3-Pyridinesulfonyl Azide: A Useful Reagent for Radical Azidation

Philippe Panchaud, Philippe Renaud*

Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, 3012 Berne, Switzerland
Fax: (+41)-31-631-3426, e-mail: philippe.renaud@ioc.unibe.ch

Received: February 9, 2004; Accepted: May 25, 2004

Abstract: Radical azidations and carboazidations have been achieved using 3-pyridinesulfonyl azide as azidating agent. Due to its base properties and its polarity, the excess of reagent is readily removed at the end of the reaction by filtration through silica gel or by extraction with either aqueous 1 M HCl or 1 M $CuSO_4$. The use of this reagent greatly facilitates the tedious purifications of the final azides frequently encountered when reactions are run according to the original procedure involving benzenesulfonyl azide.

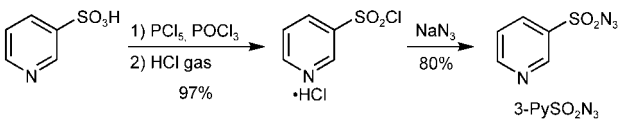
Keywords: amination; azides; carboazidation; C–C bond formation; radicals; synthetic methods

Introduction

Recently, we reported the radical carboazidation of alkenes and its application towards the concise synthesis of the core of different alkaloids.[1] This reaction is run by treating the alkene with an activated iodide, such as an α-iodo ester, in the presence of benzenesulfonyl azide and a chain transfer reagent, such as hexabutylditin in benzene[2–4] or triethylborane in water.[5] Frequently, we faced purification problems caused by the very similar chromatographic behavior of benzenesulfonyl azide (used in three-fold excess) and the azide reaction products. In order to facilitate the purification step, we decided to develop another azidating agent possessing either a very different polarity or that can be easily eliminated by extraction.

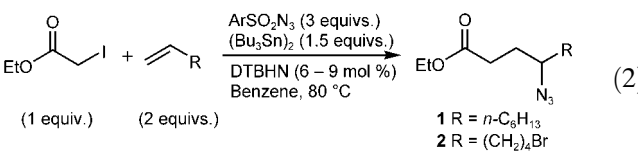
Results and Discussion

Several substituted benzenesulfonyl azides, such as 4-methoxybenzenesulfonyl azide, 4-methoxycarbonylbenzenesulfonyl azide and 3- and 4-carboxybenzenesulfonyl azides were prepared and tested. However, these compounds were either not inducing a sufficiently large shift of polarity (4-MeO-$C_6H_4SO_2N_3$ and 4-MeO_2C-$C_6H_4SO_2N_3$) or were not as efficient as benzenesulfonyl azide for the azidation process (3- and 4-HO_2C-$C_6H_4SO_2N_3$). Rapidly, 3-pyridinesulfonyl azide[6–8] (3-$PySO_2N_3$) appeared to be the most suitable candidate. It is easily prepared from 3-pyridinesulfonic acid according to Eq. (1). Treatment of 3-pyridinesulfonic acid with phosphorus pentachloride in phosphorus oxychloride gives the corresponding sulfonyl chloride that is liberated after precipitation of its hydrochloride salt by bubbling HCl gas in methylene chloride.[9] Reaction of this intermediate with sodium azide affords the desired 3-pyridinesulfonyl azide in 78% overall yield as a stable liquid that can be stored for months in a refrigerator.[10,11] Its R_f value of 0.25 in hexane/ethyl acetate (7:3) is different from that of the benzenesulfonyl azide (0.60). Moreover, extraction with either 1 M HCl or 1 M Cu_2SO_4 allows us to remove quantitatively the unreacted sulfonyl azide.



