



Cite this: *RSC Adv.*, 2023, 13, 2483

Received 22nd September 2022
Accepted 21st December 2022

DOI: 10.1039/d2ra05997e

rsc.li/rsc-advances

Tris(4-azidophenyl)methanol – a novel and multifunctional thiol protecting group†

Xujun Qiu,^a Julian Brückel,^a Christoph Zippel,^{id a} Martin Nieger,^b
Frank Biedermann^{id c} and Stefan Bräse^{id *ad}

The novel tris(4-azidophenyl)methanol, a multifunctionalisable aryl azide, is reported. The aryl azide can be used as a protecting group for thiols in peptoid synthesis and can be cleaved under mild reaction conditions via a Staudinger reduction. Moreover, the easily accessible aryl azide can be functionalised via copper-catalysed cycloaddition reactions, providing additional opportunities for materials chemistry applications.

Organic azides are a class of nitrogen-rich compounds with extraordinarily versatile chemistry. The azido group readily undergoes functional group transformations such as 1,3-dipolar cycloaddition,^{1–6} Staudinger ligation,^{7–12} or C–H bond amination.^{13–16} The facile access to organic azides and the excellent yield and selectivity of their reactions has made them highly desirable for their potential applications in various fields, including organic and bioorganic chemistry,^{17–21} material science,^{22–24} and supramolecular chemistry.^{25–27}

Aryl azides, in particular, have emerged as functional intermediates with diverse applications, among which the most well-known application is the copper(i)-catalysed azide–alkyne cycloaddition (CuAAC) click reaction.²⁸ The copper(i) catalysed cycloaddition of aryl azides with alkynes allows the construction of triazole moieties, which were applied in constructing porous organic polymers^{29–35} and for the functionalisation of surfaces.^{36–38} Another imperative application of aryl azides is the Staudinger reaction, an integral approach to synthesising amides in the biosystem, such as peptide synthesis,³⁹ bioactive molecular labelings,⁴⁰ and cell engineering.⁴¹ The Staudinger reduction of aryl azides by applying phosphines is commonly used to prepare anilines, where the aryl azide serves as a stable precursor for amines.^{42,43}

Inspired by the versatile azides, we report a multifunctional and spatially oriented aryl azide, which can be converted to triazoles *via* cycloaddition reaction and utilised as a protecting group for thiols in peptoid synthesis.

The novel aryl azide, tris(4-azidophenyl)methanol (**1**, Fig. 1), was synthesised according to a modified procedure by Kutonova *et al.*⁴⁴ The arylamine was first diazotised with *tert*-butyl nitrite in the presence of *p*-toluenesulfonic acid, followed by the reaction with sodium azide in a one-pot procedure (Scheme 1).

A set of cycloaddition reactions were performed utilising Cu(i) as catalyst to assess the potential functionalities of the synthesised aryl azide **1** (Scheme 2). The active hydroxyl group can be attached to other functional systems, such as the modification of the lipophilicity or the introduction of the other functional groups leading to a more sophisticated system.

Triphenylmethane and its derivatives, such as 4-methoxytrityl and 4-methyltrityl, were reported as excellent protecting

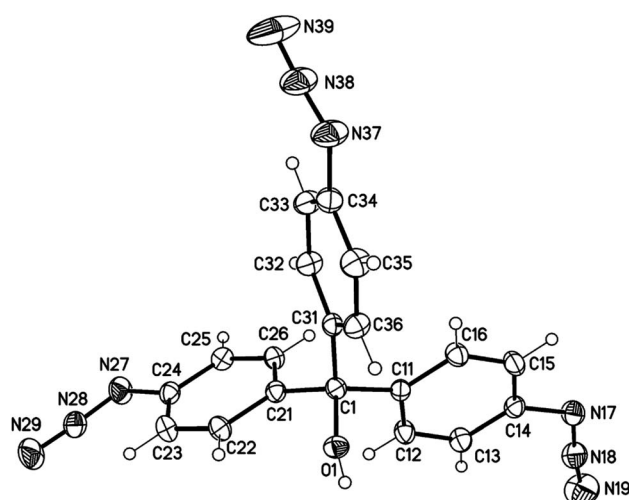


Fig. 1 Molecular structure of aryl azide **1** (displacement parameters are drawn at a 30% probability level).

