHMDS	15	100	1.0
13	DMF	NaHMDS[b]	15	95	1.0

[a] By HPLC peak area ratio. [b] Run at −40 °C.

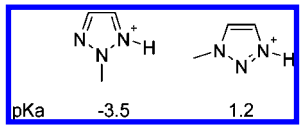


Figure 1

tion was when TfOH was used (in dimethyl carbonate at 80 °C), salt **6** could be isolated as a solid. The desired 2*H* isomer remained in solution, as well as <3% of the 1*H* isomer **5**.

It was further rationalized that by the same token, selective alkylation could also be achieved, with N-3 in the 1*H* isomer expected to be the most nucleophilic site. Indeed, when the mixture of **2** and **5** was treated with Me_2SO_4, methylation took place on **5** exclusively, providing triazolium **8** and leaving the 2*H* isomer **2** unreacted. The presence of the quinoline nitrogen did not interfere with the methylation on the triazole, presumably due to the steric congestion around it. A solvent screening showed that this reaction proceeded in a number of solvents (Table 2). The reaction tended to stall in highly basic solvents such as DMSO or DMF (entries 1 and 2), whereas in less polar solvents the conversion was noticeably slower and the cationic product tended to form an oil (entries 3−5). The reaction was best conducted in CH_3CN where the reaction mixture remained homogeneous and complete conversion could be easily achieved. Upon the consumption of the 1*H* isomer and removal of CH_3CN, a simple aqueous extraction cleanly removed the ionic **8** and left the desired product **2** as the only isomer in the organic layer (ethyl acetate or TBME).

The selective salt formation and the selective methylation provided two potential methods for isolation of the 2*H* isomer **2**. Based on the fundamental pK_a/nucleophilicity difference in the two isomeric triazoles, both methods should be general in scope and could be used as general tactics in the isolation of 2*H*-triazoles. The selective salt formation method has the advantage that it also leaves the 1*H* isomer intact and recoverable. However, it does suffer from the fact that an equal amount of the isomeric 1-alkyl-1*H* isomer is present and can potentially act as a crystallization inhibitor, its applicability therefore depends more on the crystallinity of specific substrates. In the absence of other nucleophilic sites, the selective methylation method appears to be more robust and was chosen in our work.

The optimized process proceeded smoothly in scale-up: The displacement of the bromide was carried out with NaHMDS in DMF[11] to give a 1:1 mixture of regioisomers **2** and **5**. The mixture was treated with Me_2SO_4 to selectively methylate N-3 in **5**, which was removed conveniently in the ensuing aqueous work-up. The desired 2*H*-1,2,3-triazole **2** was obtained in 40% yield over two steps and contained neither 1*H* isomer **5** nor its methylation product **8**.

In summary, a scalable, nonchromatographic isolation of **2**, an intermediate in the synthesis of NK3 receptor antagonists, was developed. This isolation method was based on the fundamental nucleophilicity difference in the isomeric triazoles and could be used as a general tactic for the isolation of 2*H*-triazoles.

(11) Although the combination of NaH/DMF gave similar selectivity, it was not chosen for safety reasons. See amEnde, D. J.; Vogt, P. F. *Org. Process Res. Dev.* **2003**, *7*, 1029, and references cited therein.

