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Synthesis of azide-alkyne fragments for 'click' chemical applications; formation of oligomers from orthogonally protected trialkylsilyl-propargyl azides and propargyl alcohols

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Abstract—A series of orthogonally protected 1,4-disubstituted-1,2,3-triazoles were prepared from the corresponding alkynols and trialkylsilyl-propargyl azides via 1,3-dipolar cycloaddition. These cycloadducts were selectively deprotected and extended in a stepwise fashion via further 'click' reactions to form oligomeric peptidomimetic compounds. This methodology gives access to triazole-based peptidomimetics in a controlled fashion and lays the foundation for a fragment-based approach to drug discovery.

Protein–protein interactions are increasingly recognised as important therapeutic targets due to their involvement in essential biological pathways.[1] Progress in this area of drug discovery has been slow as these interactions are hard to target with small molecules because the domain in which the inhibitor binds, usually via hydrophobic interactions, is often large, shallow and less defined. These challenges have led to the development of novel methods for making small molecule inhibitors of protein–protein interactions. Amongst the concepts developed, fragment-based drug discovery is particularly attractive.[2] Drug identification can be improved via the use of 'fragments' that, when used independently, have lower activity and affinity for binding sites, but when appropriately linked give significantly enhanced activity.[3] Several strategies can be implemented to screen for useful fragments: NMR,[4] X-ray crystallography[5] and tethering.[6]

Another potentially powerful fragment-based method used in the search for drug hits relies on fragments reacting in situ to form privileged high affinity binders. This technique depends on a specific linking reaction that can proceed in excellent yields under biologically compatible conditions. The 1,3-dipolar cycloaddition (1,3-DC) of azides and alkynes, as described by Sharpless and coworkers, is an example of such a reaction.[7] It has been applied to biological targets such as an acetylcholinesterase (AchE) inhibitor[8,9] and a carbonic anhydrase II inhibitor.[10]

Recently, Angelo and Arora[11] described the synthesis of novel triazole oligomers derived from α-amino acids using an iterative reaction sequence. They prepared chiral azides and alkynes from α-amino acid esters and combined them via cycloaddition and azide formation reactions to prepare triazole oligomers with four R groups or side-chains. Independently, we devised an alternative fragment-based approach to these non-peptidic oligomers that provided for an increased range of R groups and the ability to extend the oligomer in either direction through orthogonal protection of the two termini. We now wish to report the results of these studies.

In planning the synthesis of triazole oligomers we wanted to prepare fragments with the attributes of amino acids in regard to side-chain structural diversity and the possibility of peptidomimetic assemblage but without the labile amide bond (Scheme 1). Azido-alkynes met these criteria but before undertaking any biologically relevant experiments, several questions had to be addressed: Can the fragment be prepared? Can the

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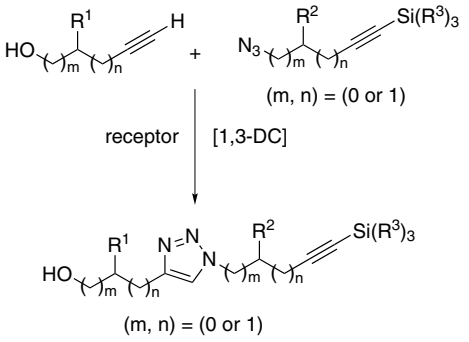


Scheme 1.

fragment be orthogonally protected in a fashion similar to amino acids? Can a sequential approach be followed to form an oligomeric (peptidomimetic) chain?

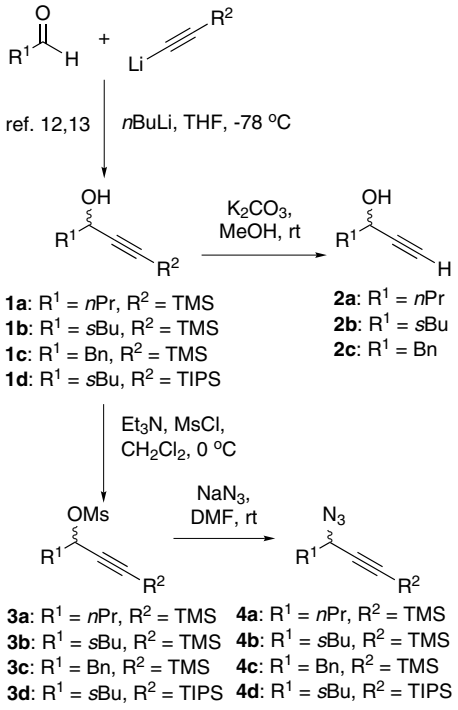
This report is focussed on answering the questions posed above using fragments where $n = 0$, $m = 0$ (Scheme 1). The preparation of fragments and their use in forming triazole oligomers is presented.

