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Palladium-Catalyzed Cross-Alkynylation of Aryl Bromides by Sodium Tetraalkynylaluminates

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Sodium tetraalkynylaluminates (**1**−**4**), prepared from $NaAlH_4$ and terminal alkynes, cross-couple with aryl bromides in the presence of Pd(0) and Pd(II) catalysts. The reactions take place in boiling THF or DME. The process is applicable to both homo- and heterocyclic aryl bromides and can be used for conversion of polybromo compounds into polyalkynes. The reactions are high yielding and selective, free of undesired homocoupling and hydrogenolysis processes. The reagents selectively react with the ring-bound bromine atoms but do not affect chloro, cyano, triflate, or ester functions.

Introduction

The high reactivity of alkynes makes them favorite building blocks for many organic preparations.[1] In addition, acetylenes are target compounds by themselves with a large spectrum of applications. Recent examples include optical and electronic devices,[2] as well as various kinds of pharmaceuticals.[3] In the past 25 years, the most common approach to arylalkynes was the palladium-catalyzed Sonogashira coupling reaction, in which iodoarenes are treated under basic conditions with either a Cu(I) or another early transition metal salt.[4] The Sonogashira process has, however, several disadvantages: The reactivity is sometimes dependent on the purity of the reactants[5] and in some cases good results are obtained only with iodoarenes.[4] In addition, the process is frequently associated with undesired homocoupling of the starting alkynes.[6,7] Some of these obstacles have recently been partly overcome by modification of the conventional cross-coupling procedures,[8] though further improvement is definitely needed.

In this paper, we report on a new, efficient, and selective cross-alkynylation process based on the interaction of aryl bromides with a THF or DME solution of sodium tetraalkynylaluminate in the presence of $PdCl_2(PPh_3)_2$. This copper-free process is generally high yielding and forms little, if any, homocoupling products.

Results and Discussion

Tetraalkynylaluminate salts were pioneered by Chini et al. in 1962,[9] but to the best of our knowledge, they have never been utilized in cross-coupling reactions. Sodium alkynylaluminates are easily prepared in excellent yields from $NaAlH_4$ and the respective terminal alkynes in THF (eq 1). They are usually moderately air- and moisture-stable solids, readily soluble in THF and DME, and withstand prolonged heating even above 150 °C. Their application as cross-coupling reagents in the process shown in eq 1 does not require isolation or purification. The reagents prepared in situ in THF or DME give equally good results as the isolated alumi-

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TABLE 1. Palladium-Catalyzed Cross-Alkynylation of Some Aryl Bromides by Sodium Alkynylaluminates 1–4[a]

entry	substrate	reagent	solvent	reaction time, h	product	yield[b] (%)	ref
1	1-$C_{10}H_7Br$	**1**	THF	12	1-$C_{10}H_7C{\equiv}CPh$	91	8c
2[c]	1-$C_{10}H_7Br$	**2**	THF	12	1-$C_{10}H_7C{\equiv}CSiMe_3$	93	13
3	1-$C_{10}H_7Br$[c]	**3**	DME	16	1-$C_{10}H_7C{\equiv}C(CH_2)_3CN$	99	
4	PhBr[c]	**4**	DME	16	$PhC{\equiv}C(CH_2)_3CH_3$	74	14
5	PhBr	**1**	THF	12	$PhC{\equiv}CPh$	90	
6	4-BrC_6H_4Cl	**2**	THF	7	4-$ClC_6H_4C{\equiv}CSiMe_3$	91	15
7	4-BrC_6H_4OMe	**1**	DME	12	4-$MeOC_6H_4C{\equiv}CPh$	86	16
8	4-$BrC_6H_4CO_2Me$	**1**	DME	12	4-$MeOCOC_6H_4C{\equiv}CPh$	89[d]	17
9	4-BrC_6H_4CN	**1**	DME	12	4-$NCC_6H_4C{\equiv}CPh$	85	16
10	4-$BrC_6H_4CF_3$	**1**	DME	6	4-$F_3C\,C_6H_4C{\equiv}CPh$	93	18
11	4-$BrC_6H_4OSO_2CF_3$	**1**	DME	12	4-$F_3CSO_3C_6H_4C{\equiv}CPh$	76[e]	19

