Report

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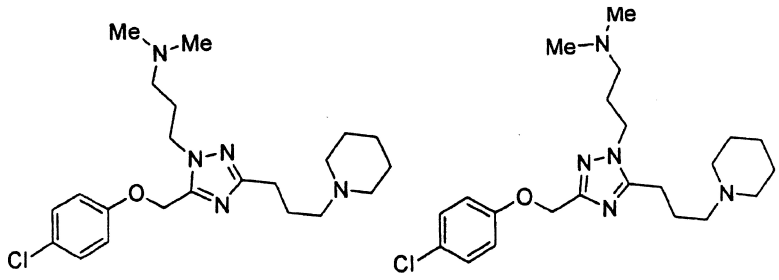

1,2,4-Triazoles

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Application of Solution-Phase Parallel Synthesis to Preparation of Trisubstituted 1,2,4-Triazoles

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Technologies associated with combinatorial chemistry have advanced organic synthesis in both solution and solid phase.[1,2] With the exception of solid-phase split−pool synthesis, most methods aim to produce a single compound per well. Multicomponent reactions in solution represent one of the few intentional preparations of product mixtures.[3,4] We report here the intentional synthesis of regioisomeric 1,2,4-triazole mixtures via parallel solution phase synthesis relying on automated preparative HPLC to provide regiochemically pure products. Mitsunobu alkylation of 1-[3-[5-[(4-chlorophenoxy)methyl]-1*H*-1,2,4-triazol-3-yl]propyl]piperidine with *N*,*N*-dimethylaminopropanol afforded an ∼1:1 ratio of two products, **1** and **2**, as depicted in Scheme 1. Reversed-phase HPLC readily separated regioisomers **1** and **2** within short run times (≤13 min) and on large scales (15−20-mg injections) and required no intervening workup before chromatography. We viewed these prospects as a viable opportunity to conduct solution-phase synthesis of a trisubstituted 1,2,4-triazole library relying on automated preparative HPLC to isolate products.

Nonpeptidic antagonists at the neuropeptide Y (NPY) receptor have received considerable attention as potential agents to modulate feeding behavior and, thus, represent a means of therapeutic intervention in obesity.[5] Reports describing NPY antagonists selective for the Y1 receptor (Figure 1) prompted us to explore the 1,2,4-triazole ring

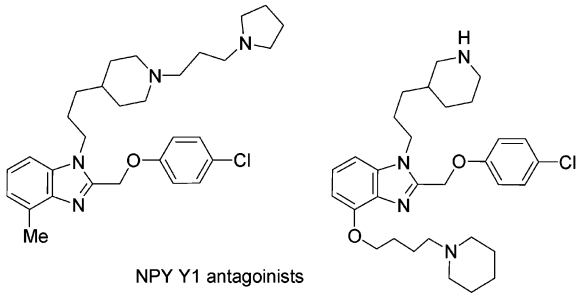
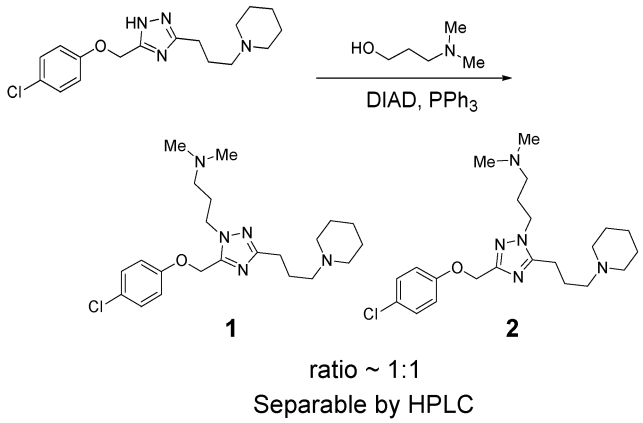


