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Modular synthesis of triazoles from 2-azidoacrylamides having a nucleophilic amino group[†]

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Assembling methods using 2-azidoacrylamides having a nucleophilic amino group are disclosed.

Divergent transformations of the amine-type trivalent platform were accomplished with a wide variety of

electrophiles to obtain a broad range of 2-azidoacrylamides involving a fluorosulfonyl group-containing

trivalent platform. Consecutive click conjugations including triazole formation, thiol-ene-type 1,4-

addition, and SuFEx reactions realized the efficient assembly of easily available simple modules.

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Introduction

Facile methods to assemble simple modules onto platform molecules having a number of functional groups for click chemistry are of great significance for the preparation of multifunctional compounds in broad research fields such as pharmaceutical science and chemical biology.^{1–4} Since click reactions have been in the construction of a vast chemical library and in the synthesis of chemical probes bearing reporter groups, various trivalent platform molecules for consecutive click reactions have been developed so far and an efficient consecutive click assembly using compact platforms is awaited (Fig. 1A).^{5,6}

We recently succeeded in the synthesis of 2-azidoacrylamides **1** bearing an alkyne or a tertiary azido moiety as compact trivalent platforms (Fig. 1B).^{6d} While 1,4-adducts were not obtained when nucleophiles including thiols and amines were treated with 2-azidoacrylamides **1**, 1,4-addition of nucleophiles proceeded efficiently using 2-(1,2,3-triazol-1-yl)acrylamides **2** synthesized from azides **1** by the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction with alkynes, clearly showing increased electrophilicity by triazole formation. We herein designed a compact 2-azidoacrylamide platform **5** possessing a sulfonyl fluoride moiety for the sulfur(vı) fluoride exchange (SuFEx) reaction, which is an emerging click reaction^{7,8} (Fig. 1C). To achieve the synthesis of trivalent platform 5, we conceived a challenging and efficient synthetic route by hydroamination of ethenesulfonyl fluoride $(4)^9$ with biphilic 2-azidoacrylamides 3 having an electrophilic *exo*methylene moiety and a nucleophilic free-amino group, paying attention to the inferior electrophilicity of 2-azidoacrylamides 1 compared to that of triazole-substituted acrylamides 2. Since diverse transformations using a free amino group have been established so far, we also expected that amine-type platform 3 can serve as a useful platform to assemble simple modules.

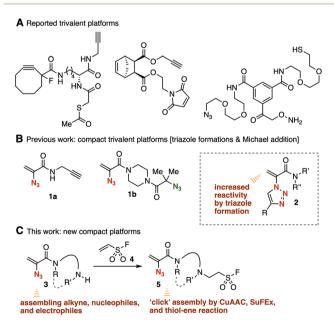


Fig. 1 (A) Trivalent platform molecules. (B) Previous study. (C) This work.

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Results and discussion

Synthesis of 2-azidoacrylamides having free amino groups

First, we succeeded in the synthesis of 2-azidoacrylamide **3a** having a free secondary amino group (Fig. 2A). Treatment of 2-acrylamide **6a** with trifluoroacetic acid in dichloromethane efficiently provided amine **3a** after aqueous workup under basic conditions. Although gradual decomposition of amine **3a** was observed at room temperature under argon, we fortunately isolated **3a** with good purity after the aqueous workup without further purification.¹⁰

A wide range of amines **3b–3e** bearing 2-azidoacrylamide moieties were prepared from 2-azidoacrylic acid (7) and amines having *tert*-butoxycarbonyl (Boc) amide moieties in good yields (Fig. 2B). For example, tertiary amide **3b** possessing a primary amino group was synthesized through condensation with 4-(*tert*-butoxycarbonylamino)piperizine using PyBOP¹¹ followed by the treatment with trifluoroacetic acid in high yield. The synthesis of secondary amides **3c** and **3d** having a primary amino group was achieved. We found that gradual decomposition of primary amine **3d** occurred at room temperature under argon,¹² showing similar stability to secondary amine **3a**. Also, acrylanilide **3e** was synthesized *via* the condensation between 2-azidoacrylic acid (7) and 4-(*tert*-butoxycarbonylamino)aniline in moderate yield.