(1)

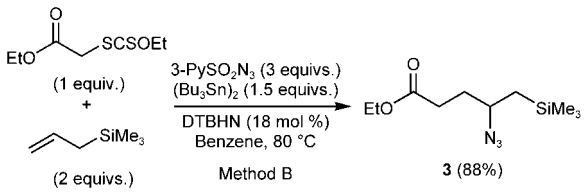
The use of this reagent was first tested on the ditin-mediated carboazidations of 1-octene and 6-bromo-1-hexene [Eq. (2), Table 1]. The products **1** and **2** were obtained in 80 and 75% yield, respectively (Table 1, entries 1 and 4) by using standard reaction conditions where 3 mol % of the initiator, di-*tert*-butyl hyponitrite (DTBHN), were added every 2 hours (Method A).[3,4] These results are very similar to those obtained with benzenesulfonyl azide (entries 2 and 5, 79% and 74%). Interestingly, when 9 mol % of initiator were added in one portion at the beginning (Method B), the reaction time was significantly reduced from 6 hours to 90 minutes. This shorter procedure reduces the amount of product degradation and leads to slightly higher yields (Table 1, entries 3 and 6).



(2)

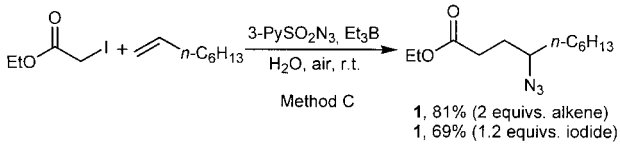
 DOI: 10.1002/adsc.200404038

Benzene- and 3-pyridinesulfonyl azides nicely complement each other since their use leads to similarly efficient carboazidation reactions even though their polarities are very different. This feature is exemplified by the synthesis of the bromo azide **2**. When the reaction is run with benzenesulfonyl azide, several purifications by column chromatography are needed to remove completely the excess of reagent from azide **2**. This procedure is not only time- and solvent-consuming but it also leads to a decrease in yield. On the other hand, when the carboazidation is run with 3-pyridinesulfonyl azide, analytically pure product **2** is isolated after a single purification by flash chromatography. Elimination of the pyridinesulfonyl azide in excess by extraction with either 1 M HCl or a copper sulfate solution is possible but unnecessary since a purification by flash chromatography is in any case required to obtain pure azide **2**. The carboazidation of allyltrimethylsilane with a dithiocarbonate derivative as radical precursor was investigated next [Eq. (3)]. The azide **3** is obtained in an excellent 88% yield under the optimized conditions (Method B). This result compares favorably (shorter reaction time, higher yield) with the reaction involving benzenesulfonyl azide according to Method A (80% in 10 h).[3,4]



(3)

Finally, the reagent was tested under tin-free conditions. Carboazidation of 1-octene according to Method C [Eq. (4)] affords azide **1** in 81% yield with a two-fold excess of alkene, and in 69% yield when ethyl 2-iodoacetate is used in excess (1.2 equivs.). These results are comparable to those obtained with benzenesulfonyl azide under similar conditions (85 and 71% yield, respectively).[5]



(4)

Conclusion

In conclusion, 3-pyridinesulfonyl azide proved to be a very useful reagent that complements efficiently benzenesulfonyl azide for carboazidation reactions. Choosing the right azidating agent, either benzene- or 3-pyridinesulfonyl azide, permits us to avoid tedious chromatographic separations. Moreover, the optimized protocol described here, where the initiator is added at once at the beginning of the reaction (Method B), allows us to shorten the reaction time down to 90 minutes and to increase the yields. These improvements are expected to facilitate the applications of radical carboazidation for the total synthesis of alkaloids and other nitrogen-containing biologically active compounds. Our results in this field will be reported in due course.

Experimental Section

Caution: Since sulfonyl azides are capable of exploding, it is strongly recommended to apply standard safety rules and to use a safety shield.

General

The 2 M solution of Et_3B in dry EtOH was freshly prepared and kept under N_2. EtOH was distilled from $Mg(OEt)_2$ under N_2. Other reagents were obtained from commercial sources and used as received. Flash column chromatography (FC): SdS silica gel (0.063–0.200 mm), EtOAc and hexane as eluents. Thin-layer chromatography (TLC): Macherey-Nagel SIL G-25 UV_{254} pre-coated TLC plates; detection either with UV or by dipping in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), 5% NaOH (3 mL) in H_2O (300 mL) and subsequent heating. NMR spectroscopy: chemical shifts δ in ppm relative to $CHCl_3$ for ^1H (δ = 7.26 ppm) and $CDCl_3$ for ^{13}C (δ = 77.0 ppm).