^aInstitute of Organic Chemistry (IOC), Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany. E-mail: braese@kit.edu; Tel: (+49)-721-6084-2903

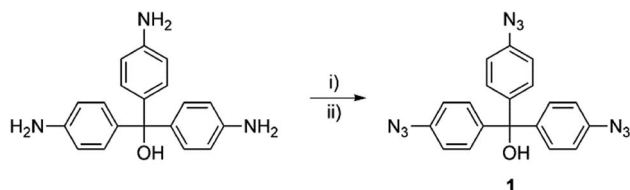
^bDepartment of Chemistry, University of Helsinki, P. O. Box 55 (A. I. Virtasen aukio 1), 00014, Finland

^cKarlsruhe Institute of Technology (KIT), Institute of Nanotechnology (INT), Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany

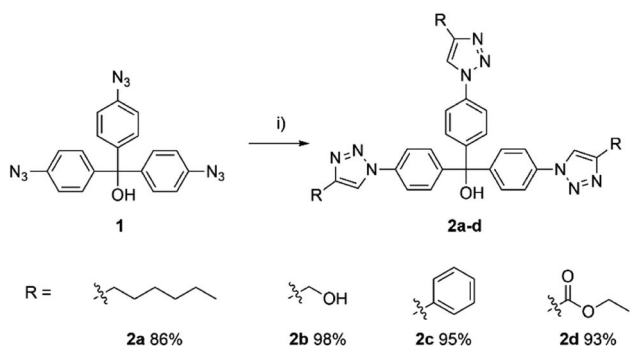
^dInstitute of Biological and Chemical Systems – Functional Molecular Systems (IBCS-FMS), Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany

† Electronic supplementary information (ESI) available. CCDC 2158276 (**1**). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2ra05997e>





Scheme 1 Syntheses of the multifunctional aryl azide **1**. Reagents and conditions: (i) *p*-TsOH·H₂O (4.50 equiv.), (CH₃)₃CONO (4.50 equiv.), CH₃CN/H₂O (2 : 1), r.t.; (ii) NaN₃ (9.00 equiv.), H₂O, r.t., (2 steps: 99%).

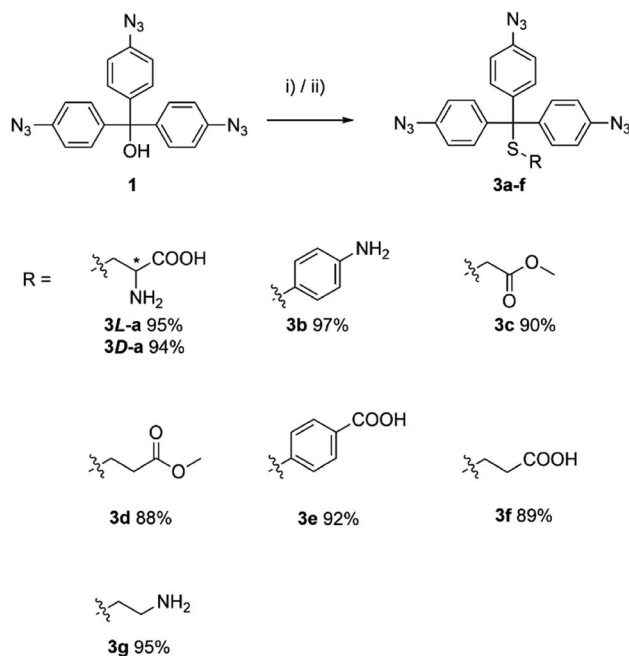


Scheme 2 Aryl azide **1** based cycloaddition reaction. Reagents and conditions: (i) alkyne (3.00 equiv.), CuSO₄·5H₂O (0.30 equiv.), sodium ascorbate (0.90 equiv.), EtOH/H₂O (1 : 1), 70 °C, 16 h.

groups for thiols.⁴⁵ To evaluate the application of the newly discovered aryl azide **1**, we explored a new strategy for protecting thiols with aryl azide **1**, accomplishing deprotection under mild reaction conditions, in which the thioether bond was cleaved by a Staudinger reduction (Fig. 2).