Transformations of 2-azidoacrylamides having free amino groups

Transformations of amine **3a** with various electrophiles enabled us to synthesize a broad range of 2-azidoacrylamides

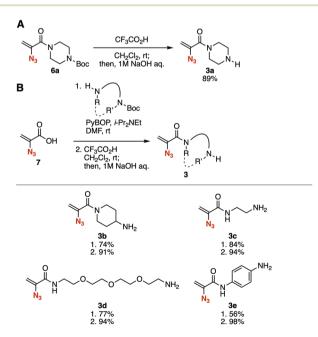


Fig. 2Synthesis of amines 3. (A) Deprotection of the Boc moiety of 6a.(B) Synthesis of various amines 3 from 2-azidoacrylic acid (7). PyBOP =(benzotriazol-1-yloxy)(trispyrrolidino)phosphoniumhexafluorophosphoniumsphate. See the ESI† for details.

9a-9i in moderate to good yields (Fig. 3). We accomplished the acetylation of amine 3a with acetic anhydride to provide amide 9a in good yield. Synthesis of amide 9b was achieved by the condensation between amine 3a and carboxylic acid 8b using PyBOP without damaging the 2-azidoacrylic amide moiety. Carbamate 9c was successfully prepared from amine 3a and isocyanate 8c under basic conditions. We also succeeded in the guanidination of amine 3a with 1-amidinopyrazole hydrochloride (8d) yielding guanidine 9d quantitatively. Sulfonamide 9e was also prepared from amine 3a using sulfonyl chloride 8e. Triazination of amine 3a with cyanuric chloride (8f) proceeded smoothly to provide triazine 9f in moderate yield. Also, we synthesized amine 9g by the reductive amination of amine 3a with aldehyde 8g using sodium triacetoxyborohydride as a reductant leaving the electrophilic 2-azidoacrylic amide moiety untouched. Arylation of amine 3a with benzyne generated in situ from o-silylphenyl triflate 8h keeping

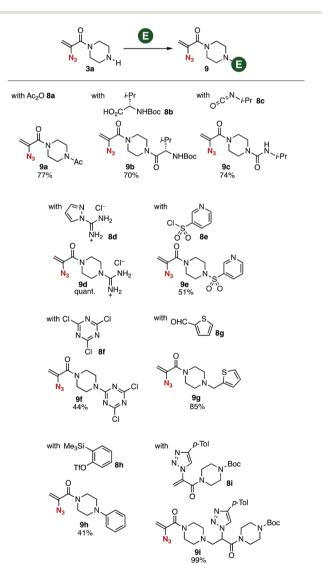


Fig. 3 Synthesis of various 2-azidoacrylamides 9. See the ESI † for details.

the azido group unreacted, although azides generally react with benzyne to afford benzotriazoles.¹³ Furthermore, we realized the 1,4-addition of amine **3a** with 2-(triazolyl)acrylamide **8i**, which was prepared from 1-(2-azidoacryl)-4-(*tert*-butoxycarbonyl)piperazine (**6a**) and 4-tolylacetylene by the CuAAC reaction¹⁴ in our previous study.^{6d} This result clearly showed that a wide variety of 2-azidoacrylamides can be prepared by sequential transformations using 2-azidoacrylamide-type platforms and alkynes in a modular synthetic manner.

Subsequent transformations of 2-azidoacrylamides **9** led to the efficient assembly of simple modules (Fig. 4). The CuAAC reaction of azide **9g** with alkyne **10a** efficiently took place affording **1**,2,3-triazole **11** in a quantitative yield. We then achieved the synthesis of amine **13** by the **1**,4-addition of 2-(triazolyl)acrylamide **11** with *n*-butylamine (**12**) in high yield. These results indicated that diverse 2-(triazolyl)acrylamides can be synthesized from 2-azidoacrylamide **3a**, electrophiles, alkynes, and nucleophiles in three steps.