[a] Reaction conditions as described in the Experimental Section; molar ratio of substrate/reagent/catalyst 120:40:1; the volume of degassed solvent was adjusted to form a 0.1 M solution of the substrate; $PdCl_2(PPh_3)_2$ was used as catalyst. [b] Isolated yield. The remaining percentage reflect on the unreacted starting material. [c] Substrate reagent ratio 2:1. [d] Forty percent at 66 °C. [e] Determined by ^{1}H NMR.

$$NaAlH_4 + 4RC{\equiv}CH \xrightarrow{-2H_2} NaAl(C{\equiv}CR)_4 \xrightarrow[{[PdCl_2(PPh_3)_2]}]{4R'Br} 4R'C{\equiv}CR + NaBr + AlBr_3 \quad (1)$$

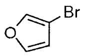
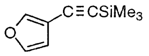
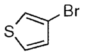
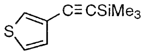
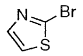
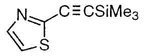
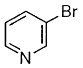
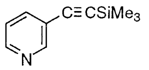
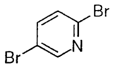
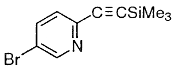
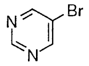
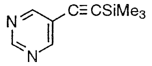
R: Ph (**1**), $SiMe_3$ (**2**), $(CH_2)_3CN$ (**3**), $(CH_2)_3Me$ (**4**)
R′: aryl, heteroaryl

nates.[9] Typically, 2–4 equiv of an appropriate organic bromide is reacted with 1 equiv of the sodium tetraalknylaluminate in the presence of 2.5 mol % of $PdCl_2(PPh_3)_2$. The results of representative experiments are summarized in Table 1.

Unlike in some other palladium-catalyzed cross-coupling reactions with aluminum alkylating reagents,[10] hardly any homocoupling or hydrodehalogenation of the bromoarenes could be found. The only side product that was occasionally formed in minute quantities was a symmetrical diyne formed from the excess reagent. All *four* alkynyl moieties of the reagent can take part in the cross-coupling process. However, because the reaction slows toward its end, it is sometimes advisable to employ a 1:3 rather than a 1:4 molar ratio of reagent/substrate in order to complete the process in a reasonable length of time. In the cases of the slow-reacting reagents **3** and **4** we even increased the ratio to 1:2 (entries 3 and 4 in Table 1). Apart from a rate dependence on the structure of the reagent, we found that the process is influenced to some extent by the nature of the solvent. In some, though not in all cases, the cross-alkynylation in DME proceeds faster than in THF. For example, under comparable conditions, at 66 °C interaction of **1** and 4-$BrC_6H_4CO_2Me$ forms 40% of 4-$MeOCOC_6H_4C{\equiv}CPh$ in DME and only 31% in THF. Likewise, reagents **3** and **4** that convert 1-bromonaphthalene into the corresponding alkynylnaphthalene in DME hardly react at all in THF (pressure tube) under identical reaction conditions of Table 1.

Up to a [substrate]/[$PdCl_2(PPh_3)_2$] ratio of 150, the reactions are independent of the amount of the palladium catalyst. Only when the molar ratio of [substrate]/[catalyst] is >200 do the reactions become significantly dependent on the palladium complex. There is, however, a small but clear dependence of the rate on the nature of the tertiary phosphine in the Pd(II) complexes $PdCl_2(PR_3)_2$. The rates of comparative cross-coupling experiments of 1-bromonaphthalene with **1** in THF in the presence of $PdCl_2(PR_3)_2$ where R = 4-C_6H_4Me, C_6H_5, 4-FC_6H_4, and 4-ClC_6H_4 under the conditions of Table 1 were measured. The average initial rates were 5.22×10^{-4}, 5.58×10^{-4}, 6.84×10^{-4}, and 8.52×10^{-4} mmol min^{-1}, respectively. These data could be expressed in terms of a Hammett plot with a ρ value of 0.6.

