Organic Process Research & Development **2009,** *13,* 1401–1406

Full Papers

A Convenient and Stable Synthon for Ethyl Azide and Its Evaluation in a [3 + 2]-Cycloaddition Reaction under Continuous-Flow Conditions

Rob Tinder,[†] Roger Farr,[†] Richard Heid,[†] Ralph Zhao,[†] Randy S. Rarig, Jr.,[‡] and Thomas Storz*[,†]

Wyeth Research, Chemical Development, and Wyeth Analytical and Quality Sciences, 401 North Middletown Road, Pearl River, New York 10965, U.S.A.

Abstract:

Azidoethyl phenyl sulfide, a readily accessible and reasonably stable synthon for ethyl azide with acceptable thermal safety properties, was investigated in a preliminary design space evaluation of a [3 + 2]-cycloaddition with cyanoacetamide under continuous-flow conditions in the Syrris AFRICA flow reactor.

Introduction

Triazoles and their derivatives are important constituents of many biologically active molecules.[1−3] For one of our development platforms, we required a straightforward and scaleable access to simple N^1-alkylated 5-amino-1,2,3-triazole carboxamides **A** (Figure 1).

The issues inherent to this structural scaffold are exemplified by one of our target compounds, the known 5-amino-1-ethyl-1*H*-1,2,3-triazole-4-carboxamide **1**.[4] The only reported synthesis[4,5] claimed for this building block suffers from low yield, structural ambiguity, as well as considerable safety hazards due to the employment of ethyl azide (Scheme 1).[6]

A safer, selective, and high-yielding synthesis for building blocks of type **A** was needed.

Results and Discussion

In principle, if completely regioselective, the [3 + 2] cycloaddition of an organic monoazide with an *in situ* generated ketenimine[7] would constitute a concise and attractive approach to the desired scaffold. Unfortunately, the hazardous properties of most small molecular weight alkyl azides preclude utilization of this strategy on any meaningful scale.[8]

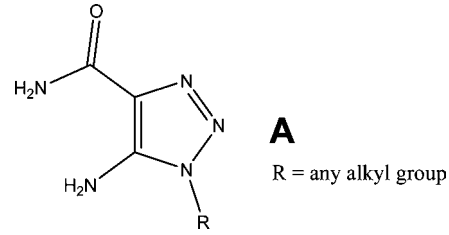


Figure 1. ***N*[1]-alkylated triazole carboxamides of interest.**

We hypothesized that by incorporation of a large sulfur substituent into the β-position both thermal stability and safety properties of the resulting azide building block should improve and hence render this approach more practical from a process point of view. Post cycloaddition, the sulfur substituent should be easily removable by known techniques, e.g. via RaNi-mediated desulfurization. To the best of our knowledge, "thio-moderated, stability-engineered" monoazides have not been investigated in [3 + 2] cycloadditions towards 1,2,3-triazoles before.

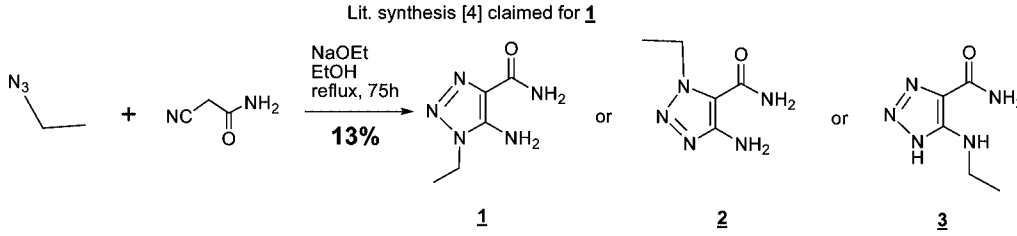
To test this concept, we prepared β-azidoethyl phenyl sulfide **4** in one step from cheap commercial β-chloroethyl phenyl sulfide and sodium azide under nonaqueous conditions (see Experimental Section).[9] It is a colorless liquid which has been reported as a distillable liquid in the literature[9] (bp 65 °C, 0.5 Torr). No safety data for this compound have been reported to date, so we set out by subjecting **4** to a variety of thermal safety

* Corresponding author. E-mail: storzt@wyeth.com.
† Wyeth Research, Chemical Development.
‡ Wyeth Analytical and Quality Sciences.