General Procedure for Method A

DTBHN (5 mg, 0.03 mmol) was added every 2 h to a mixture of radical precursor (1.0 mmol), olefin (2.0 mmol), azidating agent (3.0 mmol) and Bu_6Sn_2 (0.76 mL, 1.5 mmol) in dry C_6H_6 (2.0 mL) at reflux under N_2. The reaction was monitored by TLC. Upon completion of the reaction (6 h), the solvent was removed under reduced pressure and the crude product was filtered through silica gel. Elution with hexane allowed the re-

Table 1. Carboazidation reactions according to Eq. (2).

Entry	R	Azide	$ArSO_2N_3$	Method[a] (DTBHN)	Time [h]	Yield [%]
1	*n*-C_6H_{13}	**1**	3-$PySO_2N_3$	A (9 mol %)	9	80
2	*n*-C_6H_{13}	**1**	$PhSO_2N_3$	A (6 mol %)	6	79
3	*n*-C_6H_{13}	**1**	3-$PySO_2N_3$	B (9 mol %)	1.5	82
4	$(CH_2)_4Br$	**2**	3-$PySO_2N_3$	A (9 mol %)	9	75
5	$(CH_2)_4Br$	**2**	$PhSO_2N_3$	A (6 mol %)	6	74
6	$(CH_2)_4Br$	**2**	3-$PySO_2N_3$	B (9 mol %)	1.5	80

[a] Method A: DTBHN (3 mol %) added every 2 h; Method B: DTBHN (9 mol %) added in one portion at the beginning.

moval of unchanged Bu_6Sn_2 and other apolar tin derivatives. Elution with hexane/Et_2O or hexane/EtOAc gave a crude product that was purified by FC (hexane/Et_2O or hexane/EtOAc).

General Procedure for Method B

DTBHN (15 mg, 0.09 mmol) was added to a mixture of radical precursor (1.0 mmol), olefin (2.0 mmol), azidating agent (3.0 mmol) and Bu_6Sn_2 (0.76 mL, 1.5 mmol) in dry C_6H_6 (2.0 mL) under N_2. The reaction mixture was heated under reflux for 90 min. The solvent was removed under reduced pressure and the crude product was filtered through silica gel. Elution with hexane allowed the removal of unchanged Bu_6Sn_2 and other apolar tin derivatives. Elution with hexane/Et_2O or hexane/EtOAc gave a crude product that was purified by FC (hexane/Et_2O or hexane/EtOAc).

General Procedure for Method C

A 2 M solution of Et_3B in dry EtOH was added at room temperature over 1 h by using a syringe pump to an open-air, vigorously stirred mixture of radical precursor, olefin and azidating agent (3.0 mmol) in solvent (2.0 mL) (**important:** the needle should be immersed into the reaction mixture in order to avoid a direct contact of Et_3B drops with air). The reaction was stirred for 15 min more and hexane (5 mL) was added. After separation, the aqueous layer was extracted with Et_2O and the combined organic phases were washed with brine and dried over Na_2SO_4. The crude product was purified by FC (hexane/EtOAc).

3-Pyridinesulfonyl Azide

A mixture of 3-pyridinesulfonic acid (10.40 g, 65.0 mmol), phosphorus pentachloride (16.25 g, 78.0 mmol) and phosphorus oxychloride (20.0 mL) was stirred overnight at 120 °C under N_2. The reaction mixture was cooled to room temperature and diluted with dry CH_2Cl_2 (30 mL). The reaction mixture was further cooled to 5 °C and saturated with HCl gas. The white precipitate was collected by filtration, washed with dry CH_2Cl_2 and dried under reduced pressure. The 3-pyridinesulfonyl chloride hydrochloride was obtained as a white powder and used immediately; yield: 13.5 g (97%).[9]

