Pergamon

Tetrahedron Letters 43 (2002) 4467–4470

TETRAHEDRON LETTERS

A general Staudinger protocol for solution-phase parallel synthesis

Craig W. Lindsley,* Zhijian Zhao, Randall C. Newton, William H. Leister and Kimberly A. Strauss

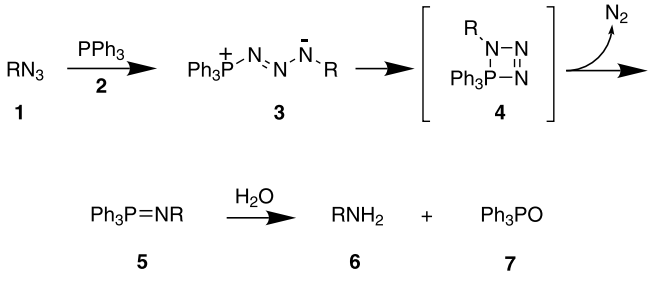
Department of Medicinal Chemistry, Technology Enabled Synthesis Group, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA

Received 8 April 2002; revised 23 April 2002; accepted 29 April 2002

Abstract—The Staudinger reaction has been adapted for parallel synthesis by the application of fluorous-tethered triphenyl phosphine. The fluorous-tethered triphenylphosphine is expediently removed in parallel by Fluoro*Flash*™ SPE columns to afford functionalized amines in high yields and purities.

During the course of our efforts to develop novel methods for solution-phase parallel synthesis, the need arose for a general protocol for the reduction of functionalized azides to the corresponding amines in high yields and purities. After surveying the literature, our laboratory was attracted to the operational simplicity of the Staudinger reaction (Scheme 1).[1] Developed in 1919 by Staudinger and Meyer, the reaction involves the treatment of azide **1** with triphenylphosphine **2** to produce phosphoazide **3** that rapidly extrudes nitrogen to deliver iminophosphorane **5**. While iminophosphoranes are powerful synthetic intermediates for aza-Wittig reactions, they can also be hydrolyzed to the amine **6** and triphenylphosphine oxide **7** by the addition of water.

The development of the Staudinger reaction into a high yielding protocol for solution-phase parallel synthesis



Scheme 1.

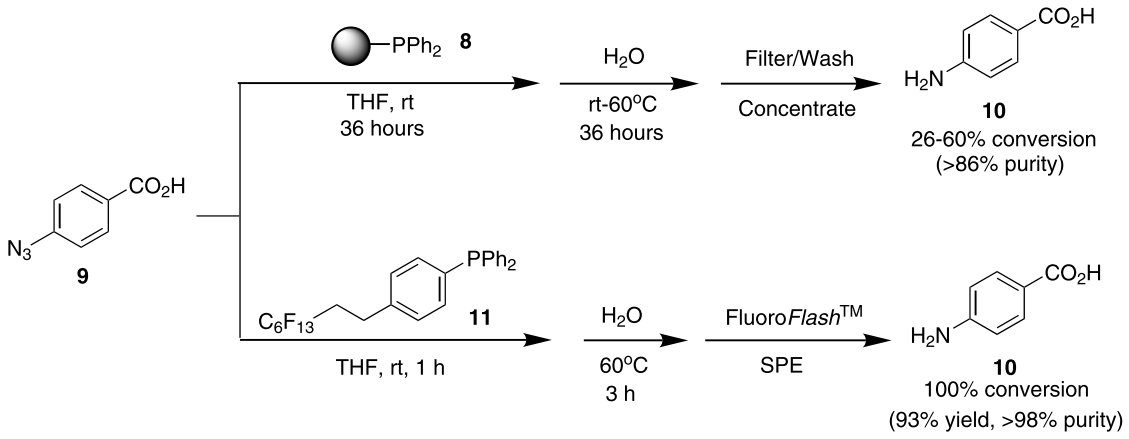
that provided products of high purity necessitated the avoidance of traditional triphenylphosphine, **2**.[2] As much of our work relies on resin-bound reagents and scavengers, our attention next focused on resin-bound triphenylphosphine **8**. In the pilot reactions, we examined two versions of **8** with either a cross-linked polystyrene-based resin or a cross-linked NovaGel™ resin.[3] From the recent work of Charette on Staudinger/aza-Wittig reactions, we anticipated that the formation and hydrolysis of a resin-bound **5** on conventional cross-linked resins might be slow.[4] In the event (Scheme 2), 4-azidobenzoic acid **9** was dissolved in THF and resin-bound PPh_3 **8** was added. After 36 h at room temperature, water was added and the reactions were warmed to 60°C for an additional 36 h. Following standard work-up protocols and analysis, the desired amine, **10**, was obtained. However, the results proved to be disappointing. Polystyrene-based **8** afforded only 26% conversion to **10** with ~86% purity while the NovaGel™ resin provided a marginally better conversion to **10** of 60% with similar purity.[5]