(1) Melo, J. O. F.; Donnici, C. L.; Augusti, R.; Ferreira, V. F.; de Souza, M. C. B. V.; Ferreira, M. L. G.; Cunha, A. C. *Quim. Nova* **2006**, *29*, 569.
(2) Kale, P.; Johnson, L. B. *Drugs Today* **2005**, *41*, 91.
(3) (a) Kadaba, P. K. *Curr. Med. Chem.* **2003**, *10*, 2081. (b) Angiolillo, D. J.; Capranzano, P. *Am. Heart J.* **2008**, *156*, 10S.
(4) Dornow, A.; Helberg, J. *Chem. Ber.* **1960**, *93*, 2001.
(5) The authors in lit. ref 4 claim that only compound **1** was formed, although the analytical data (*only elemental analysis given*) support the isomeric structures **2** and **3** as well. Additional ambiguity is added by the later observation ofAlbert, A. (*J. Chem. Soc., Perkin Trans. I* **1981**, 2344) that N^1-alkylated 5-aminotriazole amides can be in equilibrium with the corresponding 5-alkylamino-triazoles via Dimroth rearrangement. For a preparative example of a Dimroth rearrangement in the scale-up of a pyrrolopyrimidine, see: Fischer, R. W.; Misun, M. *Org. Process Res. Dev.* **2001**, *5*, 581.
(6) For a report of an ethyl azide explosion, see: (a) Burns, M. E.; Smith, R. H., Jr. *Chem. Eng. News* **1985**, *63*, 2.
(7) For references on the [3 + 2]-cycloaddition of the ketenimine generated *in situ* from cyanoacetamide with: (a) benzyl azide Hoover, J. R. E.; Day, A. R. *J. Am. Chem. Soc.* **1956**, *78*, 5832. (b) An alkoxymethyl azide Yokoyama, M.; Watanabe, S.; Seki, T. *Synthesis* **1988**, 879. (c) *n*-Propyl/cyclopentyl azide Haning, H.; Niewoehner, U.; Schenke, T.; Lampe, T.; Hillisch, A.; Bischoff, E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3900.
(8) For explosive properties of low-molecular weight alkyl azides, see: (a) Klaeboe, P.; Nielsen, C. J.; Priebe, H.; Schei, S. H.; Sjoegren, C. E. *J. Mol. Struct.* **1986**, *141*, 161. Simple cycloaddition with metal azides (i.e., sodium azide) followed by *N*-alkylation is usually not a viable strategy for the concise synthesis of N^1-alkylated triazoles due to the formation of regioisomeric mixtures, that may be difficult or even impossible to separate, see: (b) Maksimova, A. V.; Serebryakova, E. S.; Tikhonova, L. G.; Vereshchagin, L. I. *Khim. Geterotsikl. Soedin.* **1980**, 1688. (c) Livi, O.; Biagi, G.; Ferretti, M.; Lucacchini, A.; Barili, P. L. *Eur. J. Med. Chem.* **1983**, *18*, 471.

10.1021/op900078t CCC: $40.75
Published on Web 05/28/2009

Scheme 1



tests: TSU testing (2 mL neat liquid) showed a significant exotherm with onset around 155 °C with a maximum d*T*/d*t* of 135 °C/min. ARC testing of a neat sample (2.54 g) (*undiluted*) showed a significant exotherm starting around 130 °C, with a heat liberation of 608 J/g (Figure 2).

In order to check for onset of decomposition at temperature ranges realistically expected for the cycloaddition reaction, a set of isothermic DSC experiments was carried out. No exotherms were observed during the hold period in both a 20 h/100 °C and a 72 h/80 °C experiment.[10] Overall, we were encouraged by these data as they indicated a significantly improved safety profile compared to that of ethyl azide which, due to its unpredictable and explosive properties,[6] should not be handled in the laboratory at any scale.

Since the reaction still involves a potentially hazardous azide, we wanted to put an additional engineering control in place to ensure an inherently safe process. Continuous-flow reactions have the potential to be much safer than batch reactions, as only a small amount of reactive and potentially hazardous material is heated or converted to product at any given time.[11] We undertook an initial parallel screening of solvents and bases for the cycloaddition shown in Scheme 2 towards a potential continuous-flow process. The results of this screen (Table 1) provided us with a starting point for further DoE studies in the Syrris AFRICA continuous flow reactor system (Figure 3).

A series of experiments examining the interplay of temperature, stoichiometry, and base were carried out (Table 2). These data suggest a complex interaction between temperature and base resulting in degradation of cyanoacetamide. To examine this interaction, the data collected between 65 and 95 °C were analyzed using the historical data feature of Stat-Ease Design Expert Software. Figure 4 shows a graphical representation of the interaction between temperature, base, and stoichiometry of cyanoacetamide. For a given residence time at higher temperatures, base causes cyanoacetamide to decompose in a concentration-dependent manner, competing with the productive reaction pathway.