The initial plan involved use of aldehydes to form trimethylsilyl propargylic alcohols, based on several factors: a large number of aldehydes are commercially available with side-chains constituting the 'residue' of the azido-alkyne fragment. Further, there is also a significant body of literature on alkyne additions to aldehydes,[12] including enantioselective reactions.[13] It was thought that hydroxyl groups could represent a latent azide since the latter can be obtained in one step from the OH group or the hydroxyl group can be activated for subsequent azide substitution.

The trialkylsilyl-protected propargyl alcohols **1a–d** (Scheme 2) (Table 1) were generated in 86–100% yields by addition of lithiotrimethylsilylacetylide to aldehydes. The alkynols were then deprotected by exposure to K_2CO_3 in methanol, generating the free alkynes **2a–c** in 67–75% yields. It was found that fragments with a molecular weight of ~100–150 were volatile and thus gave lower isolated yields. The alkynols **2a–c**, as the triple bond partners of the 1,3-DC, were subsequently used for the generation of the triazole oligomeric chains.

Alternatively, exposure of the protected propargyl alcohols to methanesulfonyl chloride in the presence of triethylamine gave the mesylates **3a–d** in 76–92% yields. These mesylates were then treated with sodium azide in DMF to give the azides **4a–d** in 70–87% yields. This azide displacement was found to proceed readily, and was complete within 1–2 h at ambient temperature. The azides **4a–d** have the latent reactive alkyne that was required for iterative extension of the triazolic chain.

With the two partners for the 1,3-DC in hand, we sought to optimise the reaction conditions for reactants **2b** and **4b** (Table 2). In general, it was found that the reaction gave the best yields when conducted in the presence of H_2O as co-solvent (entries 6–11).



Scheme 2.

Table 1. Synthesis of alkynols and azido-alkynes

Entry	R^1	R^2	Product (%)			
1	*n*Pr	$SiMe_3$	**1a** (97)	**2a** (–)[a]	**3a** (92)	**4a** (70)
2	*s*Bu	$SiMe_3$	**1b** (86)	**2b** (67)	**3b** (89)	**4b** (85)
3	Bn	$SiMe_3$	**1c** (86)	**2c** (75)	**3c** (76)	**4c** (87)
4	*s*Bu	Si^iPr_3	**1d** (100)	—	**3d** (90)	**4d** (80)

[a] Yield was not recorded as the product is highly volatile.

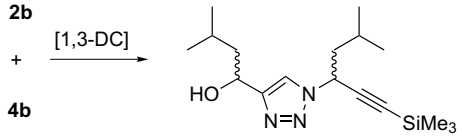
A range of fragments were then subjected to the conditions described in entry 8 (Table 2) to provide a series of 1,4-disubstituted-1,2,3-triazoles **5a–j** (Table 3).

It can be seen that as the molecular weight of the fragment increases, so does the yield of the cycloadduct, most likely due to the volatility of the unprotected alkynols **2a** and **2b**.

It was also found (via mass spectrometry) that a small amount of the dimeric cycloadduct **5** was being desilylated and was then participating in a further 1,3-DC reaction to generate a range of trimeric cycloadducts. Attempts to prevent trialkylsilyl deprotection and subsequent trimer formation led to the use of $Cu^{(0)}$ powder in a 1:2 mixture of tBuOH:H_2O. These conditions not only arrested the deprotection and trimer formation, but they also improved the yield of the cycloaddition (76%) (Table 2, entry 11). These final improvements confirmed that the problem of orthogonal protection had been solved.

