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Stille Reactions with Tetraalkylstannanes and Phenyltrialkylstannanes in Low Melting Sugar-Urea-Salt Mixtures

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Abstract: The transfer of simple alkyl groups in Stille reactions usually requires special solvents (HMPA) or certain organotin reagents (stannatranes, monoorganotin halides) to be efficient. Using low-melting mixtures of sugar, urea and inorganic salt as solvent, a fast and efficient palladium-catalyzed alkyl transfer with tetraalkyltin reagents was observed. The high polarity and nucleophilic character of the solvent melt promotes the reaction. Stille biaryl synthesis using electron-poor and electron-rich aryl bromides proceeds with quantitative yields in the sugar-urea-salt melt. Catalyst loading may be reduced to 0.001 mol% and the catalyst melt mixture remains active in several reaction cycles. Showing the same or improved performance for Stille reactions than organic solvents and allowing a very simple work up, sugar-urea-salt melts are a non-toxic and cheap alternative reaction medium available in bulk quantities for the catalytic process.

Keywords: carbohydrates; green chemistry; palladium; Stille coupling; turnover number

Introduction

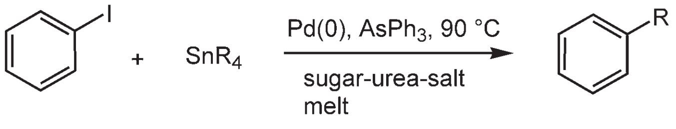
The Stille cross-coupling protocol is a powerful and widely used method for the construction of new carbon-carbon bonds.[1–4] It is defined as the Pd-catalyzed coupling of organic electrophiles, usually halides or triflates, with organotin reagents. The reaction tolerates a variety of functional groups and most organotin reagents are not sensitive to either oxygen or moisture, which makes the process very versatile. Aryl and alkenyl moieties are rapidly transferred, but the scope of the reaction is somewhat limited by the low efficiency of alkyl transfer from tetraalkyltin reagents; for this reason, they are used as non-transferable ligands in mixed organotin compounds. Several reports have addressed the problem. Stille reported the reaction to proceed well in HMPA, DMF and dioxane as solvent.[5,6] The addition of diethylamine to the Stille alkylation reaction improves yields by reducing competing β-hydride elimination and reduction.[7] Monoorganotin reagents, such as secondary alkyl halides[8] and stannatranes[9] cross couple efficiently. The effect of alkylimidazolium salt ionic liquids on the transfer of alkyl groups from simple tetraorganotin reagents to iodobenzene was recently investigated,[10,11] but found to be difficult and accompanied by formation of biphenyl.

Likewise, the synthesis of biaryls by Stille coupling has become an attractive process with a diverse spectrum of application, ranging from pharmaceuticals to material science.[12]

Low-melting sugar-urea-salt mixtures as reaction media represent a new type of solvent with interesting properties and benefits, such as low cost[13] and improved safety in comparison to classical organic solvents. The toxicity of the melt ingredients is generally very low; e.g., NaCl LD_{50} orally in rats 3.8 $g\,kg^{-1}$; no LD_{50} is reported for sorbitol, lactose, urea or dimethylurea.[14] In addition, all components of the carbohydrate-based solvents are biodegradable. Furthermore, a simplified work-up without the use of organic solvents becomes possible. The use reported here of low-melting sugar-urea-salt mixtures as solvents for efficient Stille alkylation and biaryl synthesis may therefore contribute to a more sustainable chemistry.