Only one, the desired 5-amino regioisomer, was formed in all experiments, as unambiguously proven by 2D-NMR experiments and single crystal X-ray crystallography (Figure 5); the Dimroth rearrangement product (cf. Scheme 1)[5] could not be detected. Other than small amounts of unreacted starting material no other product-related side products were observed.

The conditions chosen for a 5 g flow reactor proof-of-concept experiment are shown in Scheme 3.

We were gratified to find that RaNi-mediated desulfurization of the cycloadduct **5** proceeded cleanly to complete the proof-of-concept to the *N*-ethyl triazole **1**; no triazole ring cleavage or Dimroth rearrangement product was observed (Scheme 4).[18] Alternatively, the cycloadduct **5**, which appears to be thermally stable toward Dimroth rearrangement may also be carried forward and the reductive desulfurization carried out at a later stage in the synthetic sequence (*data not shown*). Since triazoles are high energy compounds, this has the advantage of operating with an inherently safer intermediate due to the more favorable carbon to nitrogen ratio.[23]

This high-yielding sequence has the potential to be a practical and safe addition to the synthetic arsenal for N^1-alkylsubstituted 5-amino-triazoles, valuable intermediates for the synthesis of important pharmacophores such as triazolopyridines or triazolopyrimidines and their derivatives.[4,13−17]

Conclusions

A safe and readily accessible substitute for ethyl azide has been identified and its usefulness demonstrated in a [3 + 2]-cycloaddition design space evaluation using the Syrris AFRICA continuous flow reactor setup. The dipolar cycloaddition of 2-azidoethyl phenyl sulfide appears to be much cleaner

(9) Safety data for this nucleophilic displacement had indicated a >50 °C window between reaction temperature (75 °C) and decomposition onset (*~130 °C, data not shown*). This new one-step procedure (see Experimental Section) is more convenient than the only previously reported four-step synthesis for this building block: (a) Khoukhi, M.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1986**, *27*, 1031 The corresponding sulfone (2-azidoethyl phenyl sulfone), see: (b) Carboni, B.; Vaultier, M.; Carrie, R. *Tetrahedron* **1987**, *43*, 1799. initially investigated as cycloaddition partner was quickly abandoned due to complications *(side reactions due to β-elimination*) under the basic reaction conditions (*data not shown*).

(10) The isothermal DSC experiment held at 100 °C for 20 h, when cooled and reramped to 300 °C (heating rate 10 °C/min) showed an exotherm onset at 160 °C, liberating 560 J/g.

(11) For a recent overview of this rapidly developing field, see the special issue of *Organic Process Research and Development* devoted to Continuous Processes: *Org. Process Res. Dev.* **2008**, *12*, 904.

(12) Initial safety testing for this azide substitution reaction was also carried out showing this reaction mode to be safe (*vide supra*). To minimize reaction hazards, we envisaged flow reactor integration of both reactions for further development. Appropriate safety measures should be taken as for all azide reactions; see, for instance: (a) Lunn, G.; Sansone, E. B. Azides. In: *Destruction of Hazardous Chemicals in the Laboratory*, 2nd ed.; Wiley: New York, 1979; p 57. (b) Hagenbuch, J.-P. *Chimia* **2003**, *57*, 773. (c) Wiss, J.; Fleury, C.; Heuberger, C.; Onken, U. *Org. Process Res. Dev.* **2007**, *11*, 1096. (d) Bosch, L.; Vilarrasa, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3926 (see ref 14).

(13) Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Lucacchini, A. *Farmaco* **1996**, *51*, 395.

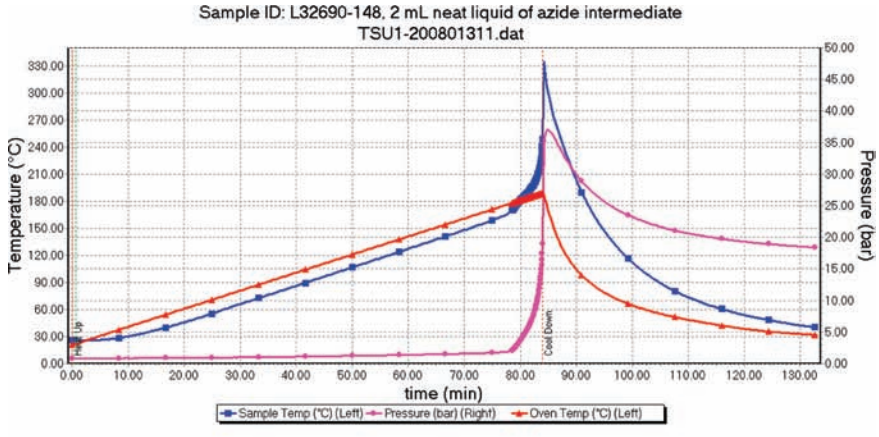
(14) Baraldi, P. G.; Manfredini, S.; Simoni, D.; Zappaterra, L.; Zocchi, C.; Dionisotti, S.; Ongini, E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2539.

