Tetrahedron Letters 49 (2008) 5190–5191

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Click chemistry for facile immobilization of cyclodextrin derivatives onto silica as chiral stationary phases

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ARTICLE INFO

Article history:
Received 24 April 2008
Revised 4 June 2008
Accepted 10 June 2008
Available online 14 June 2008

Keywords:
Click chemistry
β-Cyclodextrin
Enantioseparation
CEC

ABSTRACT

Click chemistry was applied to immobilize mono-azido-β-cyclodextrin derivatives onto the surface of silica to give novel chiral stationary phases (CSPs). The desired CSPs showed high stability and excellent enantioseparation effects in capillary electrochromatography (CEC).

In recent years, 1,2,3-triazole forming reactions—*Click chemistry* from terminal alkyne and azido groups has attracted increasing attention.[1] It is useful as a class of robust and selective chemical reactions affording high yields and is tolerant to a variety of solvents/functional groups. Immobilization of highly functionalized molecules onto solid-support surfaces by *Click chemistry* affords a facile approach to useful composite materials. The most commonly used *Click* mode is to immobilize functional molecules with a terminal alkyne group to azido-modified supports which includes immobilization of cinchona alkaloid derivatives onto azide-modified silica surfaces[2] polymers onto glass and silica surfaces,[3,4] and self-assembled monolayers onto electrode surfaces.[5] However, it is usually more difficult to introduce a terminal alkyne group to certain types of functional molecular structures, hence the reverse *Click* mode which involves anchoring terminal azido functionalized molecules onto alkyne modified supports could render the *Click* method more versatile. Yang et al. successfully modified the surface of F_3O_4 nanoparticle by this reverse *Click* mode.[6] On the other hand, cyclodextrins (CD) and their derivatives have remarkable ability in forming inclusion complexes with a variety of molecules. The chirality of CD moieties renders them useful for application in enantioseparation processes. In our previous work, we have reported on a series of structurally well-defined chiral stationary phases (CSPs) based on CD derivatives via Staudinger reaction.[7–9] These CSPs were tested on HPLC and showed good enantioseparation efficiencies.

Herein, we report the application of *Click chemistry* using organic soluble copper (I) catalyst for the immobilization of CD derivatives onto silica surfaces. This leads to novel chiral stationary phases which have good stability and excellent chiral selectivity in capillary electrochromatography (CEC). To establish synthetic routes, an alkyne group was first introduced onto a silica surface; mono-azido-β-CD derivatives and the copper(I) catalyst were prepared separately. The final immobilization step can be carried out conveniently via *Click chemistry* under relatively mild reaction conditions.

The synthetic route to the CSPs is depicted in Scheme 1, using toluenesulfonyl-β-CD[10] as starting material. Treatment of **1** with NaN_3 in DMF afforded azido-β-CD **2**. Thereafter, the complete per-functionalization products of **3** were prepared from **2** under different conditions.[11]

The introduction of an alkyne group onto silica was an important step in our approach. Firstly, 3-aminopropyltriet-hoxysilane **4** was treated with propiolic acid in dry chloroform in the presence of *N*,*N*′-dicyclohexylcarbodiim-ide to afford compound **5**, which was then anchored onto 5 μm silica in accordance with a literature procedure[9] affording alkyne functionalized silica **6** (FTIR data exhibited an absorption at 2121 cm^{-1} ascribed to the alkyne group). Since the final step would take place under heterogeneous conditions, the direct use of a cuprous iodine (CuI) catalyst could make the purification process more complicated. Accordingly, a soluble organic catalyst $CuI(PPh_3)$ was synthesized from CuI and triphenyl-phosphine.[12]

The *Click chemistry* step[13] was carried out at 80 °C for two days by adding $CuI(PPh_3)$ and compound **3** to a DMF suspension of alkyne functionalized silica **6**. After purification, successful

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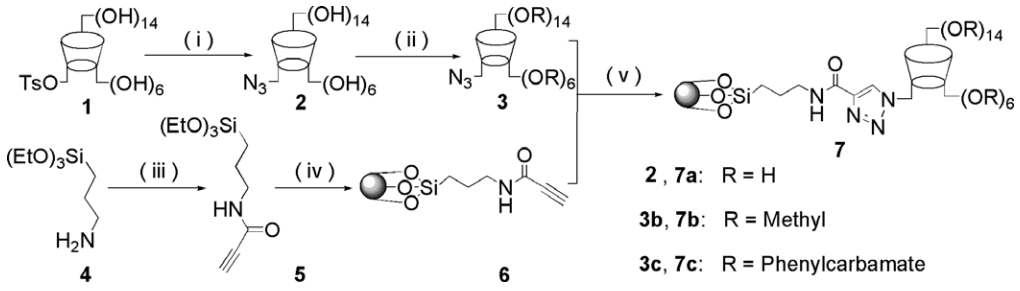
doi:10.1016/j.tetlet.2008.06.048



Scheme 1. Reagents and conditions: (i) NaN_3/DMF/rt 10 h/yield 90%; (ii) permethylation **3b**: CH_3I/DMF/NaH/rt 12 h/yield 78% and perphenylcarbamoylation **3c**: PhN=C=O/pyridine/80 °C 12 h/yield 49%; (iii) propiolic acid/DCC/CH_3Cl/rt 1 h/yield 80%; (iv) silica/toluene/reflux 2 h; (v) CuI(PPh_3)/DMF/80 °C two days.