The studied thiols were first protected with aryl azide **1**. The reaction was carried out either in TFA or in a TFA/CHCl₃ mixture, which led to the desired products **3a-f** in excellent yield (Scheme 3).

The deprotection was based on the Staudinger reduction, where the aryl azide-protected thiols were treated with trimethyl



Scheme 3 Syntheses of the aryl azide **1** protected thiols. Reagents and conditions: (i) thiol (1.00 equiv.), TFA, r.t., 2 h; or (ii) TFA/CHCl₃, r.t., 2 h.

phosphine in THF/1 M HCl mixtures for 5 min at room temperature. The first step of the deprotection process involves the reduction of the azide groups to amines by reaction with trimethyl phosphine. The positive mesomeric effect (+M effect) renders the thioether bond labile, thus facilitating the cleavage of the thiols group under acidic conditions. This deprotection process based on aryl azide **1** is promising to protect thiols in solid-state synthesis.

We then utilised aryl azide **1** as protecting group for thiols in peptoid synthesis (see ESI† for details). As shown in Scheme 4, Fmoc-Phe-OH was first loaded to the polystyrene resin **5**, then deprotected from the Fmoc group to obtain amine **6**. After acetylation with 2-bromoacetic acid, the secondary amines **8a-e** were formed by reacting primary amines with acetylated resin **7**. By reacting **3f** with **8a-e**, a series of short peptoids **9a-e** with aryl azide protected thiols were synthesised. Following the described procedure, the peptoid-peptide hybrids **14a-c** were synthesized. In contrast to the peptoids **9a-e**, the protected aminothiol was not incorporated at the end of the chain, but rather in the middle. After elongation, peptoids with a protected aminothiol as building block were obtained. In the case of **16f**, the Fmoc-protecting group of the terminal amino acid was removed using common deprotection conditions, showing that the azide protecting group remains intact under the applied basic conditions.

The deprotection and cleavage process of the peptoids involves two orderly steps: the aryl azide protecting group was first deprotected using trimethyl phosphine in a THF/1 M HCl mixture within 5 min at room temperature to afford **10a-e** and **15a-c**. Afterward, the final peptoids (**11a-e** and **16a-c**) were cleaved from the resin using a 33% solution of hexafluoro-2-

