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Glycosylated Oligo(ethynylene)s *via* a Pd/Zn-Mediated Cross-Coupling Reaction

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Abstract: The synthesis of higher oligo(ethynylene)s represents a challenge in modern organic chemistry, because of their decreasing stability with increasing length and side-product formation during the reaction. Recently, we reported the development of a mild and convenient *sp–sp* carbon heterocoupling protocol for the preparation of glycosylated oligo(ethynylene)s based on the Negishi reaction. The application of this protocol in combination with a one-step desilylation-bromination allowed for the sequential synthesis of glycosylated oligo(ethynylene)s up to the octayne.

Keywords: Carbon materials · Carbon-rich amphiphiles · Negishi cross-coupling · Oligo(ethynylene)s · Oligoynes

Introduction

The allotropes of carbon exhibit intriguingly different properties, resulting from the different hybridization states of the carbon atoms. While diamond and graphite are common materials, the *sp*-hybridized carbon allotrope 'carbyne' has not yet been isolated. The investigations conducted to prepare model compounds for this allotrope were complicated by the inherent reactivity of the higher oligo(ethynylene) homologues toward a spontaneous formation of more stable carbon allotropes.[1-3] The introduction of sterically demanding end groups was successfully used to inhibit these reactions and allowed for the synthesis of compounds with up to sixteen conjugated triple bonds.[4] While the observed instability of oligo(ethynylene)s renders their synthesis difficult, they may be the ideal energy-rich and carbon-rich molecular precursors[5] for the preparation of novel carbon materials with a tailored morphology, microstructure, and surface functionalization, if their reactivity can be exploited in a productive fashion inside supramolecular aggregates.

Symmetric and unsymmetric oligo(ethynylene)s have been prepared and elongated *via* carbon–carbon homo- and heterocoupling reactions, respectively.[6] The frequently used Cu(I)-catalyzed heterocoupling reaction according to Cadiot and Chodkiewicz, for instance, has yielded unsymmetric oligo(ethynylene)s up to the pentaynes.[3,7] The oxidative homocoupling of terminal alkynes catalyzed by Cu(II) according to Hay,[8] on the other hand, has typically been applied as the final step in the synthesis of very long symmetric oligo(ethynylene)s. Unsymmetric oligo(ethynylene)s were obtained from two different terminal alkynes in satisfying yields if one of the two reactants was used in large excess.[4,9]

More recently, novel synthetic pathways were developed by adapting the conditions of typical Pd-catalyzed *sp–sp*^{2} cross-coupling reactions to *sp–sp* heterocoupling reactions. Wityak and Chan devised a Pd/Cu-mediated protocol analogous to the Sonogashira reaction[10] for the synthesis of diacetylenes,[11] which has been employed and refined by other research groups.[12–14] The Negishi reaction[15] has provided access to oligo(ethynylene)s *via* the dehydrohalogenation of β-haloeneynes.[16] Only a few reports exist for the direct use of this protocol in *sp–sp* cross-coupling reactions, which typically suffer from low yields or an almost statistical mixture of the desired heterocoupling product with the so-called self- and homocoupling products.[17] The latter two products are formally obtained from the mutual reaction of two haloacetylenes and two terminal acetylenes, respectively, and represent the major side products in *sp–sp* heterocoupling reactions. In order to circumvent this problem, an entirely different pathway was pursued by Tykwinski and coworkers who successfully adapted and applied the Fritsch-Buttenberg-Wiechell (FBW) rearrangement to the synthesis of oligo(ethynylene) derivatives.[2,18]

We recently reported the successful application of a Negishi protocol in an *sp–sp* carbon cross-coupling reaction[19] which served as a robust and efficient step in the synthesis of glycosylated oligo(ethynylene)s. Due to their similarity to typical glycolipid surfactants, the latter are intended to be used as amphiphilic molecular precursors in the preparation of carbonaceous materials with tailored mesoscopic morphologies and surface functionalization.

Results and Discussion

For the targeted synthesis of glycosylated oligo(ethynylene)s, an efficient synthetic strategy had to be developed that would allow for the sequential elongation of the oligo(ethynylene) segments under mild conditions, on a large reaction scale as well as with high and reproducible yields. In order to explore the scope of different *sp–sp* coupling protocols, we chose the formation of the glycosylated tri(ethynylene) **3** as a model reaction (Scheme 1). While the FBW rearrangement was discarded because the intermediate generation of lithium acetylides appeared to be incompatible with the presence of the peracetylated glucose residues, cross-coupling reactions according to the Cadiot-Chodkiewicz, Sonogashira, and Negishi protocols were investigated, and parameters such as the Pd catalyst, the amine base, the haloacetylene, the solvent, and the reaction temperature were varied (Table).