Table 1
Analysis data for CSPs

Bonded silica	Elemental analysis (%)			Surface loading (μmol m^{-2})
	C	H	N	
Alkyne functionalized silica **6**	5.32	0.99	0.85	—
CSP **7a**	14.35	2.64	1.49	0.59
CSP **7b**	16.62	2.62	1.63	0.51
CSP **7c**	12.60	1.79	1.98	0.12

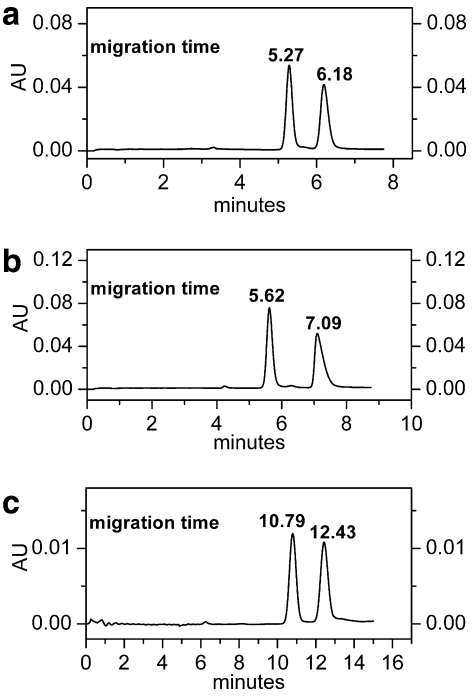


Figure 1. Capillary electrochromatography of racemates using CSP **7c**.

immobilization was confirmed from FTIR and elemental analysis. In the FTIR spectrum, the 2121 cm^{-1} absorption due to the alkyne group was sharply decreased (by 80–90% for different CSPs), instead of which there appeared typical absorbances (~1700–1730 cm^{-1}, ~2856–3000 cm^{-1}) for the derivatized β-CD. The elemental analysis data for CSPs **7a–c** are listed in Table 1.

CSP **7c** was packed into a fused-silica capillary (id. 100 μm, effective length 9 cm) and tested in a Beckman MDQ Capillary Electrophoresis System. Figure 1a–c show the results of separation of three racemic compounds on CSP **7c** using buffer (NaH_2PO_4, 5 mM, pH 7): acetonitrile (v/v = 60:40). All the three tested racemates could be separated. The selectivity and resolution of 1-(4-chlorophenyl)-ethanol reached 1.5 and 2.4. Other analytical results will be reported elsewhere.

In summary, *Click chemistry* affords an effective route to immobilize β-cyclodextrin derivatives onto silica supports. The CSPs prepared via this method have good stability and excellent chiral selectivity in capillary electrochromatography.

Acknowledgement

The authors acknowledge financial support from Singapore Ministry of Education AcRF Tier II (ARC9/06) grants.

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11. **3b** was prepared in CH_3I/DMF/NaH in a yield of 78%. mp 98–100 °C; FTIR (cm^{-1}): 2930, 2104, 1030; ESI MS (*m*/*z*): 1462.7 [M+Na^+], calcd 1462.4; ^1H NMR ($CDCl_3$) δ (ppm): 3.15–3.24 (m, 7H), 3.40–3.92 (m, 95H), 5.09–5.20 (m, 7H); Anal. Calcd ($C_{62}H_{109}N_3O_{34}$): C, 51.7; H, 7.62; N, 2.92. Found: C, 52.1; H, 7.97; N, 2.56. **3c** was prepared in phenyl isocyanate/pyridine in a yield of 49%. mp 225–227 °C; FTIR (cm^{-1}): 3396, 3317, 2106, 1739, 1602, 1500; ESI MS (*m*/*z*): 3576.2 [M+K^+], calcd 3577.1; ^1H NMR ($CDCl_3$) δ (ppm): 3.98 (m 7H), 4.44–4.63 (m, 21H), 5.15–5.22 (m, 14H), 5.59 (m, 7H), 6.88–7.45 (m, 120H); Anal. Calcd ($C_{182}H_{169}N_{23}O_{54}{\cdot}8H_2O$): C 59.3, H 5.06, N 8.73. Found: C, 59.7; H, 5.06; N, 8.53.
12. *Preparation of CuI(PPh_3)*: A solution of triphenylphosphine (0.69 g, 2.63 mmol) in 10 mL of acetonitrile was added to a solution of CuI (0.50 g, 2.63 mmol) in the same solvent (50 mL). A complex started to precipitate after a few seconds. The mixture was stirred for 1 h, the solid was filtered, washed with acetonitrile and vacuum dried (yield 80%). FTIR (cm^{-1}): 1479, 1434, 1097, 748, 695, 521, 503; Anal. Calcd ($C_{18}H_{15}PCuI$): C 47.6 , H 3.31. Found: C, 47.2; H, 3.29.
13. A general procedure for *Click chemistry*. Alkyne functionalized silica **6** (0.5 g) was suspended in a solution of β-CD derivative **3** (0.5 g) in DMF (5 mL) and then CuI(PPh_3) (10 mmol %) was added. The reaction mixture was heated to 80 °C for two days. The crude products were washed with DMF and extracted with acetone/methanol for 24 h before being vacuum dried.