TABLE 2. Palladium-Catalyzed Cross-Coupling of Some Heteroaryl Bromides with Reagent 2[a]

Entry	Substrate	Product	Yield, %[b]	Ref.
1			83[c]	13
2			81	20
3			91	21
4			87	20
5[d]			100	22
6			89	23

[a] Reaction conditions as in Table 1. Reaction time 12 h. [b] Isolated yield. [c] Contaminated with 14% of polymers. [d] Molar ratio of substrate:reagent was 4:1.

Table 1 indicates that the cross-coupling of tetraalkynylaluminates with a variety of aryl bromides proceeds well, regardless of the nature of the substituents on the substrates. Some electron-attracting groups seem, however, to enhance the reaction rate. The processes take place in a selective manner. Vulnerable functions, such as chloro, triflate, cyano, and ester groups, as well as C–C double bonds, are not affected. To activate these functions in addition to the ring-bound bromine atoms, alternative alkynylation methods have to be employed. For example, the transformation of 4-BrC_6H_4Cl to 4-$MeC_6H_4C{\equiv}CPh$ can be carried out in a (one-pot) two-step process of $PdCl_2(PPh_3)_2$-catalyzed cross-coupling with $NaAl(C{\equiv}CPh)_4$, followed by a $NiCl_2(PPh_3)_2$-catalyzed reaction with a methylating reagent such as $[Me_2AlOCH_2CH_2NMe_2]_2$.[10] In a typical experiment, 7.5 mmol of the 4-bromochlorobenzene was reacted with 2.5 mmol of $NaAl(C{\equiv}CPh)_4$ in 15 mL of THF in the presence of 0.187

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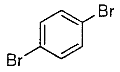
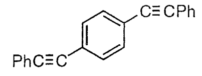
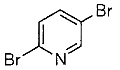
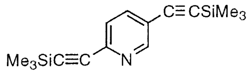
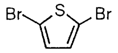
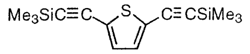
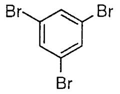
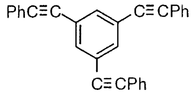
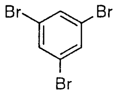
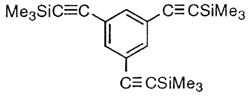
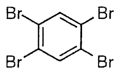
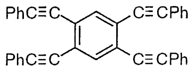
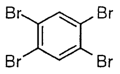
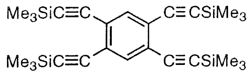
TABLE 3. Palladium-Catalyzed Cross-Alkynylation of Some Polybromoarenes by Complexes 1 and 2[a]

Entry	Substrate	Reagent	[Reagent]/ [substrate]	Reaction time, h	Product	Yield, %[b]	Ref.
1		**1**	1 : 1	16		93	8c
2		**2**	1 : 1	12		86	24
3		**2**	1 : 1	12		89	25
4		**1**	2 : 3	36		90	8c
5		**2**	2 : 3	36		88	26
6		**1**	1 : 2	36		92	27
7		**2**	1 : 2	36		71	28

[a] Reaction conditions as in Table 1 except that the amount of reagent was adjusted to the number of bromine atoms. [b] Isolated yield.

mmol of $PdCl_2(PPh_3)_2$ for 7 h at reflux. Thereafter, 7.5 mmol of $[Me_2AlOCH_2CH_2NMe_2]_2$ and 0.38 mmol $NiCl_2(PPh_3)_2$ were added. Heating at reflux for an additional 12 h gave 41% of $4\text{-}MeC_6H_4C{\equiv}CPh$.

