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Fluorous click chemistry as a practical tagging method†

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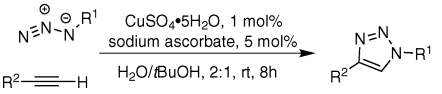
Highly efficient fluorous tagging methodology was developed based on catalytic 1,3-dipolar cycloaddition as the key step.

The unique properties of fluorous compounds, which are a direct consequence of their highly hydrophobic perfluorinated tag, have initiated significant interest in recent years.[1] In this solution-phase tagging approach, a homogeneous catalyst, reagent or scavanger was modified with perfluorinated tags, facilitating its separation from a reaction mixture with fluorous liquid–liquid[2] or solid–liquid[3] extraction.

Although several fluorous compounds (catalysts, ligands and reagents) have been synthesized (and some of them are commercially available), their syntheses are mostly challenging due to cumbersome purification steps. This problem stems from the highly hydrophobic character of the fluorinated tag which markedly changes the molecules' physical (solubility, melting point and boiling point) and chromatographical properties. Therefore, a synthetic route which has several fluorous intermediates should be avoided and, ideally, the attachment of the perfluorinated tag should occur in the very last synthetic step.[4]

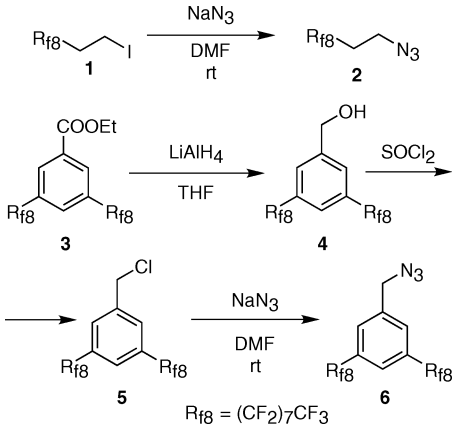
In order to broaden the existing synthetic potential in fluorous chemistry, additional methodologies are required for introducing perfluorinated tags. In theory, this method should (a) result in high yield, (b) utilize mild reaction conditions and (c) have a high functional group tolerance and chemoselectivity. Moreover, the method should have the flexibility to allow the introduction of perfluorinated tags in the final step of a synthetic route.

We anticipated that the above requirements would be best fulfilled by the recently-introduced click chemistry.[5] Sharpless and co-workers developed a Cu(I) catalyzed stepwise analogue of the Huisgen reaction between terminal alkynes and azides (eqn. 1),[6] providing a regioselective construction of 1,4 disubstituted triazoles with almost quantitative yields. Above all, this catalytic process creates a thermally and hydrolytically stable covalent connection between R_1 and R_2 with high selectivity, yield and reliability. Applications of this technique range from activity-based protein profiling to dendrimer synthesis.[7]



(1)

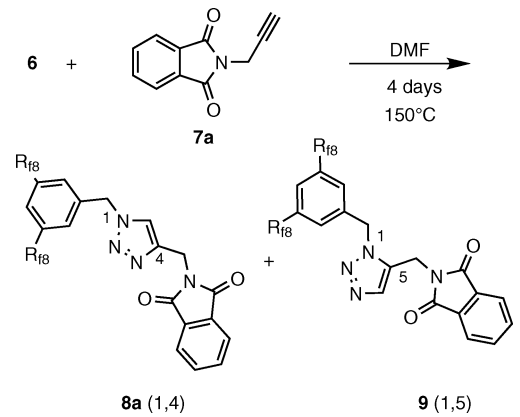
To test whether this ligation reaction could be applied in fluorous chemistry, we synthesized fluorous azides, as shown in Scheme 1. The synthesis of the one-ponytail azide **2** is based upon a literature precedent and it is easily accessible from commercially available fluorous iodide **1**.[8] As the only fluorous product, compound **2** was obtained in high purity by simple distillation. To increase the number of fluorine atoms in the azide component, the synthesis of benzylic azide **6** with two ponytails



Scheme 1 Synthesis of fluorous azides **2** and **6**.

was also accomplished. Fluorous benzoic acid ester **3**, a known substance,[9] can be conveniently converted to azide **6** in three straightforward steps. Thus, reduction of the ester group,[9a] followed by treatment with thionyl chloride, provided the fluorous chloro compound **5**. To complete the synthesis of fluorous azide **6**, it only remains to introduce the azido group *via* nucleophilic displacement. Although several steps were required, purification of the fluorous alcohol **4** and fluorous chloride **5** intermediates was easy, and the overall yield was satisfactory.

Our first exploration of fluorous click chemistry probed the ability of the fluorous azide **6** to participate in a cycloaddition reaction with terminal alkyne **7a** (Scheme 2). We found that this thermal reaction gave an inseparable 1 : 1 mixture of regioisomers **8a** and **9** after prolonged heating. The regiochemistry of the products was established by NOE experiments.



Scheme 2 Thermal Huisgen reaction of **6** and **7a**.