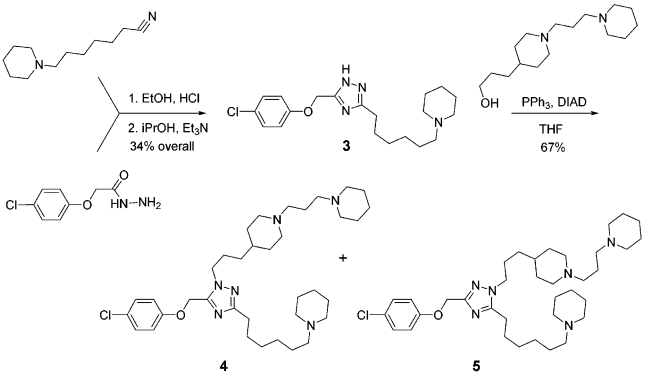
Figure 1. Nonpeptidic antagonists at the neuropeptide Y (NPY) receptor.[6,7]

system as a template for library design and as a first pass

Scheme 1. Mitsunobu Alkylation of 1,2,4-Triazoles

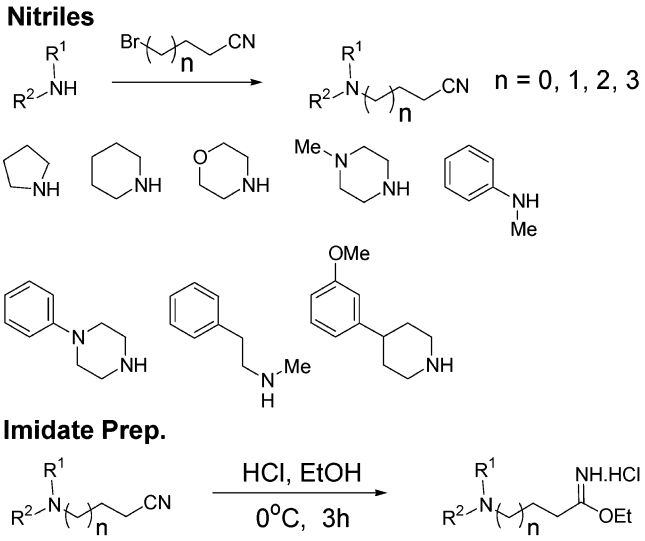


Scheme 2. Synthesis of Trisubstituted Triazoles **4** and **5**[a]



[a] Inhibitory activity against the NPY Y1 receptor (IC_{50} = 248 nM) displacing [^{125}I] peptide YY at the Y1 receptor in SK-N-MC cell membranes.

Scheme 3. Reagent Synthesis of Nitriles and Conversion to Imidate



attempt to screen for NPY Y1 antagonist activity.[6,7] Indeed, the three-step synthetic route to prepare trisubstituted triazoles outlined in Scheme 2 gave compounds **4** and **5** which displaced [^{125}I]peptide YY binding at the Y1 receptor in SK-N-MC cell membranes (IC_{50} 248 nM as 1:1 mixture).

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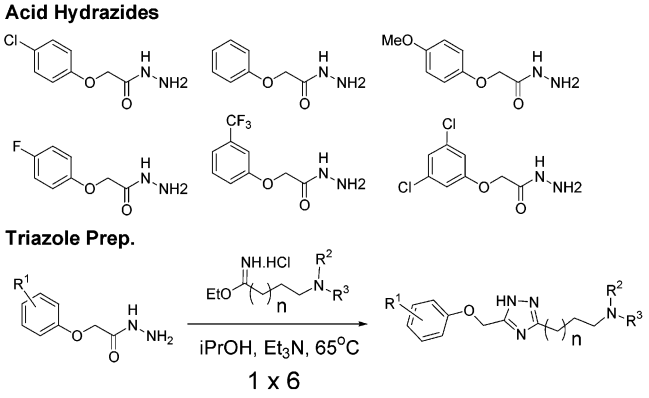
Scheme 4. Acid Hydrazides and Parallel Synthesis of Disubstitued Triazoles