Results and Discussion

Mixtures of sugars, urea and inorganic salts, which melt at around 70°C were recently introduced as solvent for Diels–Alder reactions.[15] The polarity of the melts is very high,[16] although they do not contain any water. The well-documented effect of the solvent polarity and nucleophilic assistance theory[17] on the Stille alkylation with tetraalkyltin reagents, prompted us to investigate the reaction in this unusual medium (Scheme 1). Iodobenzene was coupled at 90°C with tetravinyltin (entries 1–8, Table 1), tetramethyltin (entries 9–16) and tetrabutyltin (entries 18–24) in different sugar-urea-salt melts using a tris(dibenzylideneacetone)dipalladium(0) chloroform adduct as palladium(0) source and $AsPh_3$ as ligand. As expected, the transfer of the vinyl group to the arene is efficient and complete in all experiments. GC analysis of the crude product shows that no iodobenzene starting material remains. Alkyl group transfer from tetraalkylorganotin reagents typically requires special conditions (toxic solvents such as HMPA, DMF or dioxane) or reagents to be effective as discussed above. Therefore, we were pleasantly surprised to observe product yields for the methyl group transfer from tetramethyltin between 45% and 90% (entries 11, 13, 15 and 16) if performed in the sugar-urea-salt melt. The butyl group is even more difficult to transfer from tetrabutyltin. Three solvent melts were identified which allowed a butyl group transfer with yields from 37% to 44% (entries 19, 20 and 24).



1 2 3

Scheme 1. Stille alkylation in sugar-urea-salt melts.

The work-up of the reactions is very simple: at the end of the reaction water and 1 mL of a hydrocarbon are added. In our experiments pentane was used to simplify GC analysis; for larger scale applications hydrocarbons with a higher flash point, for example, isooctane should be used. After filtration, the separated pentane phase was analyzed by GC-MS. No additional extraction of the aqueous phase is necessary for quantitative product isolation.

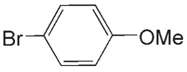
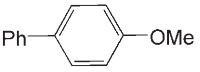
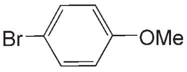
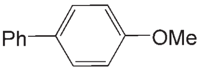
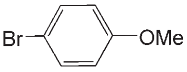
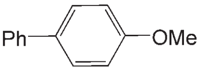
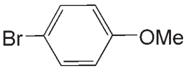
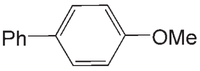
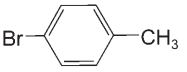
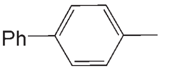
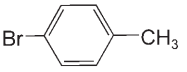
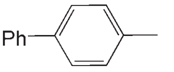
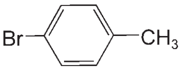
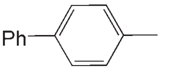
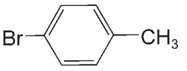
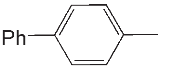
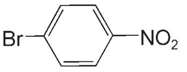
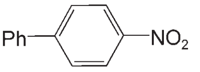
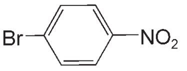
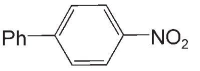
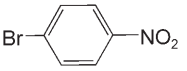
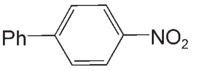
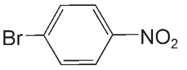
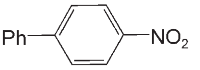
The composition of the melt significantly affects the outcome of the reaction. The mixture of mannitol-dimethylurea-ammonium chloride (50:40:10) gave best results for methyl group transfer, while maltose-dimethylurea-ammonium chloride was good for butyl group transfer. The presence of dimethylurea is not crucial; replacing it by urea does not affect the reaction, as shown in entry 6.[18] The molecular structure of the melts is complex and currently we cannot describe the molecular origin of the differences of the reaction course in different compositions. Stille alkylations in *N*-butyl-*N*-methylimidazolium salt ionic liq-

Table 1. Stille alkylations in sugar-urea-salt melts at a reaction temperature of 90°C.