Building on our recent success with fluorous-tethered scavenger reagents,[6] we next examined the utility of employing a fluorous-tethered PPh_3 congener **11** in combination with Fluoro*Flash*™ SPE as a general protocol for the Staudinger reaction.[7] In this instance (Scheme 2), **9** is dissolved in THF and **11** was added neat. Within seconds, gas evolution occurred as nitrogen was extruded. After 1 h, water was added, and the reaction warmed to 60°C for 3 h. Following standard Fluoro*Flash*™ SPE, **10** was obtained in 93% yield and >98% purity.[8] Significantly, the reaction sequence was remarkably fast, requiring only 4 h total reaction time.

Keywords: reduction; azides; combinatorial chemistry.

* Corresponding author. Tel.: 215-652-2265; fax: 215-652-6345; e-mail: craig_lindsley@merck.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00827-4



Scheme 2.

Compared to >72 h total reaction time required for resin-bound reagents, the homogeneous, fluorous-tethered reaction system provides solution-phase kinetics akin to those observed with traditional **2**.[1]

The rapid rate of reduction led us to examine the reaction more closely. Fifteen minutes after the treatment of **9** with **11**, LCMS analysis indicated the disappearance of both **9** and **11** and the formation of a single intermediate.[9] The identity of this observed intermediate was confirmed as **12**, the fluorous-tethered iminophosphorane analog of **5**, by ^{31}P NMR studies (Fig. 1).[10] In an NMR tube, **11** was dissolved in THF-d_8 to afford a single resonance at −3.3 ppm. Following the addition of 1 equiv. of **9**, the signal at −3.3 ppm steadily decreased over the following 15 min as a new peak at 4.2 ppm grew in intensity. At the 15 min time point, the major resonance was that at 4.2 ppm indicative of the formation of **12**.[4] After the addition of 3 equiv. of water to the NMR tube, a new signal at 30.7 ppm resulted, corresponding to the oxide of **11**. Since the reaction is entirely in the solution phase, the conversion to **12** can be easily monitored by TLC, LCMS and/or NMR. This is in sharp contrast to the difficulty of monitoring reactions and identifying intermediates in reaction systems that involve resin-bound entities wherein special instruments and techniques must be employed.

However, one must exercise caution when selecting the degree of fluorine substitution on the tethered triphenylphosphine. As additional fluorous chains are appended to the other phenyl rings of **11** generating **13** and **14**, the rate of reaction diminishes dramatically, and begins to approach that of resin-bound PPh_3, **8** (Fig. 2).[11]

We next surveyed a structurally diverse group of azido-containing substrates to explore the generality of this new protocol for solution-phase parallel synthesis (Table 1). Excellent chemical yields (>80%) and purities (>93%) were obtained in every case examined.[12] Of note, 1° (entry 1), 2° (entry 5) and 3° (entry 4) substrates all provided the desired amines under the standard reaction conditions. Highly functionalized substrates including an adenosine derivative (entry 3), an amino acid (entry 2) and a carbohydrate (entry 6) all smoothly underwent the mild azide reduction, delivering amines in good yields in under 4 h total reaction time. Moreover, the reduction was tolerant of carboxylic acids, ketones, amines, halogens and hydroxyl moieties. The Fluoro*Flash*™ SPE purification step also proved to be quite general with successful elution of all the amine products by 15% aqueous methanol.