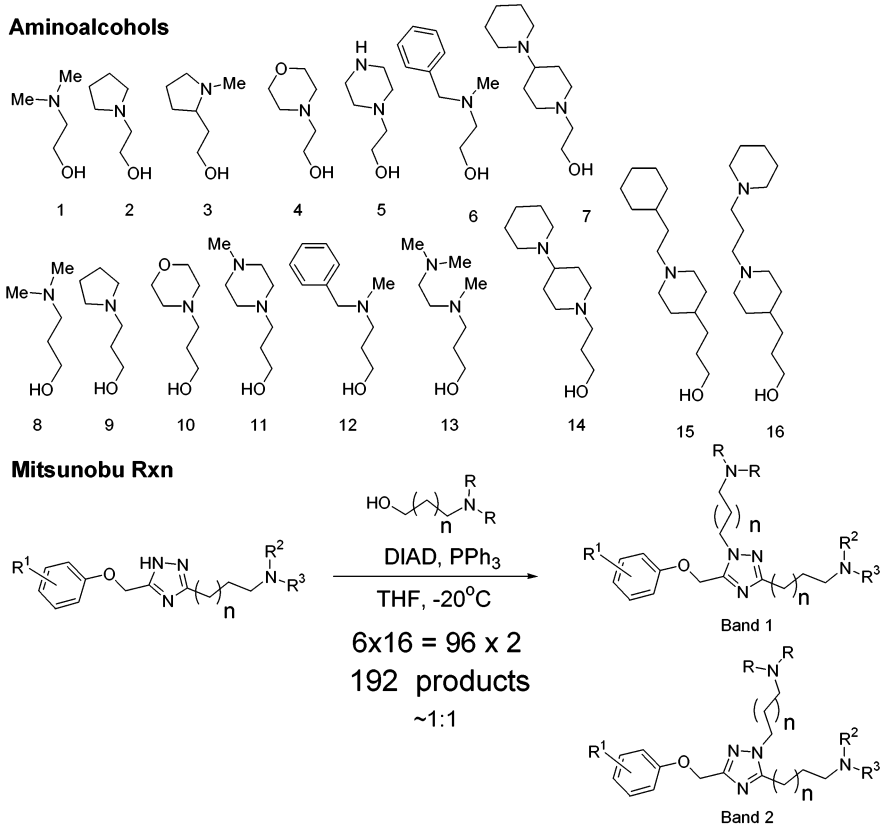


The 1,2,4-triazole ring system alkylates on both the 1 and 2 position to give two regioisomeric products;[8] thus, both products **4** and **5** were accessible from a single starting material, **3**. Retrosynthetically, this was attractive to us because the three precursors (alcohols, nitriles, acid hydrazides) were easily obtained, either being purchased commercially or prepared according to literature methods.

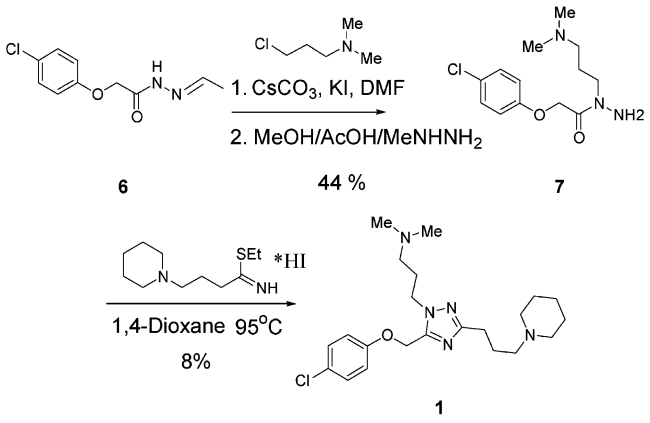
Our workflow began upon alkylation of a secondary amine with various bromonitriles (Scheme 3) followed by HCl/ethanol treatment to generate the corresponding imidate.[9] A solution of the imidate (Scheme 4) was dispensed into six reaction vessels; each was precharged with an acid hydrazide. The parallel, (1 × 6) cyclization reaction was heated at reflux (*i*-propanol/triethylamine) to give disubstituted triazoles in 40−60% isolated yields.[10] Parallel purification by normal-phase chromatography was performed using either Vac-elute, or Isco CombiFlash (System Si 10x) chromatography methods.[11]