Scheme 2

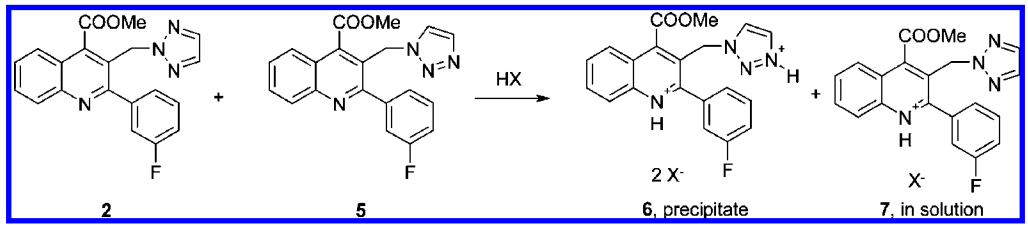
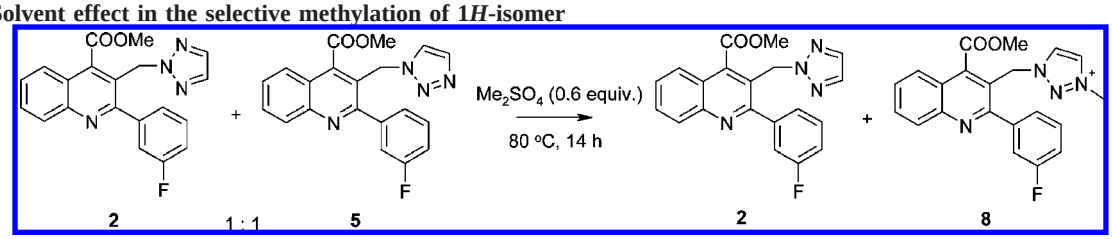


Table 2. Solvent effect in the selective methylation of 1*H*-isomer



entry	solvent	methylation of **5**/%[a]	entry	solvent	methylation of **5**/%[a]
1	DMSO	41[b]	5	Me_2CO_3	84
2	DMF	14[b]	6	CH_2Cl_2	10[c]
3	EtOAc	86	7	$CHCl_3$	99[d]
4	butanone	79	8	CH_3CN	99

[a] Conversion by HPLC peak area ratio. [b] Conversion at 3 h, reaction stalled. [c] rt, 14 h. [d] 60 °C, 20 h.

Experimental Section

Methyl 2-(3-Fluorophenyl)-3-(2*H*-1,2,3-triazol-2-ylmethyl)-4-quinolinecarboxylate (2). 1*H*-[1,2,3]Triazole (6.42 g, 92.9 mmol, 1.2 equiv) was dissolved in 145 mL of DMF and cooled to 0 °C. NaHMDS (1.0 M in THF, 93 mL, 93 mmol, 1.2 equiv) was slowly added to the solution. The resultant mixture was stirred at 0 °C for 1 h. Bromide **3** (29.0 g, 77.5 mmol) in 140 mL of DMF was slowly added to the triazole anion at 0 °C. The mixture was stirred at 0 °C for 1 h and quenched with water (290 mL). The mixture was extracted with EtOAc (290 mL + 145 mL). The combined organic layers were washed with water (290 mL × 2). The organic solution was concentrated to minimum stir, and the residue was diluted with acetonitrile to a total volume of 270 mL. Me_2SO_4 (5.87 g, 46.5 mmol, 0.6 equiv) was added to the mixture of **2** and **5**, and the resultant solution was heated to 80 °C for 4 h. LC analysis of the reaction mixture showed that methylation of 1*H* isomer was complete. The reaction mixture was cooled to rt, concentrated to minimum stir, and the residue was diluted with EtOAc to 300 mL. H_2O (300 mL) was added. The two layers were separated, and the organic layer was washed with H_2O (240 mL). The organic solution was concentrated. Heptane (130 mL) and EtOAc (15 mL) were added. The resultant slurry was heated at 60 °C for 40 min, cooled slowly to 0 °C, and stirred at 0 °C for 1 h. The product was collected by filtration and dried at 50 °C under vacuum to give a beige-colored solid: 11.3 g, 31.2 mmol, 40% over 2 steps. Purity by HPLC peak area: 96.2%. Electrospray-mass spectrometry (ES-MS): *m*/*z*, 363 ($M + H^+$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.5 Hz, 1 H), 7.77−7.86 (m, 2 H), 7.62 (ddd, J = 8.3, 7.0, 1.2 Hz, 1 H), 7.57 (s, 2 H), 7.43 (m, 2 H), 7.36 (dm, J = 9.7 Hz, 1 H), 7.17 (m, 1 H), 5.82 (s, 2 H), 3.97 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.74, 53.02, 115.92 (d, J_{FC} = 21.3 Hz), 116.23 (d, J_{FC} = 22.9 Hz), 122.62, 123.37, 124.71 (d, J_{FC} = 2.8 Hz), 124.89, 128.15, 129.50, 130.15 (d, J_{FC} = 8.3 Hz), 131.10, 134.40, 140.73 (d, J_{FC} = 7.5 Hz), 141.40, 147.11, 158.59 (d, J_{FC} = 2.2 Hz), 162.50 (d, J_{FC} = 247 Hz), 168.67. ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.2.