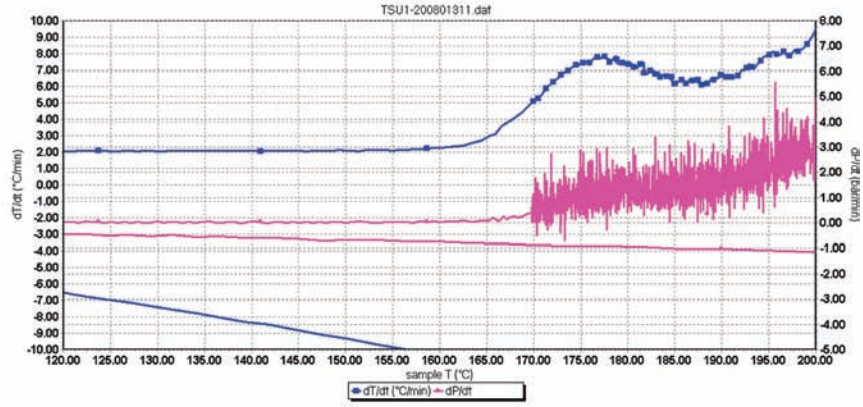
(15) L'Abbe, G.; Vandendriessche, A.; Weyns, N. *Bull. Soc. Chim. Belg.* **1988**, *97*, 85.

(16) Cacciari, B.; Spalluto, G. *Synth. Commun.* **2006**, *36*, 1177.

(17) Albert, A. *J. Chem. Soc., Perkin Trans. I* **1975**, 345.

(18) To the best of our knowledge, reductive desulfurizations of *N*-(α- or *β*-{alkyl or aryl}thioalkyl)-1,2,3-triazoles have not been reported to date.

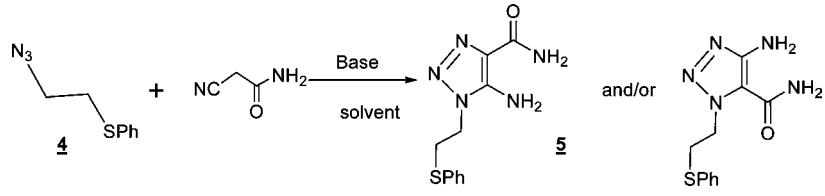




ARC L40342-12 PI3K azide intermediate			Corrected for phi			Cal/g/C		g	
		units				Cp (sampl	Cp (bomb)	W (sample	W (bomb)
phi factor	2.535433071		1.0			0.4	0.12	2.54	13
Exotherm starting temperature	135.72	(°C)	127.0				Ti 0.12 cal/C/g		
self heating rate at start of exotherm	0.02556	(°C/min)	0.025578				final wt. stir bar		0.1
Maximum observed self heating rate	224.34	(°C/min)	2227781					off gas wt.	
Temperature at maximum self heating rate	258.24	(°C)	437.6						
Exotherm final temperature	279.1	(°C)	490.5	490.5 (check)					
Adiabatic temperature increase	143.38	(°C)	363.5304						
Reaction delta H	607.82	(J/g)							
(slope of $\log_{10}$(dT/dt) vs. 1/T)	-7563.453436	(°K)							
T1 *(from log10(dT/dt) vs. 1/T graph)*	170.33	(°C)							
(dT/dt) 1 *(from log10(dT/dt) vs. 1/T graph)*	0.396	(°C/min)							
T2 *(from log10(dT/dt) vs. 1/T graph)*	190.63	(°C)							
(dT/dt) 2 *(from log10(dT/dt) vs. 1/T graph)*	2.209	(°C/min)							
Activation Energy (Ea)	1429.268534	(L-atm/mol	144820.6	(J/mol)	1 L-atm = 101 J				
A1	4.52E+16								
A2	4.52E+16		T (C)	135.72					
average Arhennius Constant (A)	4.52E+16		dT/dt)calc.	0.014248	0.02556 (check)				
Pressure at start of exotherm	12	(psi)							
Pressure at end of exotherm	1282	(psi)							
Final cool-down pressure	11	(psi)							