Mettler-Toledo Bohdan MiniBlocks,[12] two 48-vessel interleave format platforms designed to afford a 96-vessel array, were fitted with cooling jackets and employed to conduct Mitsunobu alkylations.[13] Disubstituted triazoles (6) were reacted with amino alcohols (16), each reaction yielding 2 regioisomeric products, for a total of 192 trisubstituted triazoles (Scheme 5) in a given run (6 × 16 × 2 = 192). Reagent solutions (except DIAD) were added to the reaction vessels via a High Hamilton Liquid Handler operating under nitrogen atmosphere. DIAD was subsequently added while shaking (InnOva shakers, 500 rpm) at −20 °C, and better success rates were achieved by conducting the reaction in the presence of 3-Å molecular sieves to absorb trace moister. Each run (defined by imidate) was carried out sequentially until the desired library size was reached.[14] Reverse-phase preparative HPLC [YMC ODS 5 μM, 20 × 100 mm; flow rate, 20 mL/min; detector Shimadzu SPD-10A; UV 220 nm; gradient (start B, 20%; final B, 100%); gradient time, 10 min; stop time, 13 min; mobile phase A: 10% methanol, 90% water, 0.1% trifluoroacetic acid; B: 90% methanol, 10% water, 0.1% trifluoroacetic acid] would typically consist of a 25−40 reaction vial queue run over a 24 h period.[15] The separated regioisomeric triazole product fractions were concentrated (Savant Speed Vac) into synthesis tube racks (labeled band 1 for first elution product, band 2 for second elution product) and resubjected to analytical LCMS in order to confirm purity and product identity prior to submission into the Bristol-Myers Squibb compound inventory.[16]

Scheme 5. Amino Alcohols and Mitsunobu Reaction on Disubstituted Triazoles in 6 × 16 Array



Scheme 6. Unequivocal Synthesis of Band 1 Isomer



Regiochemistry was established by unequivocal synthesis of **1** and confirmed by coelution and ^{1}H NMR. Scheme 6 depicts alkylation of acylhydrazone **6** with dimethylaminopropyl chloride, which gave N-alkylated product. Although labile to hydrolytic conditions, treatment with excess methyl hydrazine affected an exchange reaction deprotection to liberate the acyl hydrazide product **7** in 44% overall yield.[17] Condensation of **7** with the thioimidate of 4-piperidin-1-ylbutyronitrile gave trisubstituted triazole product **1** identical to the first HPLC elution (band 1) from the Mitsunobu reaction, as depicted in Scheme 1.[18,19]

In summary, we report a successful strategy for rapid isolation of trisubstituted 1,2,4-triazoles via Mitsunobu chemistry from readily available starting materials. Automated reversed-phase HPLC enabled isolation and submission of regiochemically pure products.[20]

Acknowledgment. We are grateful for the assistance of Tom Swann and Jeff Noonan (Department of Synthesis and Analysis Technology) in teaching us to use Bristol-Myers Squibb's suite of combinatorial instrumentation.

Supporting Information Available. Experimental details for synthesis of trisubstituted triazoles, both a single example and a parallel run, in addition to the unequivocal synthesis of band 1 isomer. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Triethylamine as co-solvent was necessary to suppress formation of a trisubstituted 4-aminotriazole resulting from combination of two acid hydrazides into one imidate.
(11) Vac-elute was fitted with 6 × 75-mL syringe cartridges charged with silica gel to 1/3 volume. Details are available in the Supporting Information.
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(13) For alkylation of a triazole via Mitsunobu reaction, see: Carlsen, H. J.; Gautun, O. R. *Acta Chem. Scand.* **1990**, *44*, 485−488. Carlsen, H. J.; Jorgensen, K. B. *J. Heterocycl. Chem.* **1997**, *34*, 797−806.
(14) Our success rates ranged from 45 to 72%. For an example of Mitsunobu reaction under automated conditions, see: Krchák, V.; Flegelová, Z.; Weichsel, A. S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193−6196.
(15) For another example of parallel solution phase work relying on preparative HPLC, see: Tommasi, R. A.; Whaley, L. W.; Marepalli, H. R. *J. Comb. Chem.* **2000**, *2*, 447−449.
(16) In some cases, samples were found to be contaminated with the reduction product of DIAD (only evident by 1H NMR).
(17) Larger protecting groups than acetaldehyde on the hydrazide gave predominantly O-alkylation products (benzaldehyde, acetone, propionaldehyde).
(18) We do not intend to imply that band 1 for all products is the same isomer as compound 1, but once unequivocally established, 1H NMR data of 1 vs 2 could be used in elucidation of other isomers.
(19) The major product of the condensation reaction was the intermediate acylated hydrazide (>50%) where hydrolysis of the thioamide to amide product was observed instead of cyclization.
(20) This work was presented in part at the 57th Southwest Regional American Chemical Society Meeting, San Antonio, TX, Oct 2001, by Romine, J. L., Martin, S. W., Chen, L., Poindexter, G. S., Antal-Zimanyi, I., and Matson, G.

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