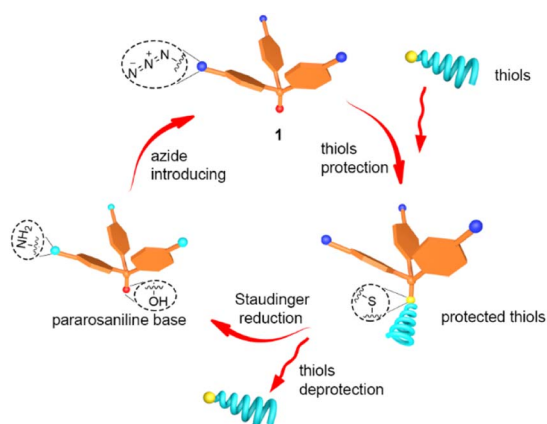
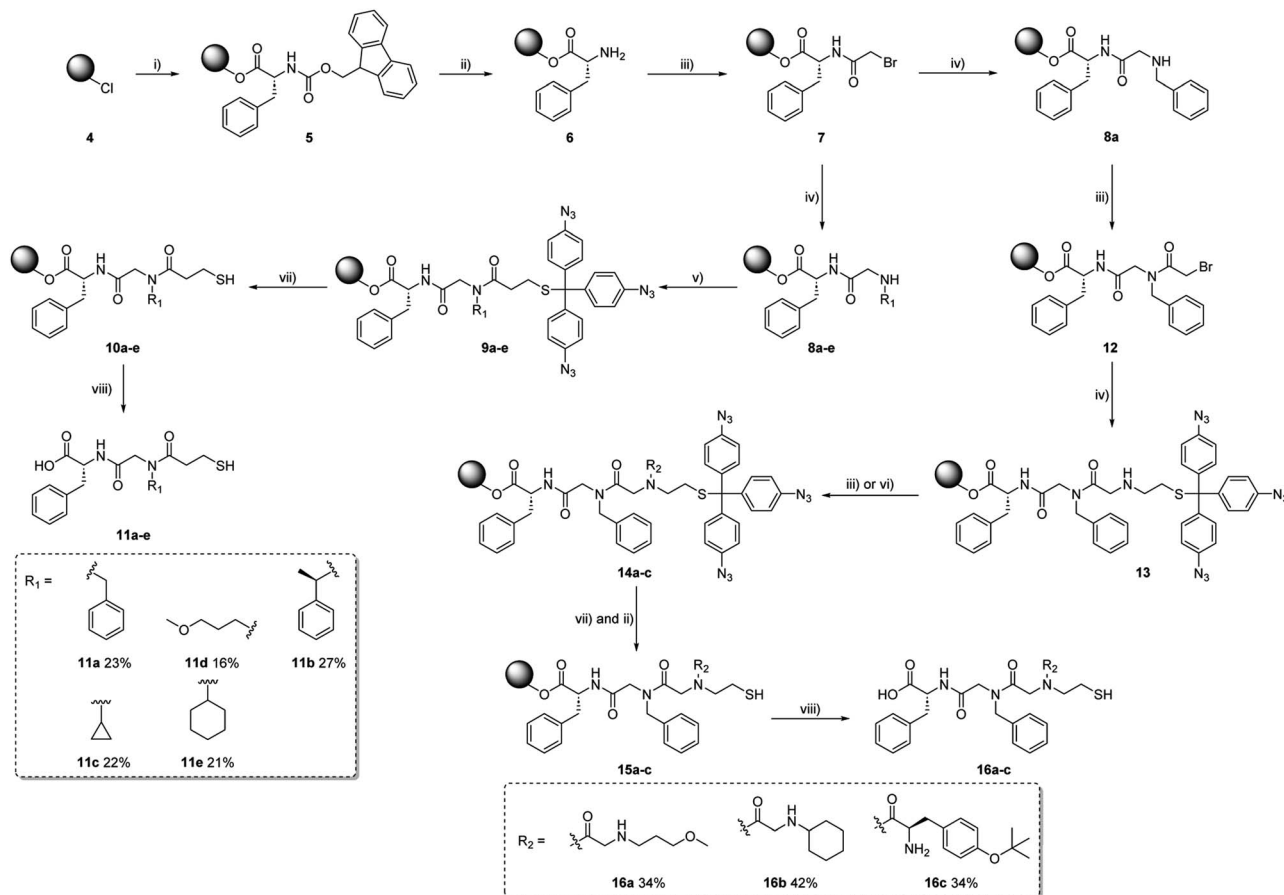


Fig. 2 Schematic diagram of the thiols protecting and deprotecting process.





Scheme 4 Peptoid synthesis. Reagents and conditions: (i) Fmoc-Phe-OH, DIPEA, NMP, r.t., 4 h; (ii) 20% piperidine in DMF, r.t., 3 × 5 min; (iii) bromoacetic acid, DIC, DMF, r.t., 0.5 h; (iv) primary amines, DMF, r.t., 1 h; (v) **3f**, DIC, DMF, r.t., 4 h; (vi) amino acid, HOBt, DIC, DMF, r.t., 4 h; (vii) PMe_3 in THF/1 M HCl, r.t., 5 min; (viii) 33% HFIP in DCM, r.t., 2 × 1 h.

propanol (HFIP) in dichloromethane, the successful synthesis was confirmed by LC-MS and ESI-MS.