Entry	Composition of melt[a]	R	Reaction time	Conversion[b] [%]	Ph-R [%][c]	By-product
1	Citric acid/DMU[d] 40:60	C_2H_3	6 h	100	95	–
2	Sorbitol/DMU[d]/NH_4Cl 70:20:10	C_2H_3	6 h	100	95	–
3	Maltose/DMU[d]/NH_4Cl 50:40:10	C_2H_3	6 h	100	100	–
4	Fructose/Urea/NaCl 70:20:10	C_2H_3	6 h	100	85	–
5	Mannitol/DMU[d]/NH_4Cl 50:40:10	C_2H_3	6 h	100	71	–
6	Glucose/Urea/NaCl 60:30:10	C_2H_3	6 h	100	97	–
7	Lactose/DMU[d]/NH_4Cl 60:30:10	C_2H_3	6 h	100	96	–
8	Mannose/DMU[d] 30:70	C_2H_3	6 h	100	92	–
9	Citric acid/DMU[d] 40:60	CH_3	6 h	25	20	–
10	Sorbitol/DMU[d]/NH_4Cl 70:20:10	CH_3	6 h	19	12	–
11	Maltose/DMU[d]/NH_4Cl 50:40:10	CH_3	6 h	55	51	–
12	Fructose/Urea/NaCl 70:20:10	CH_3	6 h	18	10	–
13	Mannitol/DMU[d]/NH_4Cl 50:40:10	CH_3	6 h	94	90	–
14	Glucose/Urea/NaCl 60:30:10	CH_3	6 h	23	18	–
15	Lactose/DMU[d]/NH_4Cl 60:30:10	CH_3	6 h	49	45	–
16	Mannose/DMU[d] 30:70	CH_3	6 h	85	81	–
17	Citric acid/DMU[d] 40:60	C_4H_9	6 h	100	6	benzene
18	Sorbitol/DMU[d]/NH_4Cl 70:20:10	C_4H_9	6 h	90	14	benzene
19	Maltose/DMU[d]/NH_4Cl 50:40:10	C_4H_9	6 h	100	42	benzene
20	Fructose/Urea/NaCl 70:20:10	C_4H_9	6 h	100	37	benzene
21	Mannitol/DMU[d]/NH_4Cl 50:40:10	C_4H_9	6 h	100	25	benzene
22	Glucose/Urea/NaCl 60:30:10	C_4H_9	6 h	75	28	benzene
23	Mannose/DMU[d] 30:70	C_4H_9	6 h	100	15	benzene
24	Lactose/DMU[d]/NH_4Cl 60:30:10	C_4H_9	6 h	100	44	benzene

[a] The ratio is given in weight%.
[b] Determined using hexamethylbenzene as internal standard.
[c] Determined by GC-MS analysis.
[d] DMU = dimethylurea.

Table 2. Stille coupling of arylbromides and tributylphenylstannane in sugar-urea-salt melts at 90 °C.[a]

Entry	Composition of melt[b]	Aryl bromide	Product	Conversion[c]/Yield[d] [%]
1	Lactose/DMU[e]/NH_4Cl 60:30:10			100/100
2	Mannitol/DMU[e]/NH_4Cl 50:40:10			100/100
3	Maltose/DMU[e]/NH_4Cl 50:40:10			100/100
4	Sorbitol/DMU[e]/NH_4Cl 70:20:10			90/80
5	Lactose/DMU[e]/NH_4Cl 60:30:10			100/100
6	Mannitol/DMU[e]/NH_4Cl 50:40:10			100/100
7	Maltose/DMU[e]/NH_4Cl 50:40:10			100/100
8	Sorbitol/DMU[e]/NH_4Cl 70:20:10			100/85
9	Lactose/DMU[e]/NH_4Cl 60:30:10			95/90
10	Mannitol/DMU[e]/NH_4Cl 50:40:10			95/90
11	Maltose/DMU[e]/NH_4Cl 50:40:10			95/90
12	Sorbitol/DMU[e]/NH_4Cl 70:20:10			89/85

[a] To 3 mL of the sugar-urea-salt melt were added 1.5 mmol of aryl bromide, 1.6 mmol of phenyltributylstannane, 1 mol% $Pd_2(dba)_3$ and 4 mol% of $AsPh_3$ as ligand. The reaction time was 6 h.

[b] The composition ratio of the melt is given as weight%.