Synthesis of 2-azidoacrylamides having sulfonyl fluoride moieties

The conjugate addition of amines with ethenesulfonyl fluoride (4) realized the preparation of novel trivalent platforms having an azido, an alkene, and a sulfonyl fluoride group (Fig. 5). Treatment of amine 3a with 4 in the presence of triethylamine provided trivalent platform 5a in an excellent yield leaving three clickable functional groups intact (Fig. 5A). We also accomplished the synthesis of dialkylated amine 5b from primary amine 3d with 4 in moderate yield (Fig. 5B). These

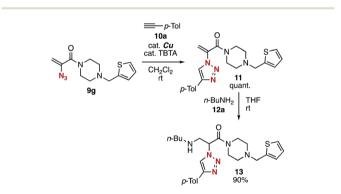


Fig. 4 Synthesis of 2-(triazolyl)amide **13**. TBTA = tris((1-benzyl-4-triazolyl)methyl)amine. See the ESI† for details.

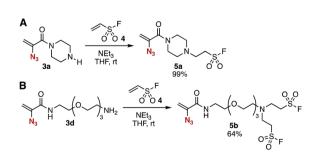


Fig. 5 Synthesis of sulfonyl fluorides 5. (A) Synthesis of 5a. (B) Synthesis of 5b.

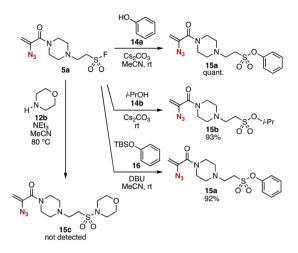


Fig. 6 SuFEx reactions of 5a. See the ESI† for details.

results suggested that amine-type trivalent platforms will help in the synthesis of a wide variety of clickable platform molecules with electrophiles bearing functional groups for the click chemistry despite the poor stability of amines **3**.

We succeeded in the synthesis of various 2-azidoacrylamides by the SuFEx reactions of sulfonyl fluoride **5a** (Fig. 6).^{7,8} For example, sulfonyl fluoride **5a** efficiently reacted with phenol (**14a**) under basic conditions to furnish phenyl sulfonate **15a** quantitatively without reacting with the 2-azidoacrylamide moiety. Treatment of sulfonyl fluoride **5a** with cesium carbonate in 2-propanol (**14b**) afforded isopropyl sulfonate **15b** in high yield. We also achieved the synthesis of phenyl sulfonate **15a** by the reaction of silyl ether **16** in the presence of **1**,8diazabicyclo[5.4.0]undec-7-ene (DBU) keeping the electrophilic 2-azidoacrylamide moiety unreacted. Unfortunately, synthesizing sulfonyl amide **15c** from sulfonyl fluoride **5a** and amine **12b** resulted in failure probably due to undesired side reactions such as **1**,4-addition.

Sequential conjugation using trivalent platform 5a

Sequential conjugation of trivalent platform **5a** was achieved with alkyne **10a** and amine **12a** to provide 3-amino-2-triazolyl amide **18** having the sulfonyl fluoride moiety (Fig. 7). Indeed,

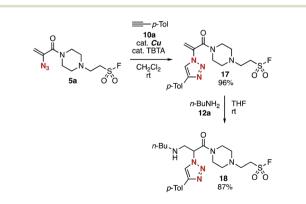


Fig. 7 Modular synthesis of 18.

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triazole formation of azide **5a** with alkyne **10a** catalyzed by tetrakis(acetonitrile)copper and TBTA occurred smoothly to yield **17** in an excellent yield. Then, we successfully prepared amine **18** by efficient conjugate addition using *n*-butylamine (**12a**) at room temperature without damaging the amine-susceptive fluorosulfonyl group. These results clearly showed that the 2-azidoacrylamide moiety can react with alkynes and nucleophiles prior to the SuFEx reaction.