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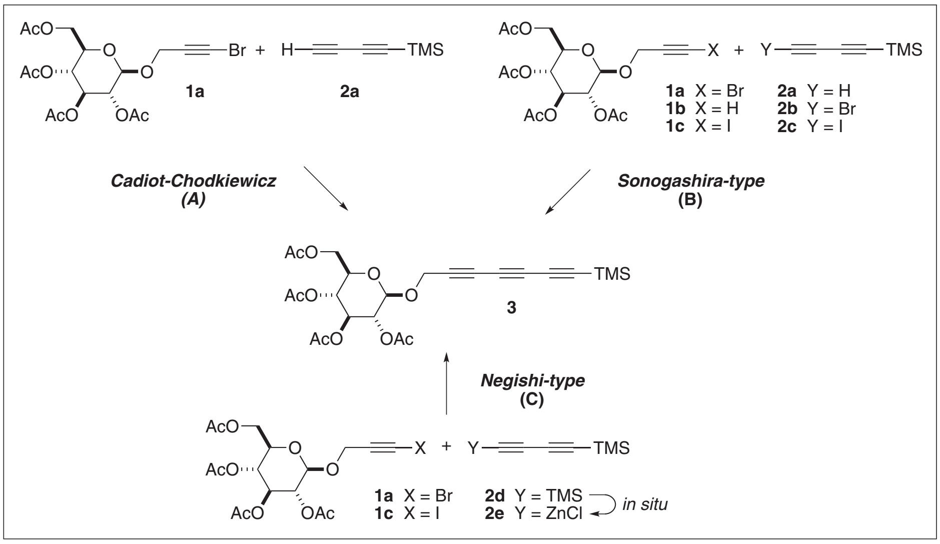


Scheme 1. Possible approaches to the synthesis of glycosylated tri(ethynylene) **3**.

Table. Results obtained in the synthesis of tri(ethynylene) **3** *via* (A) Cadiot-Chodkiewicz, (B) Sonogashira-type, and (C) Negishi-type coupling reactions.

Entry	Method[a]	X	Y	Conditions[c]	Yield[d]
1	A	Br	H	a	–
2	A	Br	H	b	23%
3	B	H	I	c	23%
4	B	H	I	d	14%
5	B	H	Br	c	33%
6	B	H	Br	d	35%
7	B	H	Br	e	34%
8	B	H	Br	f	22%
9	B	I	H	c	16%
10	B	Br	H	c	7%
11	C	I	TMS[b]	g	23%
12	C	I	TMS[b]	h	30%
13	C	I	TMS[b]	i	40%
14	C	Br	TMS[b]	i	26%
15	C	Br	TMS[b]	j	48%
16	C	Br	TMS[b]	k	80%

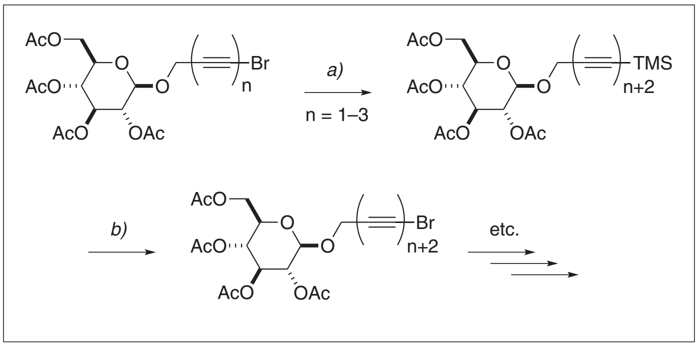
[a] Cadiot-Chodkiewicz couplings (method A), Sonogashira-type couplings (method B) and Negishi-type couplings (method C). [b] In the case of the Negishi couplings, the Zn-organyl was generated from bis(trimethylsilyl)butadiyne **2d** *in situ* by addition of MeLi·LiBr, followed by ZnCl$_2$ in THF; the obtained reaction mixture was then applied in the actual heterocoupling reaction. [c] Reaction conditions and reagents: a) 10 mol% CuI, pyrrolidine, 0 °C; b) 2 mol% CuCl, *n*-BuNH$_2$, DMF/THF, NH$_2$OH · HCl; c) 2 mol% PdCl$_2$(PPh$_3$)$_2$, 10 mol% CuI, DIPA, THF, 0 °C; d) 2 mol% Pd(PPh$_3$)$_4$, 10 mol% CuI, DIPA, THF, 0 °C; e) 5 mol% PdCl$_2$(PPh$_3$)$_2$, 10 mol% CuI, DIPA, THF, 0 °C; f) 3 mol% Pd$_2$dba$_3$, 2.5 mol% CuI, 0.2 equiv. LiI, 2.8 equiv. 1,2,2,5,5-pentamethylpiperidine, DMSO, r.t.; g) 5 mol% Pd(PPh$_3$)$_4$, THF, r.t.; h) 5 mol% PdCl$_2$(dppf) · DCM, THF, 0 °C; i) 5 mol% PdCl$_2$(dppf) · DCM, THF/toluene (3:7 *v/v*), r.t.; j) 5 mol% PdCl$_2$(dppf) · DCM, THF/toluene (3:7 *v/v*), 50 °C; k) 10 mol% PdCl$_2$(dppf) · DCM, THF/toluene (3:7 v/v), 0 °C. [d] Isolated yield of the heterocoupling product **3**.