Methyl 2-(3-Fluorophenyl)-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-quinolinecarboxylate (5). The 1*H* isomer could be purified by chromatography from the reaction mixture in the triazole alkylation reaction. ES-MS: *m*/*z*, 363 ($M + H^+$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (dm, J = 8.3 Hz, 1 H), 7.85−7.71 (m, 2 H), 7.66−7.56 (m, 1 H), 7.55 (d, J = 1.0 Hz, 1 H), 7.44−7.32 (m, 1 H), 7.28 (d, J = 1.0 Hz, 1 H), 7.18−7.03 (m, 3 H), 5.69 (s, 2 H), 3.96 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.38, 53.02, 115.67 (d, J_{FC} = 22.4 Hz), 115.91 (d, J_{FC} = 20.7 Hz), 121.86, 123.00, 123.53, 124.07 (d, J_{FC} = 2.8 Hz), 124.79, 128.24, 129.68, 130.30 (d, J_{FC} = 8.3 Hz), 131.11, 133.47, 140.64 (d, J_{FC} = 7.5 Hz), 141.14, 147.36, 158.43 (d, J_{FC} = 1.9 Hz), 162.43 (d, J_{FC} = 248 Hz), 166.81. ^{19}F NMR (282 MHz, $CDCl_3$) δ −111.6.

1-({2-(3-Fluorophenyl)-4-[(methyloxy)carbonyl]-3-quinolinyl}methyl)-3-methyl-1*H*-1,2,3-triazol-3-ium Methylsulfate (8). The 1*H* isomer **5** (24.8 mg, 0.0684 mmol) was dissolved in CD_3CN (1 mL): ^{1}H NMR (300 MHz, CD_3CN) δ 8.10 (d, J = 8.4 Hz, 1 H), 7.96−7.81 (m, 2 H), 7.77−7.64 (m, 1 H), 7.52 (s, 1 H), 7.50−7.37 (m, 2 H), 7.27−7.17 (m, 2 H), 7.14 (d, J = 9.6 Hz, 1 H), 5.69 (s, 2 H), 3.98 (s, 3 H). Dimethyl sulfate (7.0 μL, 0.074 mmol, 1.1 equiv) was added. The mixture was heated to 70 °C for 17.5 h, and HPLC analysis showed the reaction was complete. ES-MS: *m*/*z*, 377 (M^+). ^{1}H NMR (300 MHz, CD_3CN) δ 8.34 (d, J = 1.4 Hz, 1 H), 8.29 (ddd, J = 0.6, 1.1, 8.5 Hz, 1 H), 8.18 (d, J = 1.4 Hz, 1 H), 8.08 (ddd, J = 0.7, 1.3, 8.5 Hz, 1 H), 8.02 (ddd, J = 1.4, 7.0, 8.5 Hz, 1 H), 7.85 (ddd, J = 1.3, 7.0, 8.4 Hz, 1 H), 7.59−7.49 (m, 1 H), 7.37−7.17 (m, 3 H), 5.93 (s, 2 H), 4.12 (s, 3 H), 4.11 (s, 3 H), 3.45 (s, 3 H). The triazole Hs shifted from 7.45 and 7.52 ppm in **5** to 8.18 and 8.34 ppm in **8**.

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