Attempts were then made to generate higher order cycloadducts via a sequential process (Scheme 3). We decided to extend in the alkyne direction, as trialkylsilyl deprotection requires simple conditions, is a clean

Table 2. Optimisation studies for the 1,3-DC between azide **4b** and alkyne **2b**



5e

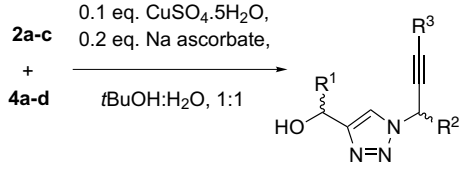
Entry	Ratio **2b**/**4b**	Reagents (equiv)	Solvent	T (h)	Yield (%)
1	1	—	Et_2O	15	—
2	1	CuI (2) DIPEA (5)	THF	21	—
3	1	CuI (2) DIPEA (2)	MeOH	31	—
4	1	CuI (1) DIPEA (1.1)	CH_2Cl_2	18	41
5	1	$CuSO_4{\cdot}5H_2O$ (0.1) Na asc.[a] (0.2)	MeCN	78	<10
6	1	$CuSO_4{\cdot}5H_2O$ (0.5) Na asc.[a] (1)	*t*BuOH:H_2O 1:1	22	37
7	1	$CuSO_4{\cdot}5H_2O$ (0.1) Na asc.[a] (0.2)	*t*BuOH:H_2O 1:1	17	50
8	1	$CuSO_4{\cdot}5H_2O$ (0.1) Na asc.[a] (0.2)	*t*BuOH:H_2O 1:1	19	62
9	1	$Cu^{(0)}$ (2) 0.5 mM $CuSO_4$ (0.01)	*t*BuOH:H_2O 1:1	25	57
10	0.5	Cu triflate (0.1) Na asc.[a] (0.2)	*t*BuOH:H_2O 1:1	21	46
11	1	$Cu^{(0)}$ (xs)	*t*BuOH:H_2O 1:2	18	76

[a] Sodium ascorbate.

reaction and applies to a range of structures. The cycloadduct **5e** was deprotected with potassium carbonate in methanol (92% yield) and then subjected to the latter optimum conditions (Table 2, entry 11). 1,3-DC conditions with compound **4b** gave a trimeric compound **7** (76% yield). Repeating this sequence afforded the acetylene **8** (100%) and then tetrameric compound **9** (73%).

Extending the chain in the other direction was difficult and required more careful conditions. Attempts to mesylate the dimeric cycloadduct failed, so we instead prepared the azido dimer **10** under Mitsunobu conditions

Table 3. 1,3-Dipolar cycloaddition of acetylenes **2a–c** and azides **4a–d** to form triazoles **5a–j**



5a-j

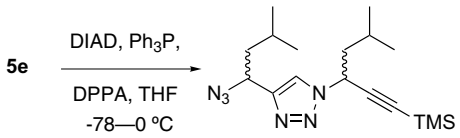
Entry	R^1	R^2	R^3	Time (h)	Product (%)
1	*n*Pr	*n*Pr	TMS	6	**5a** (6)
2	*n*Pr	*s*Bu	TMS	4	**5b** (17)
3	*n*Pr	Bn	TMS	19	**5c** (18)
4	*s*Bu	*n*Pr	TMS	7	**5d** (41)
5	*s*Bu	*s*Bu	TMS	6	**5e** (62)
6	*s*Bu	Bn	TMS	7	**5f** (53)
7	Bn	*n*Pr	TMS	8	**5g** (33)
8	Bn	*s*Bu	TMS	5	**5h** (45)
9	Bn	Bn	TMS	5	**5i** (52)
10	*s*Bu	*s*Bu	TIPS	15	**5j** (71)

in 82% yield (Scheme 4). Compound **10** constitutes the precursor for chain extension from the azide terminus.

Reaction of the propargyl amine carbamate with the azide **4b** gave cycloadduct **11** in 71% yield (Scheme 5). This first 'azide' direction extension is a variation in the reactions of the azides **4** with the alcohols **2** shown in Table 3. In addition, the azide cycloadduct **10** reacts with similar efficiency to give the 'trimeric' cycloadduct **12**.

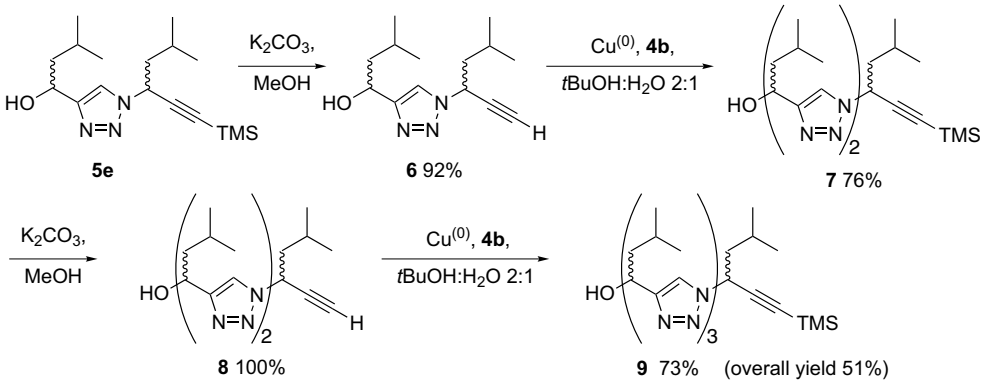
Thus in summary the conditions described afford the possibility to grow the cycloadduct on either side (alkyne or azide/alcohol).

