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Optimization of the Pd^{II}/Cu^{I}-catalyzed Cross-Coupling of Alkynylglucopyranoses

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With biographical summary

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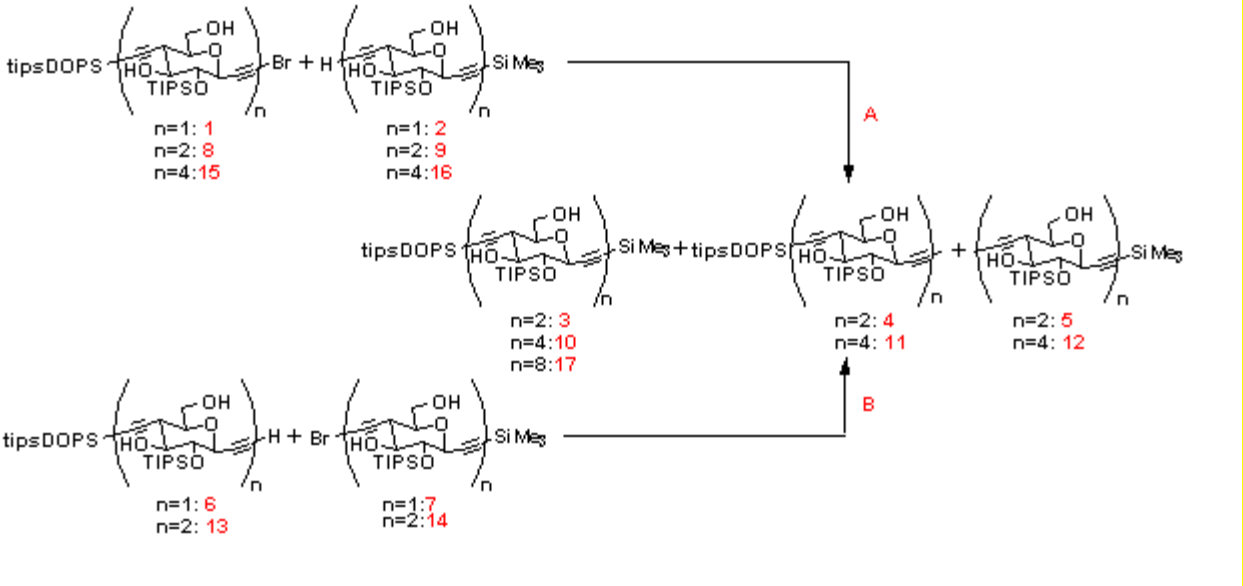
Abstract: The optimization of the cross-coupling of alkynylglucopyranoses is reported in this communication.

Keywords: Cross-coupling, alkynylglucopyranose.

Introduction

Acetylenosaccharides, analogues of polysaccharides in which the glycosidic O-atom is replaced by a butadiynediyl moiety, are most efficiently prepared by a binomial synthesis [1]. The full potential of a binomial synthesis can only be realized by maximizing the yield of each step of the cycle doubling the molecular size, i.e. the regioselective deprotection and a Pd^{II}/Cu^{I}-catalyzed cross-coupling of the saccharide-derived alkynes and haloalkynes. Since the introduction of the orthogonal protecting groups for alkynes by *Cai et al.* [2] and *Ernst et al.* [3] has led to high deprotection yields (95-97%), only the cross-coupling remained to be optimized.

Scheme 1



Results and Discussion

For the synthesis of heterocoupled dimers one can start either from a homopropargylic terminal alkyne and a propargylic haloalkyne (*Scheme 1*, A) or from a propargylic terminal alkyne and a homopropargylic haloalkyne (B). The cross-coupling of a simple homopropargylic alkyne and a propargylic haloalkyne has been investigated [4]. Application of the best conditions resulting from this study ($Pd_2(dba)_3$, CuI, LiI and PMP in DMSO) to the similar coupling of the partially protected saccharide analogues 1 and 2 (*Scheme 1*, path A; *Table 1*, *entry 1*) led to 70% of the desired heterodimer 3 after 30h. Under the same conditions, cross-coupling of the dimers 8 and 9 required 70h (*Table 2*, *entry 1*) and gave significantly lower yields (45-55%). Coupling of the corresponding tetramers 15 and 16 to the octamer 17 did not go to completion (<20% of 17 after 110h). Hence, conditions of the monomer and dimer coupling had to be optimized.