The successful synthesis of 2-triazolylamide **21** by three component assembly indicated the good diversifiable reactivity of trivalent platform **5a** (Fig. 8). The CuAAC reaction of phenyl sulfonate **15a** followed by the thiol–ene reaction¹⁵ with **20** promoted by a base took place efficiently to provide 2-triazolylamide **21** in high yield (Fig. 8A). Moreover, the three component assembly onto platform **5a** with phenol (**14a**), alkyne **10a**, and

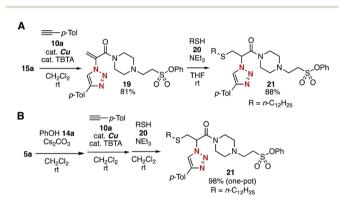


Fig. 8 Modular synthesis of 21. (A) Synthesis of 21 *via* isolated intermediates. (B) One-pot synthesis of 21 from 5a.

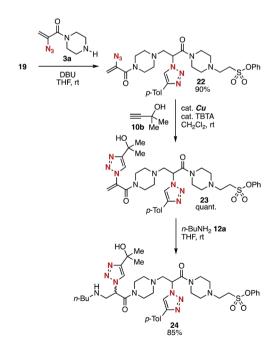


Fig. 9 Modular synthesis of multi(triazole) 24.

thiol **20** was achieved by the consecutive click reactions in a one-pot fashion (Fig. 8B).

Synthesis of bis(triazole) 24

To showcase the divergent potential of platforms 3 and 5, we then examined a synthesis of diamide 24 from simple modules (Fig. 9). First, the treatment of amine-type platform 3a with 2-(triazolyl)acrylamide 19 synthesized from trivalent platform 5a, silvl ether 16, and alkyne 10a provided diamide 22 in good yield. Second, CuAAC reaction of diamide 22 proceeded smoothly without damaging amino, triazolyl, and phenoxysulfonyl groups. Third, amine 24 was synthesized efficiently as a mixture of diastereomers by the conjugate addition of n-butylamine (12a) with 2-(triazolyl)acrylamide 23. The good reactivity of 2-(triazolyl)acrylamide 23 as a Michael acceptor will allow us to repeat the conjugation using amine-type platforms 3 to synthesize multi(triazole)s in an iterative manner. Diamide 24 was prepared from trivalent platforms 3a and 5a, alkynes 10a and 10b, amine 12a, and silyl ether 16 in 5 steps. Since alkynes, phenols, silvl ethers, and nucleophiles for 1,4addition are easily available, the efficient modular synthetic method will be used for synthesizing diverse multi(triazole)s in an iterative manner from simple modules.