Figure 2. **Thermal safety data of 2-azidoethyl phenyl sulfide 4.**

Scheme 2



and higher yielding compared to those of typical low-molecular weight alkyl azides.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. All the melting points are uncorrected and were determined on a DSC instrument (*vide infra*). ^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 200 MHz on a Bruker DRX-500 NMR instrument. Assignments were confirmed by the appropriate 2D-NMR experiments. IR spectra were measured on a Bruker IFS660 spectrometer. Exact mass determinations were performed on a ABI QSTARXL qtof instrument (calibrated in positive ion mode with CsI and sex

Table 1

solvent	base	temperature °C	time	prod LC area %	SM	solids?
NMP	KOtBu	40	14 h	83	0	no
DMF	KOtBu	40	14 h	88	0	no
THF	KOtBu	40	14 h	33	52	
EtOH	KOtBu	40	14 h	73	17	yes
NMP	LiHMDS	40	14 h	70	0	no
NMP	LiHMDS	40	15 min	70	0	no
THF	LiHMDS	40	14 h	48	29	yes
EtOH	LiHMDS	40	14 h	47	35	yes
DMF	NaOH	40	15 min	100	0	no
DMF	NaOH	40	14 h	100	0	no
THF	NaOH	40	14 h	11	77	yes
EtOH	NaOH	40	14 h	44	47	yes
NMP	Et_3N	40	14 h	0		no
DMF	Et_3N	40	14 h	0		no
THF	Et_3N	40	14 h	0		no
EtOH	Et_3N	40	14 h	0		no

pheromone inhibitor iPD1 (*Bachem*)). For reaction monitoring, a Waters Acquity UPLC system with a BEH-C18 column (100 mm × 2.1 mm, 1.8 μm particle size) was used, employing a 0.1% H_3PO_4/CH_3CN gradient (0 to 100%, 5 min gradient) and UV detection (λ = 220 nm). Safety testing: (A) Differential Scanning Calorimetry ("DSC", from TA Instruments, Inc.): The sample in mg scale is tightly crimped into an aluminum pan and loaded onto the sample cell holder with an empty crimped aluminum pan as a reference. The scanning rate is 10 °C/min or slower, unless otherwise indicated. The thermal event of the sample is recorded along with the temperature. No pressure data is available from this testing. (B) Thermal Screening Unit ("TSU", from HEL Ltd.): The sample is charged into a 9-mL (hastelloy C unless otherwise indicated) test cell, which is then sealed into an oven. The oven temperature is ramped up to 250 at 2 °C/min, unless otherwise indicated. Sample temperature is monitored with a thermocouple immersed into the sample. Pressure and oven temperature are also monitored throughout the run. The containment volume—test cell, pressure transducer and piping—is approximately 10 mL. (C) Accelerating Rate Calorimeter ("ARC", from Arthur D. Little Inc.): The sample is charged into an 8.6-mL round-bottom or a 10 mL cylindrical test cell, made of hastelloy C or titanium. The cell is sealed to the calorimeter assembly and placed into a thermally insulated cavity. A thermocouple clipped to the external surface of the cell is used to track sample temperature, while pressure is monitored with a transducer. Heating elements, which are distributed throughout the cavity, are used to increase sample temperature according to a Heat-Wait-Search (HWS) pattern,

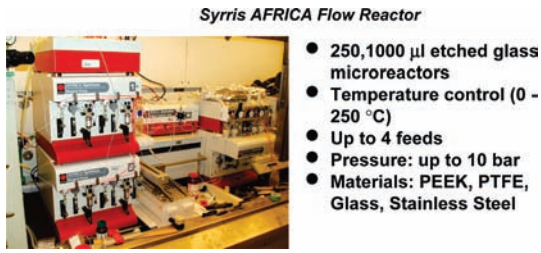


Figure 3. **Syrris AFRICA flow reactor.**

Table 2. **Continuous-flow experiments in the Syrris AFRICA reactor (1 min residence time) using 1 equiv of azide 4 (base: NaOH, solvent: NMP)**

temperature (°C)	cyanoacetamide (equiv)	base (equiv)	conversion (%)	starting azide (%)
65	1.5	1.5	30	70
65	1.5	2	98	2
65	2	1.5	98	2
65	2	2	100	0
75	1.5	1.5	47	46
75	1.5	2	70	30
75	2	1.5	98	2
75	2	2	76	23
85	1.5	1.5	5	95
85	1.5	2	60	40
85	2	1.5	98	0
85	2	2	95	5
95	1.5	1.5	7	93
95	1.5	2	2	98
95	2	1.5	3	97
95	2	2	0	100