Applying Sharpless conditions, the Cu(I) catalyst promoted this reaction at room temperature to provide the 1,4 isomer **8a** with a 93% yield (Table 1).[10] In common organic solvents (toluene, DCM, DMF, ACN), however, we always observed the

† Electronic supplementary information (ESI) available: experimental procedures, ^{1}H and ^{13}C NMR spectra for all new compounds. See http://www.rsc.org/suppdata/ob/b5/b504973c/

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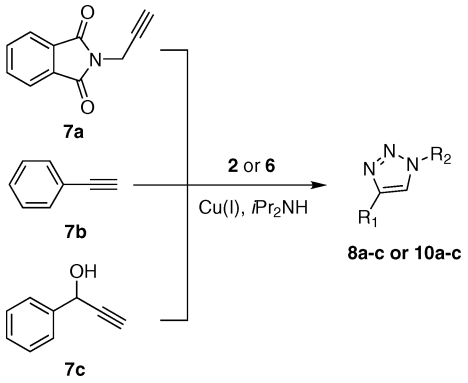
Table 1 Catalytic regioselective addition of fluorous azides (**2** or **6**) to terminal alkynes **7a**–**c**[a]



Entry	Azide	R_1	Product	Yield (%)[b]
1	**6**	Phthalimido-N–CH_2	**8a**	93
2	**2**	Phthalimido-N–CH_2	**10a**	96
3	**2**	Phthalimido-N–CH_2	**10a**	95[c]
4	**6**	Ph	**8b**	32
5	**2**	Ph	**10b**	69
6	**6**	PhCH(OH)	**8c**	86
7	**2**	PhCH(OH)	**10c**	92

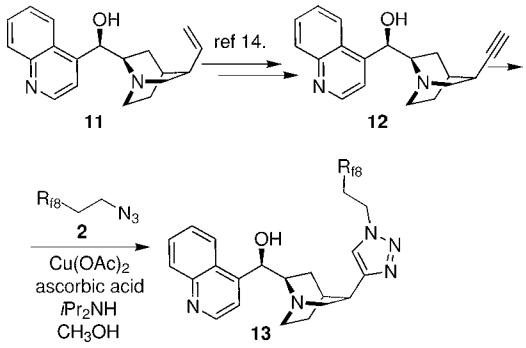
[a] The Schlenk tube was charged with **2** or **6** (0.20 mmol), **7a**–**c** (0.021 mmol), diisopropylamine (0.20 mmol), CuI catalyst (5 mol%) and trifluoroethanol (3 mL) Then the mixture was stirred overnight under argon atmosphere at 25 °C. [b] Yield of isolated product after work up. [c] *In situ* generated Cu(I) was used in MeOH (from copper(II) acetate with ascorbic acid).

formation of an undesired fluorous trace impurity. Running the click reaction in 2,2,2-trifluoroethanol, a solvent which can solubilize an appreciable amount of both fluorous and organic compounds, avoided the formation of this unwanted by-product. Following a simple workup,[10] the fluorous triazole **8a** was obtained in almost quantitative yield as a pure compound.

The substrate scope was investigated using the above optimized conditions. In addition to terminal alkynes **7b** and **7c**, the one-ponytail azide **2** was also screened (Table 1). These data show that both fluorous azides can be utilized in click chemistry with a very similar efficiency.[11] Furthermore, tolerance for variations in the acetylene component is also good in these reactions. Due to the excellent yields, the purification of products **8a,c** and **10a,c** from non-conjugated alkynes **7a** and **7c** did not require any classical chromatography.[10] This synthetic simplicity could be an advantage in multigram synthesis. Since one-ponytail azide **2** is more soluble in common organic solvents, it was possible to further simplify the reaction conditions by running the reaction in methanol and using an *in situ* generated Cu(I) source (entry 3). Following a simple workup,[10] we obtained **10a** in roughly the same yield (95 *vs.* 96%) and purity.

The successful application of click chemistry to fluorous chemistry gave us impetus to demonstrate its utility in the fluorous synthesis of a more complex molecule. Since the cinchona alkaloids are a broadly employed class of chiral catalysts and ligands in asymmetric organic synthesis, their immobilization is highly desirable.[12] Therefore, we attempted the synthesis of a fluorous cinchonidine, as a potentially reusable cinchona alkaloid.[13]

The synthesis of **13** commenced with commercially available **11** (Scheme 3). First, in a simple two step sequence, the terminal alkyne alkaloid **12** was formed based on a literature precedent.[14] Then, introduction of the fluorous ponytail *via* click chemistry was attempted. Using *in situ* generated Cu(I) in MeOH, this reaction proceeded to completion in 10 h at ambient temperature. After operationally simple workup, the



Scheme 3 Synthesis of fluorous cinchonidine **13** using fluorous click chemistry.

fluorous alkaloid **13** was obtained in excellent yield (95%) as a pure compound.

In summary, we have developed a fluorous version of azide click chemistry, and demonstrated its utility in the synthesis of the fluorous cinchona alkaloid **13**. This fluorous tagging procedure offers an improvement in both efficiency and practical simplicity. Further applications of this methodology are in progress.

Acknowledgements

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