Conclusions

In summary, we synthesized novel trivalent platforms 5 having azido, alkene, and fluorosulfonyl groups through 2-azidoacrylamides having a free amino group. A wide variety of triazoles were synthesized from trivalent platforms 5 and simple modules by click reactions. Since diverse multi(triazole)s can be prepared in a modular synthetic manner, the combinatorial chemistry using trivalent platforms will be used in constructing a vast chemical library of mid-sized multi(triazole)s. Further studies on the transformations of trivalent platforms 3 and 5 involving the scope and limitations are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- 1 J. Lahann, *Click Chemistry for Biotechnology and Materials Science*, John Wiley & Sons, West Sussex, 2009.
- 2 For reviews of sequential click reactions, see: (a) A.-C. Knall and C. Slugovc, *Chem. Soc. Rev.*, 2013, 42, 5131;
 (b) Z.-J. Zheng, D. Wang, Z. Xu and L.-W. Xu, *Beilstein J. Org. Chem.*, 2015, 11, 2557; (c) S. Yoshida, *Org. Biomol. Chem.*, 2020, 18, 1550; (d) D. Sato, Z. Wu, H. Fujita, J. S. Lindsey, D. Sato, Z. Wu, H. Fujita and J. S. Lindsey, *Organics*, 2021, 2, 161.
- 3 For recent examples of sequential click reactions, see: (a) I. E. Valverde, A. F. Delmas and V. Aucagne, Tetrahedron, 2009, 65, 7597; (b) B. C. Sanders, F. Friscourt, P. A. Ledin, N. E. Mbua, S. Arumugam, J. Guo, T. J. Boltje, V. V. Popik and G.-J. Boons, J. Am. Chem. Soc., 2011, 133, 949; (c) J. Dommerholt, O. van Rooijen, A. Borrmann, C. F. Guerra, F. M. Bickelhaupt and F. L. van Delft, Nat. Commun., 2014, 5, 5378; (d) P. R. Werkhoven, H. van de Langemheen, S. van der Wal, J. A. W. Kruijtzer and R. M. J. Liskamp, J. Pept. Sci., 2014, 20, 235; (e) M. Robert, J. Vallée, P. Majkut, D. Krause, M. Gerrits and C. P. R. Hackenberger, Chem. - Eur. J., 2015, 21, 970; (f) R. R. Ramsubhag and G. B. Dudley, Org. Biomol. Chem., 2016, 14, 5028; (g) D. A. Sutton, S.-H. Yu, R. Steet and V. V. Popik, Chem. Commun., 2016, 52, 553; (h) N. Münster, P. Nikodemiak and U. Koert, Org. Lett., 2016, 18, 4296; (i) D. Svatunek, N. Houszka, T. A. Hamlin, F. M. Bickelhaupt and H. Mikula, Chem. - Eur. J., 2019, 25, 754.
- 4 For our recent studies on click chemistry, see:
 (a) S. Yoshida, T. Kuribara, H. Ito, T. Meguro, Y. Nishiyama,
 F. Karaki, Y. Hatakeyama, Y. Koike, I. Kii and T. Hosoya, *Chem. Commun.*, 2019, 55, 3556; (b) K. Adachi, T. Meguro,
 Y. Sakata, K. Igawa, K. Tomooka, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, 56, 9823; (c) N. Makio, T. Kuribara,
 K. Adachi, Y. Hatakeyama, T. Meguro, Y. Sakata, K. Igawa,
 K. Tomooka, T. Hosoya and S. Yoshida, *Chem. Commun.*,
 2020, 56, 11449; and references therein.
- 5 For recent examples of sequential click reactions using trivalent platforms, see: (a) V. Vaněk, J. Pícha, B. Fabre, M. Buděšínský, M. Lepšík and J. Jiráček, Eur. J. Org. Chem., 2015, 3689; (b) B. Fabre, J. Pícha, V. Vaněk, M. Buděšínský and J. Jiráček, Molecules, 2015, 20, 19310; (c) B. Fabre, J. Pícha, V. Vaněk, I. Selicharová, M. Chrudinová, M. Collinsová, L. Žáková, M. Buděšínský and J. Jiráček, ACS Comb. Sci., 2016, 18, 710; (d) A.-C. Knall, M. Hollauf, R. Saf and C. Slugovc, Org. Biomol. Chem., 2016, 14, 10576; (e) T. Yokoi, H. Tanimoto, T. Ueda, T. Morimoto and K. Kakiuchi, J. Org. Chem., 2018, 83, 12103; (f) T. Yokoi, T. Ueda, H. Tanimoto, T. Morimoto and K. Kakiuchi, Chem. Commun., 2019, 55, 1891; (g) K. Maegawa, H. Tanimoto, S. Onishi, T. Tomohiro, T. Morimoto and K. Kakiuchi, Org. Chem. Front., 2021, 8, 5793.
- 6 For our recent studies on sequential click reactions using trior tetravalent platforms, see: (a) T. Meguro, Y. Sakata, T. Morita, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020,

56, 4720; (*b*) N. Terashima, Y. Sakata, T. Meguro, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 14003; (*c*) H. Takemura, S. Goto, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 15541; (*d*) S. Yoshida, Y. Sakata, Y. Misawa, T. Morita, T. Kuribara, H. Ito, Y. Koike, I. Kii and T. Hosoya, *Chem. Commun.*, 2021, **57**, 899; and references therein.