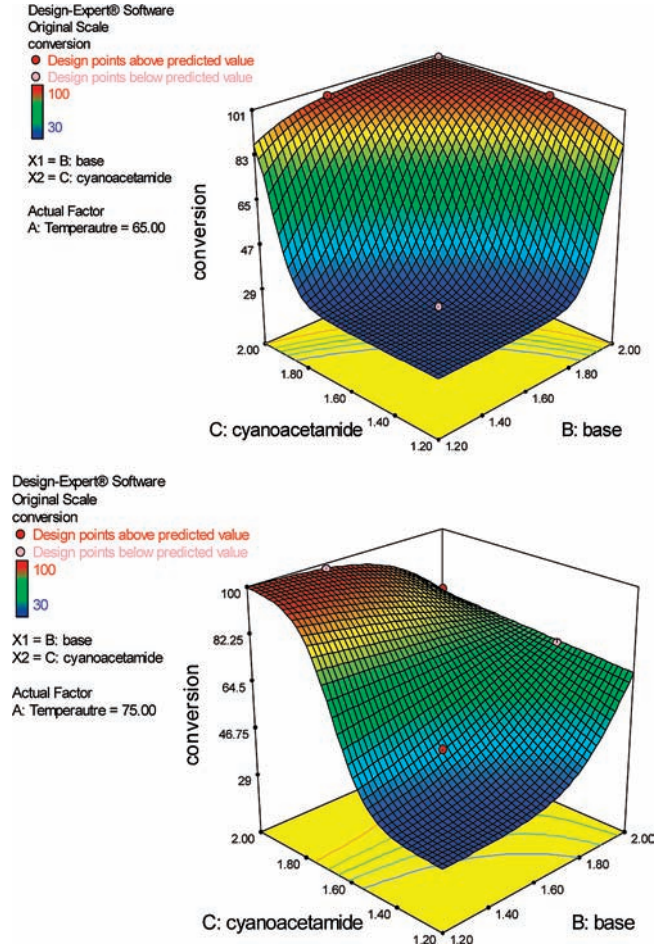


Figure 4. **Design Expert response surfaces of the cycloaddition screen under continuous-flow conditions in the Syrris AFRICA reactor (1 min residence time) at 65 and 75 °C (base: NaOH, solvent: NMP).**

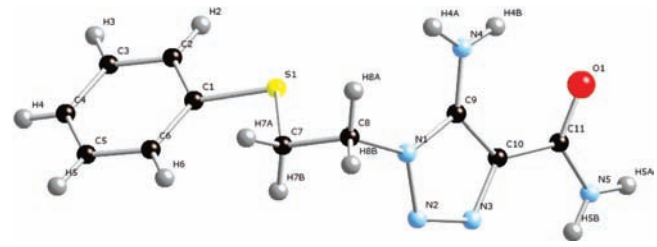
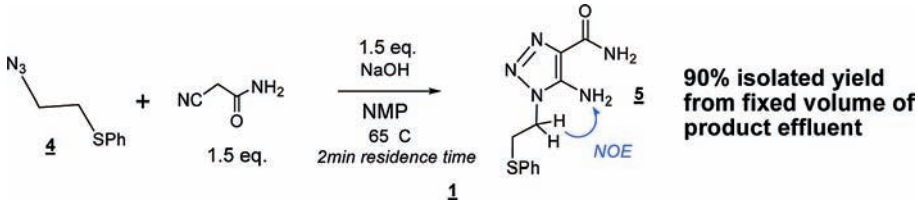
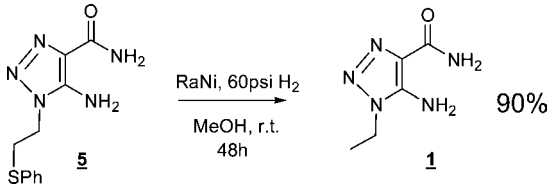