The reactions according to the Cadiot-Chodkiewicz protocol proceeded with overall disappointing results. For example, the CuI-promoted coupling of 3-bromopropargyl β-D-glucopyranoside **1a** and trimethylsilylbutadiyne (**2a**) in pyrrolidine[20] failed due to a premature deprotection of the glucose residues and subsequent problematic isolation of the product. The CuCl-catalyzed reaction of **1a** and **2a** in a mixture of dimethylformamide (DMF), tetrahydrofuran (THF), and butylamine represented the best result obtained with this reaction, but afforded the desired heterocoupling product **3** in a low yield along with large amounts of side products. These unsatisfactory results are representative for other attempts using the Cadiot-Chodkiewicz protocol and, hence, discouraged further investigations of copper-catalyzed protocols.

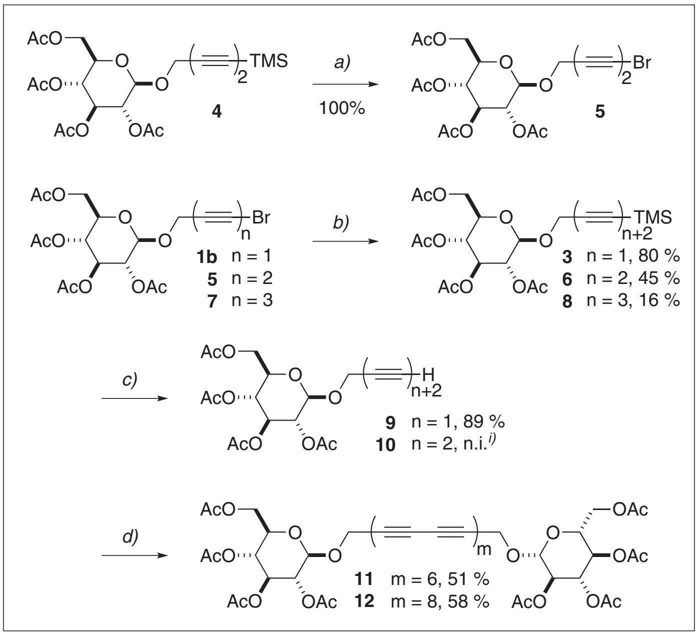
The Sonogashira-type reactions were carried out in THF using different Pd-catalysts, copper cocatalysts, and amine bases. The best yield observed in these reactions amounted to 35%, achieved in the cross-coupling of propargyl β-D-glucopyranoside **1b** and 4-bromo-1-trimethylsilylbutadiyne (**2b**) catalyzed by Pd(PPh$_3$)$_4$, CuI and diisopropylamine (DIPA). Variations of the conditions showed that neither the catalyst precursor nor the amount of catalyst had a significant influence on the yield of the reaction and that bromoacetylenes gave superior results compared to the iodoacetylenes. No improvement was observed when conditions according to Cai and Vasella were applied.[12] In the reaction of the halogen-terminated propargyl glucosides **1a** and **1c** with trimethylsilylbutadiyne (**2a**), the yield dropped below 20%, and, interestingly, propargyl β-D-glucopyranoside **1b** was isolated as a side product, indicating a scrambling of the functional groups.