- 7 For reviews of the SuFEx chemistry, see: (a) J. Dong, L. Krasnova, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2014, 53, 9430; (b) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dongd and J. E. Moses, *Chem. Soc. Rev.*, 2019, 48, 4731; (c) Y.-P. Meng, S.-M. Wang, W.-Y. Fang, Z.-Z. Xie, J. Leng, H. Alsulami and H.-L. Qin, *Synthesis*, 2020, 673.
- 8 For recent examples of the SuFEx chemistry, see: (a) R. Zelli, S. Tommasone, P. Dumy, A. Marra and A. Dondoni, Eur. J. Org. Chem., 2016, 5102; (b) Q. Chen, P. Mayer and H. Mayr, Angew. Chem., Int. Ed., 2016, 55, 12664; (c) H.-L. Qin, Q. Zheng, G. A. L. Bare, P. Wu and K. B. Sharpless, Angew. Chem., Int. Ed., 2016, 55, 14155; (d) O. Zheng, J. Dong and K. B. Sharpless, J. Org. Chem., 2016, 81, 11360; (e) X. Chen, G.-F. Zha, G. A. L. Bare, J. Leng, S.-M. Wang and H.-L. Qin, Adv. Synth. Catal., 2017, 359, 3254; (f) H. Wang, F. Zhou, G. Ren, Q. Zheng, H. Chen, B. Gao, L. Klivansky, Y. Liu, B. Wu, Q. Xu, J. Lu, K. B. Sharpless and P. Wu, Angew. Chem., Int. Ed., 2017, 56, 11203; (g) J. Leng and H.-L. Qin, Chem. Commun., 2018, 54, 4477; (h) C. J. Smedley, M.-C. Giel, A. Molino, A. S. Barrow, D. J. D. Wilson and J. E. Moses, Chem. Commun., 2018, 54, 6020; (i) D. Gahtory, R. Sen, S. Pujari, S. Li, Q. Zheng, J. E. Moses, K. B. Sharpless and H. Zuilhof, Chem. - Eur. J., 2018, 24, 10550; (j) J. Thomas and V. V. Fokin, Org. Lett., 2018, 20, 3749; (k) X. Zhang, B. Moku, J. Leng, K. P. Rakesh and H.-L. Qin, Eur. J. Org. Chem., 2019, 1763; (l) C. Li, Y. Zheng, K. P. Rakesh and H.-L. Qin, Chem. Commun., 2020, 56, 8075; (m) M.-C. Giel, C. J. Smedley, E. R. R. Mackie, T. Guo, J. Dong, T. P. Soares da Costa and J. E. Moses, Angew. Chem., Int. Ed., 2020, 59, 1181; (n) S. Li, G. Li, B. Gao, S. P. Pujari, X. Chen, H. Kim, F. Zhou, L. M. Klivansky, Y. Liu, H. Driss, D.-D. Liang, J. Lu, P. Wu, H. Zuilhof, J. Moses and K. B. Sharpless, Nat. Chem., 2021, 13, 858.
- 9 (a) B. M. Gladshtein, E. I. Polyanskaya and L. Z. Soborovskii, *Zh. Obshch. Khim.*, 1961, 31, 855;
 (b) J. A. Hyatt and J. J. Krutak, *J. Org. Chem.*, 1977, 42, 169.
- 10 When **3a** was placed at room temperature under argon for 3 days, we observed that 65% of **3a** was decomposed.
- 11 J. Coste, D. Le-Nguyen and B. Castro, *Tetrahedron Lett.*, 1990, 31, 205.
- 12 When **3d** was placed at room temperature under argon for 3 days, we observed that 66% of **3d** was decomposed.
- 13 F. Shi, J. P. Waldo, Y. Chen and R. C. Larock, *Org. Lett.*, 2008, **10**, 2409.
- 14 (a) C. W. Tornøe, C. Christensen and M. Meldal, J. Org. Chem., 2002, 67, 3057; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, Angew. Chem., Int. Ed., 2002, 41, 2596; (c) T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, Org. Lett., 2004, 6, 2853.
- 15 A. B. Lowe, Polym. Chem., 2014, 5, 4820.