[c] Determined by ^1H NMR of the crude product mixture.

[d] Isolated yield of the analytically pure product after column chromatography (3:1 petrol ether:ethyl acetate).

[e] DMU = dimethylurea.

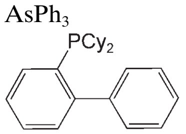
uids yield up to 30% biphenyl as a side product.[10] In melted sugar-urea-salt mixtures no biphenyl, but benzene formation was observed, in the case of tetrabutyltin coupling. A reductive process competes with the slow butyl group transfer.

We started our investigation of Stille biaryl synthesis in sugar-urea-salt melts with the coupling of tributylphenylstannane with 4-bromoanisole and 1-bromo-4-methylbenzene, as electron-rich arenes, and 1-bromo-4-nitrobenzene, as an electron-poor arene, using 1 mol% tris(dibenzylideneacetone)dipalladium(0) as catalyst and $AsPh_3$ as ligand. The melts consisting of lactose/dimethylurea/NH_4Cl, maltose/dimethylurea/NH_4Cl, mannitol/dimethyluera/NH_4Cl and sorbitol/dimethylurea/NH_4Cl showed the best results for Stille alkylations and were selected for the biaryl synthesis. Table 2 summarizes the results.

Best results were obtained using a melt consisting of lactose, maltose or mannitol. Reactions in the melt tolerate electronic variation of the aryl bromide component and yield cleanly and in most cases quantitatively the biaryl coupling products. Next, the catalyst loading was reduced to 0.001% and the coupling of 4-bromoanisole and phenyltributylstannane was investigated using three different ligands. Table 3 summarizes the results. Using $Pd_2(dba)_3$ and triphenylarsine as ligand an 87% yield of isolated product was obtained after 48 h, which corresponds to a catalyst turnover number of 87,000. Using (2-biphenyl)dicyclohexylphosphine as ligand or ligandless conditions gives lower conversion and yields. To benchmark the results obtained in sugar-urea-salt melts the identical reaction was performed in 1,4-dioxane (entry 4) yielding comparable conversion and yield as entry 1.

To test the robustness of the palladium catalyst under the sugar-urea-salt melt conditions the coupling of 4-bromoanisole with phenyltributylstannane was performed at 90 °C in three subsequent batches using

Table 3. Stille coupling of 4-bromoanisole and phenyltributylstannane at 90 °C with different ligands and low catalyst loading; reaction time 48 h.[a]

Entry	Solvent[b]	Pd (mol %)	Ligand	Conversion[c]/yield[d] [%]
1	Lactose/DMU[e]/NH_4Cl 60:30:10	0.001 %	$AsPh_3$	92/87
2	Lactose/DMU[e]/NH_4Cl 60:30:10	0.001 %		65/61
3	Lactose/DMU[e]/NH_4Cl 60:30:10	0.001 %	No ligand	30/27
4	Dioxane	0.001 %	$AsPh_3$	87/81

[a] To 3 mL of sugar-urea-salt melt was added 1.5 mmol of aryl bromide, 1.6 mmol of phenyltributylstannane, 0.001 %mol of $Pd_2(dba)_3$ and $AsPh_3$ as ligand.

[b] Composition of the melt given in weight %.

[c] Determined by ^1H NMR of the crude product mixture.

[d] Isolated yield of the analytically pure product after column chromatography (3:1 petrol ether:ethyl acetate).

[e] DMU = dimethylurea.

the same catalyst-melt mixture with 0.01 mol % $Pd_2(dba)_3$ and 0.04 mol % $AsPh_3$ as ligand. The conversion of the reaction was determined by removing the organic phase under an argon atmosphere after 12, 24 and 36 h and work-up of this phase. New starting material was added to the remaining melt. The catalyst remained active over the three cycles, although a decrease in conversion from 83 % (first run) to 70 % (second run) and 66 % (third run) indicates some loss of activity.