In summary, the results achieved with the Sonogashira reaction were unsatisfactory because the overall low yields would not allow to scale the reaction up to the multigram scale, as it is required for the intended conversion of the molecular precursors into carbonaceous materials. Moreover, the formation of side products renders the purification difficult. Finally, the use of 1-bromo-4-trimethylsilylbutadiyne (**2b**) is unattractive, since it decomposes quickly at room temperature, and, reportedly, explodes upon heating.[21]

Interest in the Negishi protocol arose when we discovered that 4-(trimethylsilyl)-butadinynyl zinc chloride (**2e**) could be conveniently generated *in situ* from stable 1,4-bis(trimethylsilyl)butadiyne (**2d**).[22] The latter can be prepared easily on a 30 g scale, purified by sublimation and stored under ambient conditions for months. Preliminary experiments on the monodesilylation[23] of **2d** and subsequent transmetallation to ZnCl$_2$ proved these steps to proceed quantitatively within a few minutes. The reaction of 3-iodopropargyl β-D-glucopyranoside **1c** in THF with freshly prepared **2e** catalyzed by Pd(PPh$_3$)$_4$ yielded 23% of the desired tri(ethynylene) **3**. Changing the catalyst to PdCl$_2$(dppf)·DCM, exchange of the iodoacetylene to a bromoacetylene as well as an apolar reaction mixture of 3:7 (*v*/*v*) THF/toluene finally increased the yield to excellent 80%. Since the reaction proceeded in



Scheme 2. Sequential synthesis of higher glycosylated oligo(ethynylene) homologues *via* repetitive Negishi-type coupling and direct bromination of the silyl derivatives. Reagents and conditions: a) **2e**, Pd(dppf)Cl_2·DCM, THF/toluene 3:7 (*v/v*); b) AgF, NBS, MeCN.



Scheme 3. Synthesis of higher oligo(ethynylene) homologues. Reagents and conditions: a) AgF, NBS, MeCN, rt; b) **2e**, $PdCl_2$(dppf) · DCM, THF/toluene (3:7 v/v), 0 °C; c) $AgNO_3$, DCM/MeOH, then KI; *d)* CuCl, TMEDA, DCM air; i) not isolated.

a reasonable timeframe of one day at 0 °C with only trace amounts of side products formed and the alkynyl zinc derivative had been generated *in situ* from a stable precursor, this reaction represents a valuable alternative to existing heterocoupling protocols. The optimized Negishi-type protocol was then applied to the sequential synthesis of longer oligo(ethynylene)s (Scheme 2), in combination with a highly efficient direct conversion of the obtained silyl derivatives to the corresponding bromides, following the conditions developed by Kim and coworkers.[14]

Thus, the glycosylated diacetylene **4** was converted into the corresponding bromodiacetylene **5**, and Pd-catalyzed cross-coupling according to the established protocol afforded the glycosylated tetra(ethynylene) **6**. For the synthesis of the penta(ethynylene), TMS-protected tri(ethynylene) **3** was subjected to the desilylation-bromination conditions to furnish bromotri(ethynylene) **7** in quantitative yield (Scheme 2). Reaction of **7** with trimethylsilylbutadiynyl zinc chloride (**2e**) using the developed protocol gave penta(ethynylene) **8**. Hence, longer oligo(ethynylene)s are available *via* this route, and an optimisation of the conditions for the synthesis of higher homologues is underway. Tri(ethynylene) **3** and the tetra(ethynylene) **6** were desilylated using $AgNO_3$ in DCM/MeOH to furnish the terminal acetylenes **9** and **10**. While the terminal tri(ethynylene) **9** could be isolated, compound **10** decomposed upon evaporation of the solvent and was, therefore, applied in the subsequent synthetic steps without purification. Finally, oxidative homocoupling according to Hay conditions[8] furnished hexa(ethynylene) **11** and octa(ethynylene) **12**, both of which were stable in pure form at room temperature, supposedly due to the sterically demanding peracetylated carbohydrate end groups (Scheme 3).

The complete deprotection of the peracetylated and silylated oligo(ethynylene)s in a mixture of THF/MeOH catalyzed by sodium methoxide proceeded readily in a single step at room temperature. Preliminary results suggest the formation of colloidal aggregates in aqueous suspension, and UV irradiation of the obtained yellowish aqueous dispersions effected a color change suggesting a cross-linking of the oligo(ethynylene) moieties.

In summary, a convenient and copper-free *sp–sp* carbon cross-coupling protocol was developed and applied to the synthesis of unsymmetric oligo(ethynylene) up to the penta(ethynylene), and symmetric compounds up to the octa(ethynylene). The combination with the highly efficient *in situ* desilylation-bromination renders the chosen sequential pathway attractive for the preparation of higher oligo(ethynylene) homologues. These molecules represent important intermediates in the synthesis of molecular precursors for the preparation of carbonaceous materials with tailored morphology and surface functionalization.

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