In summary, a general Staudinger protocol was developed for solution-phase parallel synthesis by virtue of fluorous-tethered PPh_3 **11** in conjunction with Fluoro*Flash*™ SPE columns. In less than 4 h of total reaction time, structurally diverse azides were smoothly reduced to the corresponding amines in excellent yields and purities. It is worthy to note that resin-bound PPh_3 failed to afford complete reduction even if extended time or excess reagents are used. An additional highlight of this protocol is that standard methods of analysis (LCMS, NMR) can be used to monitor reaction progress and identify intermediates. Current work is focused on the development of this protocol for the Staudinger/aza-Wittig reaction as well as other novel fluorous-tethered reagents for solution-phase parallel synthesis and will be reported in due course.

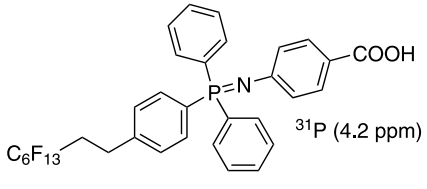


Figure 1. Fluorous-tethered iminophosphorane, **12**.

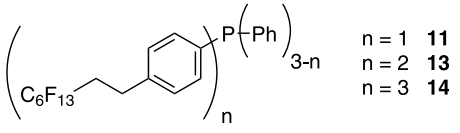
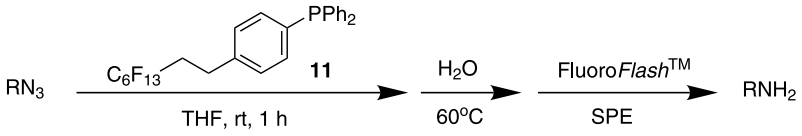
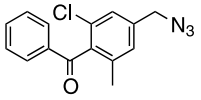
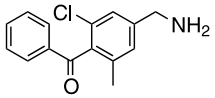
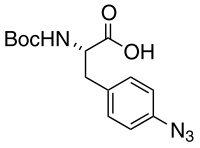
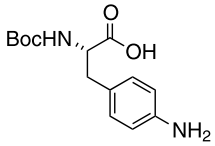
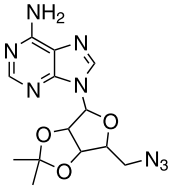
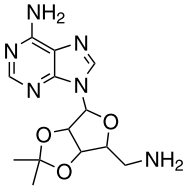
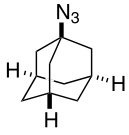
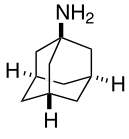
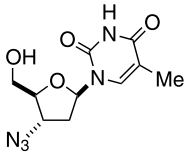
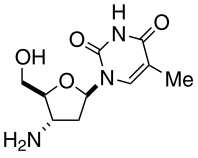
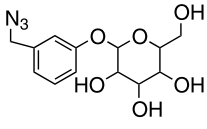
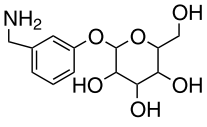


Figure 2.

Table 1. Azide reduction with **11** and Fluoro*Flash*™ SPE



entry	RN_3	RNH_2	yield (%)[a]	purity (%)[b]
1			86	98/95
2			91	98/95
3			88	98/95
4			92	98/95
5			82	95/92
6			80	97/93

a: yields for compounds fully characterized by LCMS, NMR and HRMS; b: crude purities by LCMS - 214 nm or ELSD/NMR.