In conclusion, a novel multifunctional aryl azide was efficiently synthesised in a one-pot reaction from a commercially available pararosanine base. Thereby, a new strategy for protecting thiols in peptoid synthesis with the aryl azide **1** was established, for which deprotection can be accomplished by a Staudinger reduction under acid catalysis. Moreover, the spacious aryl azide can be functionalised by cycloaddition reaction, which provides additional options for use in materials chemistry.

Conflicts of interest

No conflicts of interest to declare.

Acknowledgements

The authors acknowledge the support of the China Scholarship Council (CSC grant: 202010190002) and the Deutsche Forschungsgemeinschaft (DFG) under Germany's Excellence Strategy – 3DMM20 – EXC-2082/1–390761711. We thank the technical and analytical staff at IOC (KIT) for their assistance.

Notes and references

- 1 N. Z. Fantoni, A. H. El-Sagheer and T. Brown, *Chem. Rev.*, 2021, **121**, 7122–7154.
- 2 M. J. Arévalo, Ó. López and M. V. Gil, in *Click Reactions in Organic Synthesis*, 2016, ch. 3, pp. 77–97, DOI: [10.1002/9783527694174](https://doi.org/10.1002/9783527694174).
- 3 J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302–1315.
- 4 M. Liu and O. Reiser, *Org. Lett.*, 2011, **13**, 1102–1105.
- 5 J.-A. Shin, Y.-G. Lim and K.-H. Lee, *J. Org. Chem.*, 2012, **77**, 4117–4122.
- 6 T. Schröder, M. Gartner, T. Grab and S. Bräse, *Org. Biomol. Chem.*, 2007, **5**, 2767–2769.
- 7 C. Bednarek, I. Wehl, N. Jung, U. Schepers and S. Bräse, *Chem. Rev.*, 2020, **120**, 4301–4354.
- 8 F. L. Lin, H. M. Hoyt, H. van Halbeek, R. G. Bergman and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2005, **127**, 2686–2695.
- 9 I. Currie and B. E. Sleebs, *Org. Lett.*, 2021, **23**, 464–468.
- 10 D. C. Lenstra, J. J. Wolf and J. Mecnović, *J. Org. Chem.*, 2019, **84**, 6536–6545.
- 11 J. Xiong, X. Wei, Z.-M. Liu and M.-W. Ding, *J. Org. Chem.*, 2017, **82**, 13735–13739.