Figure 5. **Single crystal X-ray of 5.**

Scheme 3. **Proof-of-concept experiment in the Syrris AFRICA flow reactor**

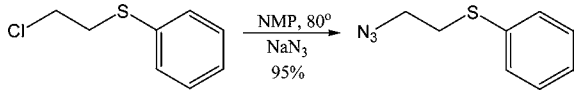


Scheme 4. **RaNi desulfurization of 5**



unless otherwise indicated. If a self-heat rate of typically 0.02 °C/min or greater is detected during the "Search" phase, the ARC goes into exotherm mode. In this mode the sample-test cell system is kept in adiabatic conditions, i.e. the cavity temperature follows the measured sample temperature. Truly adiabatic results are obtained from experimental data by correcting for heat absorption by the test cell. The containment volume−test cell, pressure transducer and piping−is approximately 11 mL. Structural measurements were performed on a Bruker-AXS SMART-CCD diffractometer at low temperature (90 K) using graphite-monochromated Mo K radiation (Mo K = 0.71073 Å).[19] The data were corrected for Lorentz and polarization[20] effects and absorption using *SADABS*.[21] The structures were solved by direct methods. All non-H atoms were refined anistropically. After all of the non-H atoms were located, the model was refined against *F*,[20] initially using isotropic and later anisotropic thermal displacement parameters. H atoms were introduced in calculated positions and refined isotropically. Neutral atom scattering coefficients and anomalous dispersion corrections were taken from the *International Tables*, Vol. C. All calculations were performed using *SHELXTL* crystallographic software packages.[22]

2-Azidoethyl Phenyl Sulfide (4).[9]



2-Chloroethyl phenyl sulfide (116 g, 671 mm), was charged to a 2 L three-neck flask equipped with a mechanical stirrer, nitrogen inlet, and a rubber septum. NMP (500 mL) was then added followed by 87 g (2.0 equiv, 1.33 M) of sodium azide. The thin slurry was heated to 75−80 °C,[12] maintained at that temperature for 3 h (reaction monitored by UPLC) and then cooled to 20 °C in an ice bath. MTBE (500 mL) was added followed by the addition of water (700 mL) over 15 min while maintaining an internal temperature of 20−25 °C. The aqueous layer was cut and the organic layer washed with 1 M sodium bicarbonate (100 mL) and water (100 mL). The volatiles were removed *in vacuo*, and the product (oil) was used as is in the next step without further purification (114 g, 95%). UPLC: 98A%, RT 3.4 min; NMR:[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.05 (t, 2 H, CH_2-S, J = 6.9 Hz), 3.40 (t, 2 H, CH_2-N, J = 6.9 Hz), 6.92 − 7.62 (m, 5 H, CH (Ph)). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.0 (C_{ipso} (SPh)), 130.8 (C_{ortho} (SPh)), 129.6 (C_{meta} (SPh)), 127.4 (C_{para} (SPh)), 50.7 (NCH_2), 34.0 (SCH_2).; IR[9] (cap film/KBr, cm^{-1}): 3059w, 2926w, 2867w, 2505w, 2102s, 1687w, 1584m, 1481m, 1439m, 1348m, 1306m, 1256m, 1180w, 1089w, 1025w, 902w, 740s, 692s.

Continuous Flow Reactor Screen (Syrris AFRICA Experiments To Establish Design Expert Response Surfaces). Stock solutions were prepared and loaded as needed into 10 mL loops of the Syrris AFRICA instrument. Cyanoacetamide (4 g, 47.5 mmol) was dissolved in 20 mL of NMP. Likewise 2-azidoethylphenylsulfide (4 g, 22.3 mmol) was also dissolved in 20 mL of NMP. A stock solution of 10 M NaOH was used. Using the flow manager program, flow rates were calculated on the basis of the prescribed stoichiometry. Reactions were performed in a 250 μL, three-input glass reactor chip, heated to the prescribed temperature prior to equilibration. Approximately 1.5-fold volume excess was required for the reactor to reach steady state, and 500 μL of steady-state reaction mixture was collected using an automated fraction collector, and analyzed by UPLC.