A solution of sodium azide (14.3 g, 220 mmol) in water (40 mL) was added dropwise at 0 °C to a solution of 3-pyridinesulfonyl chloride hydrochloride (22.5 g, 105 mmol) in acetone (100 mL) and water (20 mL). The mixture was stirred overnight at room temperature. Acetone was removed under reduced pressure and the resulting aqueous phase was extracted with EtOAc (200 mL), washed with water (2 × 100 mL), 5% Na_2CO_3 (2 × 100 mL), water (2 × 100 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by precipitation in hexane/Et_2O (10:1) at −78 °C to give 3-$PySO_2N_3$ as a colorless liquid; yield: 15.40 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.18 (d, J = 2.6 Hz, 1H), 8.95 (dd, J = 4.8, 1.5 Hz, 1H), 8.24 (ddd, J = 8.1, 2.6, 1.5 Hz, 1H), 7.58 (ddd, J = 8.1, 4.8, 0.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.9, 147.8, 135.1, 134.9, 124.0; IR (film): ν = 3064, 2358, 2340, 2136, 1575, 1469, 1419, 1375, 1328, 1175, 1124, 1104 cm^{-1}. MS (EI, 70 eV): m/z (%) = 185 (MH^+, 5), 184 (M^+, 35), 142 (80), 78 (93), 65 (48), 51 (100), 38 (78); anal. calcd. for $C_5H_4N_4O_2S$ (184.18): C 32.61, H 2.19, N 30.42; found: C 32.46, H 2.30, N 30.49.

Ethyl 4-Azidodecanoate (1)

(a) Prepared according to General Procedure A from ethyl 2-iodoacetate (214 mg, 1.0 mmol), 1-octene (0.31 mL, 2.0 mmol), 3-$PySO_2N_3$ (553 mg, 3.0 mmol), Bu_6Sn_2 (0.76 mL, 1.5 mmol) and DTBHN (16 mg, 0.09 mmol). Filtration (hexane then hexane/EtOAc, 90:10) and FC (hexane/EtOAc, 95:5) gave **1** as a colorless oil; yield: 194 mg (80%). Physical and spectral data were in accordance to literature data.[4] ^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.15 (q, J = 7.3 Hz, 2H), 3.35–3.27 (m, 1H), 2.50–2.31 (m, 2H), 1.95–1.81 (m, 1H), 1.80–1.64 (m, 1H), 1.62–1.21 (m, 10H), 1.26 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 173.0, 62.2, 60.5, 34.4, 31.6, 30.9, 29.5, 29.0, 26.0, 22.5, 14.2, 14.0.

(b) Prepared according to General Procedure B from ethyl 2-iodoacetate (214 mg, 1.0 mmol), 1-octene (0.31 mL, 2.0 mmol), 3-$PySO_2N_3$ (553 mg, 3.0 mmol), Bu_6Sn_2 (0.76 mL, 1.5 mmol) and DTBHN (16 mg, 0.09 mmol). Filtration (hexane then hexane/EtOAc, 90:10) and FC (hexane/EtOAc, 95:5) gave **1**; yield: 197 mg (82%).

(c) Prepared according to General Procedure C from ethyl 2-iodoacetate (214 mg, 1.0 mmol), 1-octene (0.31 mL, 2.0 mmol), 3-$PySO_2N_3$ (553 mg, 3.0 mmol) and Et_3B (1.50 mL, 3.0 mmol) in water (2.0 mL). FC (hexane/EtOAc, 95:5) gave **1**; yield: 196 mg (81%).

(d) Prepared according to General Procedure C from 1-octene (112 mg, 1.0 mmol), ethyl 2-iodoacetate (257 mg, 1.2 mmol), 3-$PySO_2N_3$ (553 mg, 3.0 mmol) and Et_3B (1.75 mL, 3.5 mmol) in water (2.0 mL). FC (hexane/EtOAc, 95:5) gave **1**; yield: 167 mg (69%).