- 12 C. I. Schilling, N. Jung, M. Biskup, U. Schepers and S. Bräse, *Chem. Soc. Rev.*, 2011, **40**, 4840–4871.
- 13 D. Intrieri, P. Zardi, A. Caselli and E. Gallo, *Chem. Commun.*, 2014, **50**, 11440–11453.
- 14 Y.-D. Du, C.-Y. Zhou, W.-P. To, H.-X. Wang and C.-M. Che, *Chem. Sci.*, 2020, **11**, 4680–4686.
- 15 T. Uchida and T. Katsuki, *Chem. Rec.*, 2014, **14**, 117–129.
- 16 K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040–1052.
- 17 S. Bräse and K. Banert, *Organic Azides: Syntheses and Applications*, John Wiley & Sons, 2010.
- 18 S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188–5240.
- 19 J. C. Jewett and C. R. Bertozzi, *Chem. Soc. Rev.*, 2010, **39**, 1272–1279.
- 20 S. Pothukanuri and N. Winssinger, *Org. Lett.*, 2007, **9**, 2223–2225.
- 21 H. Hayashi, A. Kaga and S. Chiba, *J. Org. Chem.*, 2017, **82**, 11981–11989.
- 22 S.-H. Hwang, H. Kim, H. Ryu, I. E. Serdiuk, D. Lee and T.-L. Choi, *J. Am. Chem. Soc.*, 2021, **144**(4), 1778–1785.
- 23 M. Schock and S. Bräse, *Molecules*, 2020, **25**, 1009.
- 24 S. Xie, M. Sundhoro, K. N. Houk and M. Yan, *Acc. Chem. Res.*, 2020, **53**, 937–948.
- 25 D. D. Díaz, K. Rajagopal, E. Strable, J. Schneider and M. G. Finn, *J. Am. Chem. Soc.*, 2006, **128**, 6056–6057.
- 26 K. Hema and K. M. Sureshan, *Acc. Chem. Res.*, 2019, **52**, 3149–3163.
- 27 T. Kakuta, T. Yamagishi and T. Ogoshi, *Chem. Commun.*, 2017, **53**, 5250–5266.
- 28 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.
- 29 M. J. Kim, S. Ahn, J. Yi, J. T. Hupp, J. M. Notestein, O. K. Farha and S. J. Lee, *Catal. Sci. Technol.*, 2017, **7**, 4351–4354.
- 30 L. Li, H. Zhao, J. Wang and R. Wang, *ACS Nano*, 2014, **8**, 5352–5364.
- 31 P. Pandey, O. K. Farha, A. M. Spokoyny, C. A. Mirkin, M. G. Kanatzidis, J. T. Hupp and S. T. Nguyen, *J. Mater. Chem.*, 2011, **21**, 1700–1703.
- 32 L. Monnereau, T. Muller, M. Lang and S. Bräse, *Chem. Commun.*, 2016, **52**, 571–574.
- 33 H. Zhong, C. Liu, Y. Wang, R. Wang and M. Hong, *Chem. Sci.*, 2016, **7**, 2188–2194.
- 34 T. Muller and S. Bräse, *Angew. Chem., Int. Ed.*, 2011, **50**, 11844–11845.
- 35 P. Lindemann, M. Tsotsalas, S. Shishatskiy, V. Abetz, P. Krolla-Sidenstein, C. Azucena, L. Monnereau, A. Beyer, A. Götzhäuser, V. Mugnaini, H. Gliemann, S. Bräse and C. Wöll, *Chem. Mater.*, 2014, **26**, 7189–7193.
- 36 V. Castro, H. Rodríguez and F. Albericio, *ACS Comb. Sci.*, 2016, **18**, 1–14.
- 37 C. M. Nimmo and M. S. Shoichet, *Bioconjugate Chem.*, 2011, **22**, 2199–2209.
- 38 N. Moini, M. J. Zohuriaan-Mehr, K. Kabiri and H. A. Khonakdar, *Appl. Surf. Sci.*, 2019, **487**, 1131–1144.
- 39 I. Wilkening, G. d. Signore and C. P. R. Hackenberger, *Chem. Commun.*, 2011, **47**, 349–351.
- 40 T. Meguro, N. Terashima, H. Ito, Y. Koike, I. Kii, S. Yoshida and T. Hosoya, *Chem. Commun.*, 2018, **54**, 7904–7907.
- 41 M. Sundhoro, S. Jeon, J. Park, O. Ramström and M. Yan, *Angew. Chem., Int. Ed.*, 2017, **56**, 12117–12121.
- 42 R. J. Griffin, E. Evers, R. Davison, A. E. Gibson, D. Layton and W. J. Irwin, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1205–1211, DOI: [10.1039/P19960001205](https://doi.org/10.1039/P19960001205).
- 43 B. Lukasak, K. Morihito and A. Deiters, *Sci. Rep.*, 2019, **9**, 1470.
- 44 K. V. Kutonova, M. E. Trusova, P. S. Postnikov, V. D. Filimonov and J. Parello, *Synthesis*, 2013, **45**, 2706–2710.
- 45 R. J. Spears, C. McMahon and V. Chudasama, *Chem. Soc. Rev.*, 2021, **50**, 11098–11155.