5-Amino-1-(2-phenylthioeth-1-yl)-1,2-3-triazole-4-carboxamide (5). (*Continuous Flow Reactor 5 g Proof-of-Concept Experiment*): A medium-scale plugflow reactor consisting of two pumps, a 4 mL tube reactor, hot plate, and mixing tee (T) was constructed using equipment from Syrris Ltd. (Syrris FRX system). A reagent solution was prepared by dissolving 2-cyanoacetamide (4.22 g, 50.2 mmol) and 2-azidoethyl phenyl sulfide (6 g, 33.45 mmol) to 60 mL of NMP. A commercial stock solution of 10 M aq sodium hydroxide was used directly. The reactor temperature was set to 70 °C and the reactor pumped with approximately 1.5 volumes (6 mL) of reagents at 0.9 mL/min for the reagent solution and 0.1 mL/min for the sodium hydroxide solution. After the reactor reached equilibrium, 38 mL of output was collected into 150 mL of water while stirring vigorously. The colorless precipitate was filtered off and the filter cake washed twice with 20 mL of water each and dried overnight at high vacuum to afford 4.55 g (90%) of the triazole **5** as a colorless crystalline solid. UPLC: RT 2.4 min, mp (DSC) 155.9 °C. DSC (*dynamic*): no exotherm up to 250 °C, ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.38 (t, 2 H, CH_2-S, J = 7.0 Hz), 4.35 (t, 2 H, CH_2-N, J = 7.0 Hz), 6.24 (br s,

(19) *SMART, Data Collection Software*, version 5.630; Bruker AXS Inc.: Madison, WI, 1997−2002.
(20) *SAINT Plus, Date Reduction Software*, version, 6.45A; Bruker AXS Inc.: Madison, WI, 1997−2002.
(21) Sheldrick, G. M. *SADABS*; University of Göttingen: Göttingen, Germany, 1996.
(22) *SHELXTL PC*, version 6.12; Bruker AXS Inc.: Madison, WI, 2002.
(23) Compared with cycloadduct **5**, the triazole **1** releases almost 3 times the decomposition energy upon thermally induced decomposition (*data not shown*).

2 H, C(5)-NH_2), 6.98 (br s, 1 H, CONH_2), 7.22 (br s, 1 H, CONH_2), 7.23 (m, 1 H, C*H* (Ph)), 7.34 (m, 2 H, C*H* (Ph)), 7.38 (m, 2 H, C*H* (Ph)). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.0 (*C* = O), 144.6 (C(5)), 134.7 (C_{ipso} (SPh)), 128.9 (C_{ortho} (SPh)), 128.8 (C_{meta} (SPh)), 126.0 (C_{para} (SPh)), 121.7 (C(4)), 44.5 (N*C*H_2), 31.1 (S*C*H_2). IR (KBr disk, cm^{-1}): 3414m, 3315m, 3165m, 2920w, 2852w, 1664s, 1636s, 1569s, 1512m, 1481m, 1438m, 1292m, 1248m, 1090w, 1014w, 944w, 899w, 788w, 750m, 689m. HR-MS: exact mass calculated for $C_{11}H_{14}N_5OS \times H^+$: 264.0914, found: 264.0945.

5-Amino-1-ethyl-1,2-3-triazole-4-carboxamide (1). A mixture of 1.0 g (3.8 mmol) **5** and RaNi 2800 (Aldrich) slurry (~2 g wet) in methanol (25 mL) was hydrogenated in a Parr Shaker at 58−60 psi hydrogen pressure at room temperature until UPLC shows complete conversion (~48−60 h). The supernatant was decanted and the RaNi residue filtered off and washed with methanol/acetonitrile (1:1, 50 mL). Combined filtrate and supernatant were evaporated to dryness under reduced pressure, and the residue was taken up in dichloromethane/methanol (20:1) and filtered over a small silica gel plug. **1** (550 mg, 90%) was obtained as a colorless solid after drying at oil pump vacuum. UPLC: RT 0.8 min, 100%. Mp (DSC) 204.9 °C; DSC (*dynamic*): no exotherm up to 250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.30 (t, 3 H, CH_3, J = 7.2 Hz), 4.14 (q, 2 H, CH_2, J = 7.2 Hz), 6.26 (br s, 2 H, C(5)-NH_2), 7.06 (br s, 1 H, CONH_2), 7.41 (br s, 1 H, CONH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.2 (*C* = O), 144.1 (C(5)), 121.7 (C(4)), 38.6 (*C*H_2), 14.0 (*C*H_3). IR (KBr disk, cm^{-1}): 3432m, 3402m, 3311s, 3165m, 2990w, 1672s, 1652s, 1636s, 1571s, 1517m, 1464w, 1433m, 1282m, 1249m, 1192w, 1087w, 1033w, 960w, 759m, 613w. HR-MS: exact mass calculated for $C_5H_9N_5O \times H^+$: 156.0879, found: 156.0913.

Acknowledgment

We are grateful to Dr. Mahendra Suryan for LC−MS assistance and Dr. Russ Tsao for the exact mass determinations. Yumin Gong is thanked for help with NMR structure determinations.

Supporting Information Available

X-ray structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review March 31, 2009.

OP900078T