Acknowledgements

We would like to thank Dr. Charles W. Ross, III for obtaining HRMS (Accurate Mass Measurements) and Dr. Steve Pitzenberger for aid in obtaining ^{31}P NMR spectra.

References

1. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646; (b) Gololobov, Y. G.; Zhumurova, I. N.; Kashukin, L. F. *Tetrahedron* **1981**, *37*, 437–472; (c) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763–764; (d) *Handbook of Reagents for Organic Synthesis*; Burke, S. D.; Danhesier, R. L., Ed. Oxidizing and reducing agents. John Wiley & Sons: New York, 2000; pp. 495–496; (e) For a biphasic approach, targeted at 3*H*-quinazolin-4-ones via an intramolecular aza-Wittig reaction, see: Barthelemy, S.; Schneider, S.; Bannwarth, W. *Tetrahedron Lett.* **2002**, *43*, 807–810.
2. Attempts to employ **2** in parallel synthesis, followed by SCX SPE column to separate **6** from **7**, did indeed work; however, the protocol was limited by the pK_a and steric hindrance of the amine, **6**, being generated and failed to be general. With SCX SPE, we were limited to unhindered basic amines. For example, anilines, pyridines and many tertiary amines failed to be retained; therefore, pure compounds were not obtained.
3. PPh_3 resins were purchased from Argonaut and Novabiochem. PS-PPh_3 (cat#: 800379) had a loading of 1.7 mmol/g and the Novagel PPh_3 (cat#: 01-64-0347) had a loading of 0.48 mmol/g.
4. Charette, A. B.; Bozeio, A. A.; Janes, M. K. *Org. Lett.* **2000**, *2*, 3777–3779 and references cited therein.