The sodium tetraalkynylaluminates were also shown to cross-couple with a variety of heteroaryl bromides. Some typical experiments are listed in Table 2. This observation is noteworthy, since other stable aluminum-derived alkylating and alkynylating reagents such as $R_2Al(CH_2)_3NMe_2$ (R = alkyl, alkynyl) studied in our laboratory[11] failed to cross-couple with nitrogen-containing heterocycles.

Entry 6 in Table 2 indicates that by using the exact amount of $NaAl(C{\equiv}CR)_4$ required for the replacement of one of the two bromine atoms of 2,5-dibromopyridine (reagent/substrate = 1:4) it is possible to obtain selectively the 2-alkynyl-5-bromopyridine free of even traces of the dialkynyl product. When excess reagent is employed, however, both halogen atoms are affected (see Table 3, entry 2). In fact, the sodium tetraalkynylaluminates are excellent reagents for complete cross-alkynylation of polybromoarenes. Several cross-coupling experiments of di-, tri-, and tetrabromoarenes are summarized in Table 3. Finally, it should be noted that under the conditions of Table 1 reagent **1** couples with $PhC(Br){=}CH_2$ to give within 12 h 47% of $PhC(C{\equiv}CPh){=}CH_2$.[16] This suggests that the cross-alkynylation is not restricted to aryl bromides alone.

Experimental Section

General Procedure for Cross-Alkynylation of Aryl Bromides. Typically, to a solution of 0.4 mmol of the appropriate sodium tetraalkynylaluminate (either solution of the isolated reagent or of the *in situ* prepared compound) in dry degassed THF or DME (2 mL), was added under Ar atmosphere, 1.2 mmol of the monobromoarene and 3.7×10^{-2} mmol of $PdCl_2(PPh_3)_2$ in an amount of solvent that gave a 0.1 M solution of the substrate. The solution was heated at reflux

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for the desired length of time. The reaction mixture was concentrated under reduced pressure, quenched with 5% aqueous HCl, and diluted with dichloromethane. Phase separation and extraction of the products from the aqueous layer was followed by concentration of the combined organic solutions and purification by flash chromatography. The products were characterized either by direct comparison with authentic samples obtained by synthetic routes described in the literature or by analysis of their characteristic IR, MS, and NMR spectra.

For polybromoarenes, the amount of reagent was increased as specified in Table 3.

5-Cyano-1-(1-naphthyl)pent-1-yne was obtained in 99% yield by the above procedure from 1-bromonaphthalene, $NaAlH_4$, and 5-cyano-1-pentyne as a pale yellow oil: 400-MHz ^1H NMR ($CDCl_3$) δ 2.17 (m, 2), 2.74 (t, 2, $J = 7$ Hz), 2.88 (t, 2, $J = 7$ Hz), 7.55 (t, 1, $J = 7$ Hz), 7.65 (m, 2), 7.75 (d, 1, $J = 8$ Hz), 7.92 (d, 1, $J = 8$ Hz), 7.96 (d, 1, $J = 8$ Hz), 8.41 (d, 1, $J = 8$ Hz); 100-MHz ^{13}C NMR ($CDCl_3$) δ 16.3, 18.3, 24.8, 80.4, 91.8, 119.1, 120.8, 125.1, 125.9, 126.3, 126.7, 128.3, 128.4, 130.3, 133.1, 133.3; EIMS (70 eV) *m*/*z* (rel intensity) 219 ($M^{\bullet+}$, 13), 218 [$(M - H)^+$, 83], 178 [$(M - C_2H_2N)^+$, 31], 164 [$(M - C_3H_4N)^+$, 100]. Anal. Calcd for $C_{16}H_{13}N$: C, 87.63; H, 5.97; N, 6.38. Found: C, 87.33; H, 6.25; N, 6.48.

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Supporting Information Available: Spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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