Ethyl 4-Azido-8-bromooctanoate (2)

(a) Prepared according to General Procedure A from ethyl 2-iodoacetate (214 mg, 1.0 mmol), 6-bromo-1-hexene (0.27 mL, 2.0 mmol), 3-$PySO_2N_3$ (553 mg, 3.0 mmol), Bu_6Sn_2 (0.76 mL, 1.5 mmol) and DTBHN (16 mg, 0.09 mmol). Filtration (hexane then hexane/EtOAc, 90:10) and FC (hexane/EtOAc, 95:5) gave **2** as a colorless liquid; yield: 218 mg (75%). Physical and spectral data were in accordance to literature data.[4] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.15 (q, J = 7.3 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 3.38–3.29 (m, 1H), 2.52–2.36 (m, 2H), 1.96–1.83 (m, 3H), 1.81–1.69 (m, 1H), 1.66–1.49 (m, 4H), 1.27 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 61.8, 60.4, 33.4, 33.1, 32.2, 30.6, 29.3, 24.5, 14.1.

(b) Prepared according to General Procedure B from ethyl 2-iodoacetate (214 mg, 1.0 mmol), 6-bromo-1-hexene (0.27 mL, 2.0 mmol), 3-$PySO_2N_3$ (553 mg, 3.0 mmol), Bu_6Sn_2 (0.76 mL, 1.5 mmol) and DTBHN (16 mg, 0.09 mmol). Filtration (hexane then hexane/EtOAc, 90:10) and FC (hexane/EtOAc, 95:5) gave **2**; yield: 234 mg (80%).

Ethyl 4-Azido-5-(trimethylsilyl)pentanoate (3)

Prepared according to General Procedure B from ethyl 2-{[(ethyloxy)carbothioyl]sulfanyl}acetate (208 mg, 1.0 mmol), allyltrimethylsilane (0.31 mL, 2.0 mmol), 3-$PySO_2N_3$ (553 mg, 3.0 mmol), Bu_6Sn_2 (0.76 mL, 1.5 mmol) and DTBHN (31 mg, 0.18 mmol). Filtration (hexane then hexane/EtOAc, 90:10) and FC (hexane/EtOAc, 95:5) gave **3** as a colorless oil; yield: 213 mg (88%). Physical and spectral data were in accordance to literature data.[4] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.14$ (q, $J = 7.2$ Hz, 2H), 3.46–3.39 (m, 1H), 2.48–2.37 (m, 2H), 1.94–1.88 (m, 1H), 1.79–1.72 (m, 1H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.00 (dd, J = 14.7, 7.5 Hz, 1H), 0.88 (dd, $J = 14.7$, 7.3 Hz, 1H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.0$, 60.5, 59.8, 32.3, 30.9, 22.3, 14.2, −1.08.

Acknowledgements

We thank the Swiss National Science Foundation (Grant 20–0677106.01) and the University of Berne for financial support.

References and Notes

[1] For a review, see: P. Panchaud, L. Chabaud, Y. Landais, C. Ollivier, P. Renaud, S. Zigmantas, *Chem. Eur. J.* **2004**, *10*, in press.
[2] C. Ollivier, P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.
[3] P. Renaud, C. Ollivier, P. Panchaud, *Angew. Chem. Int. Ed.* **2002**, *41*, 3460.
[4] P. Panchaud, C. Ollivier, P. Renaud, S. Zigmantas, *J. Org. Chem.* **2004**, *69*, 2755.
[5] P. Panchaud, P. Renaud, *J. Org. Chem.* **2004**, *69*, 3205.
[6] B. K. Warren, E. E. Knaus, *J. Heterocyclic Chem.* **1987**, *24*, 1413.
[7] B. K. Warren, E. E. Knaus, *J. Heterocyclic Chem.* **1988**, *25*, 1379.
[8] J. K. Buolamwini, E. E. Knaus, *Eur. J. Med. Chem.* **1993**, *28*, 447.
[9] R. Karaman, A. Blasko, O. Almarsson, R. Arasasingham, T. C. Bruice, *J. Am. Chem. Soc.* **1992**, *114*, 4889.
[10] R. J. Cremlyn, G. P. Jones, F. J. Swinbourne, K. Yung, *Phosphorus Sulfur Relat. Elem.* **1980**, *8*, 189.
[11] Benzenesulfonyl azide and 3-pyridinesulfonyl azide are both stable liquids that start to decompose upon heating at 130 °C (benzenesulfonyl azide) and 126 °C (3-pyridinesulfonyl azide) according to a differential scanning calorimetry study.