5. Conversion and purity were determined by analytical LCMS and NMR analysis.
6. Lindsley, C. W.; Zhao, Z.; Leister, W. H. *Tetrahedron Lett*., submitted.
7. (a) Fluoro*Flash*™ SPE columns and fluorous-tethered phosphines are commercially available from FTI, Fluorous Technologies Incorporated; www.fluorous.com; (b) or prepared according to Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866–8873.; (c) For excellent reviews of the area, see: (1) Curran, D. P. *Synlett* **2001**, 1488–1496; (2) Curran, D. P. *Pure A Chem.* **2000**, *72*, 1649–1653; (d) Lou, Z. Y.; Williams, J.; Read, R. W.; Curran, D. P. *J. Org. Chem.* **2001**, *66*, 4261–4266.
8. In a typical experiment, 4-azidobenzoic acid **9** (82 mg, 0.50 mmol), **11** (334 mg, 0.55 mmol) and THF (3 mL) are placed in an 8 mL vial. The vial is placed on a rotator for 50 min. Immediately, gas evolution is observed. After 50 min, 500 μL of water is added, and the vial is placed in a heater/shaker block at 60°C for 3 h. Analytical LCMS indicates a 1:1.1 ratio of **10**: fluorous-tethered PPh_3O. The crude reaction is applied to a silica transfer column (Part #: 622-0057S) atop a 5 g Fluoro*Flash*™ column (Part #: 801-0058S), pre-washed with aqueous methanol and attached to a multi-port vacuum manifold. Air is drawn through for 2 min, and then 10 mL of a 15% aqueous methanol solution is added and slowly eluted under an ~ -5 psi vacuum and collected into a test tube. The test tube is concentrated in a Genevac HT II-12 to afford 64 mg (93%) of amine **10** as a white solid. Analytical LCMS indicated a single peak (0.474 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD. (^{1}H NMR, 300 MHz, $CDCl_3$): δ 11.9 (s, 1H), 7.58 (d, $J=8.7$ Hz, 2H), 6.51 (d, $J=9$ Hz, 2H), 5.85 (s, 2H). HRMS: calcd for $C_7H_7NO_2$ (M+H), 137.0477; found 137.0480.
9. Analytical LCMS: **12** a single peak (3.270 min, CH_3CN/H_2O/0.1%TFA, 4 min gradient) >98% pure by UV (214 nm) and 100% pure by ELSD, 744.2 (M+1).
10. ^{31}P NMR recorded at 122.7 MHz on a Varian VXR-300 spectrometer.
11. For the reaction sequence in Scheme 2, **13** required 10 h for 100% conversion of **9** to **10** and **14** required overnight for complete conversion of **9** to **10**. As to why the reaction rate is depressed to such a degree is unclear. We observe that as the fluorine content increases on going from **11** to **14**, the solubility in THF decreases; therefore, the reaction may become heterogeneous (i.e. a fluorous phase and an organic phase) and demonstrated the kinetics of a biphasic system like those exhibited by **8**. Alternatively, the decreased reaction may be due solely to the increased steric hindrance about the phosphorous in **13** and **14**. One other possibility for the diminished reactivity is decreased electron density of the phosphorous lone pair and hence decreased nucleophilicity of the phosphine. ^{31}P NMR spectra of **13** (−5.7 ppm) and **14** (−6.5 ppm) indicate upfield shifts relative to **11** (−3.3 ppm) indicating electronics may contribute to the diminished activity.
12. All compounds were fully characterized by LCMS, NMR and HRMS. Spectral data for Table 1. Entry 1 (^{1}H NMR, 300 MHz, $CDCl_3$): δ 7.75 (d, $J=7.2$ Hz, 2H), 7.59 (t, $J=15$ Hz, 1H), 7.4 (m, 3H), 7.13 (s, 1H), 4.40 (s, 2H), 2.63 (s, 2H), 2.1 (s, 3H); HRMS calcd for $C_{15}H_{14}NOCl$ (M+H), 260.0837; found 260.0845. Entry 2 (^{1}H NMR, 300 MHz, DMSO-d_6): δ 13.1 (s, 1H), 6.86 (d, $J=7.5$ Hz, 2H), 6.43 (d, $J=7.5$ Hz, 2H), 3.93 (m, 1H), 2.77 (m, 1H), 2.62 (m, 1H), 1.31 (s, 9H); HRMS calcd for $C_{14}H_{20}N_2O_4$ (M+Na), 303.1315; found 303.1325. Entry 3 (^{1}H NMR, 300 MHz, DMSO-d_6): δ 8.37 (s, 1H), 8.15 (s, 1H), 7.33 (s, 2H), 6.08 (m, 1H), 5.45 (m, 1H), 4.98 (m, 1H), 4.08 (s, 1H), 2.69 (m, 2H), 1.53 (s, 6H), 1.32 (s, 2H); HRMS calcd for $C_{13}H_{18}N_6O_3$ (M+H), 307.1513; found 307.1510. Entry 4 (^{1}H NMR, 300 MHz, $CDCl_3$): δ 2.14 (s, 4H), 2.03 (s, 6H), 1.67 (s, 6H); HRMS calcd for $C_{10}H_{17}N$ (M+H), 152.1434; found 152.1437. Entry 5 (^{1}H NMR, 300 MHz, DMSO-d_6): δ 7.7 (s, 1H), 6.08 (m, 1H), 4.95 (s, 1H), 3.56 (m, 2H), 3.36 (m, 2H), 2.0 (m, 2H), 1.74 (s, 3H); HRMS calcd for $C_{10}H_{15}N_3O_4$ (M+H), 242.1149; found 249.1136. Entry 6 (^{1}H NMR, 300 MHz, DMSO-d_6): δ 7.99 (bs, 2H), 7.36 (m, 1H), 7.15 (m, 2H), 5.73 (s, 1H), 4.81 (m, 1H), 4.04 (m, 1H), 3.4 (m, 12H); HRMS calcd for $C_{13}H_{19}NO_6$ (M+H), 286.1285; found 286.1285.