Increasing the reaction temperature to 50°C (*Table 1*, *entry 2* and *4*) led to a faster reaction (24h) but also to higher amounts of homodimer 4, formed by reductive dimerization of 1a [4].
LiI had a negligible influence on the selectivity of the reaction (*entry 3*). Use of $P(fur)_3$ to increase the solubility of $Pd_2(dba)_3$ in DMSO (*entry 4* and *5*) gave slightly better yields of 3. Replacing the bulky PMP by Et_3N (*entry 6*) did not only reduce the reaction time from 30h to 10h but also improved the selectivity in favour of the heterodimer 3. This result diverges from those obtained with the model system where bulky amines suppressed homocoupling [4].

Coupling in pyrrolidine (*entry 7*) where $Pd_2(dba)_3$ is completely soluble led to desilylation of the base-labile 3 (11%). This desilylation was almost completely suppressed by using DMSO/pyrrolidine 5:1 (*entry 8*), but this system showed no advantage over the one specified in *entry 6*. Changing the Pd-catalyst to $Pd(PPh_3)_4$ (*entry 10* and *11*) lowered the yields and the ratio 3:4.
The optimized conditions described in *entry 6* have been applied to the coupling of the dimers 8 and 9 (*Table 2*, *entry 3*). The reaction went to completion in a short time and led to over 75% of the desired heterotetramer 10.

Coupling of the terminal alkyne 6 and bromide 7 according to path B (*Scheme 1*, *Table 3*, *entry 1*) resulted in a significantly decreased yield of the heterodimer (61%) and an increased amount of the homodimer 7 (12%). In keeping with this result, coupling of the dimer 13 to the halodimer 14 (*Table 3*, *entry 2*) gave 58% only of the tetramer 10 besides 11% of the homotetramer 12. Thus, path B proved less advantageous than path A.

In conclusion, best results were obtained by coupling a propargylic bromide and a homopropargylic terminal

alkyne in the presence of $Pd_2(dba)_3$, CuI, $P(fur)_3$ and Et_3N in DMSO, leading in over 75% yield to the dimer and tetramer. The optimized reaction conditions differ from those derived from studying the model compounds [4], and illustrates the sensitivity of the reaction to both the nature of the coupling partners and the reaction conditions.

Tables

Table 1: Coupling of Monomers, path A.

entry	reaction conditions		3	4	5	time
	Coupling of 1 and 2		in %	in %	in %	
1	$Pd_2(dba)_3$,[a] CuI, DMSO	LiI, PMP	69-71	3	<1	30h
2		LiI, PMP, 50°C	64	8	<1	24h
3		PMP	67-69	5	<1	30h
4		$P(fur)_3$[b], PMP[c]	76-79	2	<1	30h
5		$P(fur)_3$, PMP, 50°C	72	5-6	<1	15h
6		$P(fur)_3$, Et_3N	78	2	<1	10h
7	$Pd_2(dba)_3$, CuI, pyrrolidine		43[d]	8	<1	10h
8	$Pd_2(dba)_3$, CuI, DMSO	pyrrolidine[e]	75	3	<1	12h
9	$Pd_2(dba)_3$, CuI, benzene	Et_3N	55	12	<1	20h
10	$Pd(PPh_3)_4$, CuI, DMSO	Et_3N	49	8	<1	10h
11	$Pd(PPh_3)_4$, CuI, benzene	Et_3N	52	9	<1	10h

[a] dba = dibenzylideneacetone [b] $P(fur)_3$ = trifurylphosphine [c] PMP = 1,2,2,5,5-pentamethyl-piperidine [d] + 11% cleavage of TMS group [e] 16 eq. pyrrolidine; + 2% cleavage of TMS group

Table 2: Coupling of Dimers 8 and 9, path A.

entry	reaction conditions		10	11	12	time
1	$Pd_2(dba)_3$, CuI, DMSO	LiI, PMP	45-55	4	<1	70h

2		$P(fur)_3$, PMP	75	3	<1	70h
3		$P(fur)_3$, Et_3N	76	3-5	<1	12h

Table 3: Coupling of Inverse System, path B.

entry	reaction conditions					time
	Coupling of 6 and 7		3	4	5	
1	$Pd_2(dba)_3$, CuI, DMSO	$P(fur)_3$, Et_3N	61	3	12	10h
	Coupling of 13 and 14		10	11	12	
2	$Pd_2(dba)_3$, CuI, DMSO	$P(fur)_3$, Et_3N	58	2	11	14h

If not otherwise stated, the reactions were carried out as follows: At 22°, a 0.1M soln. of the two alkynes in the indicated degassed solvent with 0.3 eq. Pd-catalyst, 0.3 eq. CuI, 3 eq. of base and 0.5 eq. of $P(fur)_3$ or LiI were stirred for the indicated time required for completion.

References

[1] J. Alzeer, C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 242.
[2] C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 732.
[3] A. Ernst, A. Vasella, *Helv. Chim. Acta* **1996**, *79*, 1279.
[4] C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 2053.

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Comments

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