It should be stressed that the adducts **5a–j**, **7**, **9** and **12** in this study were all prepared from compounds **1a–d**

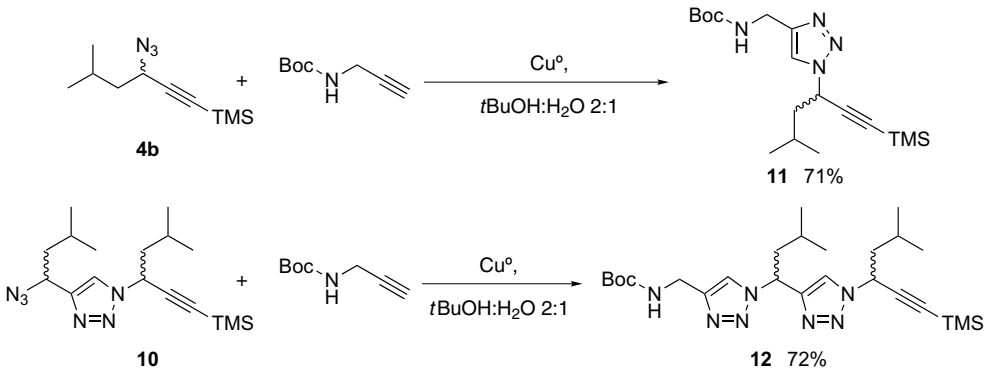


10 82%

Scheme 4. Mitsunobu reaction of **5e** to form azide **10**.



Scheme 3. Generation of triazole oligomers in the 'alkyne' direction.



Scheme 5. Generation of triazole oligomers in the 'azide/alcohol' direction.

(Scheme 1), which are racemic. Thus the adducts are mixtures of diastereomers. There was no evidence of diastereoselection in the formation of the compounds **5a**–**j**, **7**, **9** and **12**. Thus a study of the conformations of these materials was deemed inappropriate and will be addressed in subsequent investigations.

In this account, we have shown that the 1,3-DC-based strategy of selective and efficient construction of higher order cycloadducts is valid. We have also demonstrated that it is possible to do so in a sequential and controlled fashion in either direction (azide or alkyne terminus) where the alcohol and TMS moieties act as precursors/protecting groups for the azide and alkyne reactive groups, respectively. We are confident that the results presented will transpose to chiral substrates. We are currently working on chiral fragments with $n = 0$, $m = 0$ (Scheme 1) and also $n = 1$, $m = 0$ via enantioselective epoxide openings. This will enable access to a broad range of fragments. A full account of this work will be reported in due course. This preliminary study constitutes a promising starting point for our ultimate goal of fragment-based drug discovery.

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References and notes

1. Yin, H.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4130–4163.
2. Erlanson, D. A.; McDowell, R. S.; O'Brien, T. J. *J. Med. Chem.* **2004**, *47*, 3463–3482.
3. Rees, D. C.; Congreve, M.; Murray, C. W.; Carr, R. *Nat. Rev. Drug Disc.* **2004**, *3*, 660–672.
4. Schade, M.; Oschkinat, H. *Curr. Opin. Drug Disc. Dev.* **2005**, *8*, 365–373.
5. Burley, S. K. *Mod. Drug Disc.* **2004**, *7*, 53–56.
6. Erlanson, D. A.; Wells, J. A.; Braisted, A. C. *Annu. Rev. Biophys. Biomol. Struct.* **2004**, *33*, 199–223.
7. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
8. Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053–1057.
9. Manetsch, R.; Krasinski, A.; Radic, Z.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2004**, *126*, 12809–12818.
10. Mocharla, V. P.; Colasson, B.; Lee, L. V.; Röper, S.; Sharpless, K. B.; Wong, C.-H.; Kolb, H. C. *Angew. Chem., Int. Ed.* **2004**, *44*, 116–120.
11. Angelo, N. G.; Arora, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 17134–17135.
12. (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095–4105; (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886.
13. (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605–2606; (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688, and references therein.