Work-up and product isolation determines significantly the overall efficiency of a chemical transformation. Here, the melt mixtures offer a very simple handling: after completion of the reaction, simply water is added. The components of the melt dissolve in water and organic products precipitate amorphously, the organic product was washed two times with water and analytically pure samples are obtained from the crude product after recrystallization. Solids with low melting points or liquids are isolated from the water phase with minimal amounts of organic solvents. In any case, the work-up is simple and requires no or very small amounts of organic solvents for product isolation.

Conclusions

In summary, we have reported the use of sugar-urea-salt melts as solvent for Stille alkylations and biaryl synthesis. The transfer of simple alkyl groups, such as methyl or butyl, which usually requires special reagents or conditions, proceeds smoothly with tetraalkyltin in this unusual solvent. The high solvent polarity and the presence of nucleophilic groups may promote the alkyl transfer. The Stille alkylation reaction in sugar-urea-salt melts is therefore a suitable alternative to the use of HMPA as solvent or the preparation of stannatranes for efficient alkyl group transfer.

The synthesis of biaryls by Stille coupling proceeds in sugar-urea-salt melts with good yields for electron-poor and electron-rich aryl bromides. The catalyst loading may be reduced to 0.001 mol % still achieving a turnover number of 87,000. Repeated use of the catalyst-melt mixture is possible and product isolation does not require the use of organic solvents.

Overall, the reported reaction conditions allow one to perform Stille coupling reactions of aryl iodides and aryl bromides as efficiently as in organic solvents. The use of polar additives, such as HMPA, is avoided and the work-up is simplified. In addition, the reaction medium is non-toxic,[14] has a low vapour pressure[15] and presumably high flash points,[19] is rather cheap[13] and readily available in bulk quantities. The recycled use of a carbohydrate reaction melt was demonstrated in three cycles of a Stille coupling. However, the economic or ecological benefit from melt recycling in batch reactions strongly depends on the individual application. Being biodegradable, the disposal of carbohydrate melts may use typical organic waste streams.

Experimental Section

General Procedure for Stille Alkylation in Sugar-Urea-Salt Melts

All reactions were carried out at 90 °C (oil bath temperature) in 10-mL sealed tubes under argon. The use of sealed tubes avoids any loss of reagents or products under the reaction conditions and ensures a quantitative reaction monitoring. Chemicals were used as purchased. In a typical experiment 0.025 mmol of catalyst [tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct], 0.1 mmol of Ph_3As, 0.4 mmol of iodobenzene and 0.6 mmol of the organostannane were added to the sugar-urea-salt mixture (2.5 mL) under argon. The reaction mixture was stirred for 6 h at 90 °C. After cooling to room temperature water was added and the product was extracted with pentane (1×1 mL; the first extraction collects all organic products) and analyzed by GC-MS after the addition of hexamethylbenzene as an internal standard.

General Procedure for Stille Biaryl Synthesis in Sugar-Urea-Salt Melts

All reactions were carried out at 90°C (oil bath temperature) in 10-mL sealed tubes under argon. The use of sealed tubes avoids any loss of reagents or products under the reaction conditions and ensures a quantitative reaction monitoring. Chemicals were used as purchased. In a typical experiment 1 mol% of catalyst [tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct], 4 mol% of Ph_3As, 1.5 mmol of aryl bromide and 1.6 mmol of the organostannane were added to the sugar-urea-salt mixture (3 mL) under argon. The reaction mixture was stirred for 6 h at 90°C. After cooling to room temperature, water was added to the mixture, which precipitates the organic product. The crude organic products were collected by filtration and washed with water (2×15 mL). The NMR analysis indicated that the crude product was $>95\%$ pure. The slightly yellow crude product was further purified by recrystallization or filtration over silica gel (3:1 petrol ether:ethyl acetate) to give colorless pure products with analytical data matching all literature reported values.

Supporting Information

Gas chromatographic analyses of Stille alkylations with tetravinyltin, tetramethyltin and tetrabutyltin in different sugar-urea-salt melts.

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