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Synthesis of Unsymmetric Ketones *via* Ligandless Pd-Catalyzed Reaction of Acyl Chlorides with Organoboranes

Nikolay A. Bumagin*, Dmitriy N. Korolev

Department of Chemistry, Moscow State University, Moscow, 119899, Russia
E-mail: bna@bumagin.chem.msu.su

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Abstracts: The cross-coupling reaction of sodium tetra-arylborates with acyl chlorides to give high yields of unsymmetric ketones has been carried out at 20°C in the presence of $Pd(OAc)_2$ and Na_2CO_3 in dry or aqueous acetone. Under aqueous conditions arylboronic acids react smoothly with benzoyl chloride resulting in substituted benzophenones. © 1999 Elsevier Science Ltd. All rights reserved.

The palladium-catalyzed cross-coupling reaction of organoboron compounds with organic electrophiles is a very attractive method for new carbon-carbon bond formation in organic synthesis.[1] This reaction proceeds most effectively in the presence of phosphine-free palladium catalysts in basic aqueous media.[2] Recently we have successfully applied such a modified Suzuki coupling for the allyldeboration of arylboronic acids and sodium tetraphenylborate with allyl electrophiles.[3] It would be interesting from the viewpoint of organic synthesis to extend this approach (The use of phosphine-free Pd-catalysts in basic aqueous media) to the synthesis of unsymmetric ketones by means of acyldeboration of organoboron compounds. Uemura[4] reported that Pd(0)-catalyzed reaction of acyl chlorides and $NaBPh_4$ proceeded in THF at 25°C to give the corresponding phenyl ketones. However, only one phenyl group out of four in the borate was available for transfer.

In connection with our project to use organoboranes as nucleophiles for Pd-catalyzed C-C bond formation, herein we report the phosphine-free palladium-catalyzed acyldeboration of sodium tetra-arylborates and arylboronic acids with acyl chlorides under mild conditions. The results of catalytic coupling of sodium tetra-arylborates with acyl chlorides in dry acetone (nonaqueous procedure)[5] are summarized in Table 1. Sodium tetraphenylborate (0.25 equiv.) reacted with benzoyl, 3-nitrobenzoyl, cinnamoyl, 2-furoyl, 2-thienoyl and octanoyl chlorides (1 equiv.) in the presence of Na_2CO_3 as a base and $Pd(OAc)_2$ (1 mol.%) as the catalyst precursor in dry acetone for 1-6 h to give high yields of ketones (Table 1, entries 1-10). Sodium tetra(*p*-tolyl)borate and tetra(*p*-ethoxyphenyl)borate were also coupled with acyl chlorides to yield substituted benzophenones (entries 11-12).

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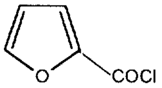
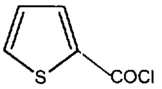
$$\mathrm{NaBAr_4 + 4RCOCl \xrightarrow[Na_2CO_3, acetone, 20^{o}C]{Pd(OAc)_2} 4ArCOR}$$

59-100%

Ar = Ph, p-MeC_6H_4, p-$EtOC_6H_4$; R = Ph, m-$NO_2C_6H_4$, 2-furyl, 2-thienyl, (E)-PhCH=CH, n-C_7H_{15}.

Table 1. Cross-Coupling Reaction of $NaBAr_4$ with RCOCl [a]

Entry	Ar	RCOCl	Time, h	Yield[b], %
1	Ph	PhCOCl	6	96
2[c]	Ph	PhCOCl	1.5	98
3[d]	Ph	PhCOCl	1	96
4[e]	Ph	PhCOCl	15 min	98
5[f]	Ph	PhCOCl	5	97
6	Ph	m-NO_2-C_6H_4COCl	2.5	64
7	Ph	(E)-PhCH=CHCOCl	3	96
8	Ph		1	88
9[7]	Ph		1	95
10	Ph	n-$C_7H_{15}COCl$	5 min	100
11	p-MeC_6H_4	m-NO_2-C_6H_4COCl	2.5	61
12	p-$EtOC_6H_4$	m-NO_2-C_6H_4COCl	1.5	59

a) Reactions were carried out in acetone (9 ml) at 20°C using $NaBAr_4$ (0.25 mmol), RCOCl (1 mmol), Na_2CO_3 (1.5 mmol), and $Pd(OAc)_2$ (0.01 mmol) under argon, unless otherwise noted. b) Isolated yields. c) In acetone-water (10:1). d) In acetone-water (4:1). e) In acetone-water (1:1). f) In pure water.

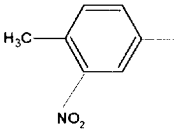
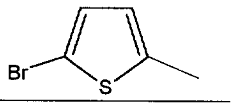
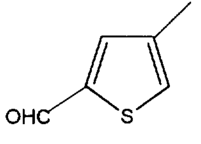
It is important that all four aryl groups of $NaBAr_4$ are available for transfer in the presence of a base. In the case of acyl chlorides, which are stable to hydrolysis, i.e. benzoyl chloride, acyldeboration of sodium tetraphenylborate can be carried out in aqueous acetone. Water strongly effects the reaction time as shown in Table 1. For example, reaction of PhCOCl (1 equiv.) with $NaBPh_4$ (0.25 equiv.) was completed within 6 h in dry acetone and within 15 min in acetone-water mixture (1:1) despite the lower solubility of benzoyl chloride (entry 4).

The participation of all four phenyl groups of $NaBPh_4$ in cross-coupling under basic aqueous conditions prompted us to study the reaction of benzoyl chloride with arylboronic acids under the same conditions. To our knowledge, there have been no reports of ketone synthesis by Pd-catalyzed coupling of acyl halides with arylboronic acids. The results of ligandless Pd-catalyzed acyldeboronation of arylboronic acids are summarized in Table 2 (aqueous procedure).[6] Benzoyl chloride underwent facile coupling with o-, m- and p-tolylboronic acids in the presence of Na_2CO_3 and $PdCl_2$ (1 mol.%) in acetone-water (3:1) to give isomeric methylbenzophenones in high yields (entries 1-2, 6).When the coupling of m-tolylboronic acid with PhCOCl was carried out in dry acetone, THF or under phosphine palladium catalysis, the reaction proceeded more slowly, but yields remained high (entries 3-5). 4-Bromo-2-thienylboronic and 5-formyl-3-thienylboronic acids reacted smoothly with PhCOCl under aqueous conditions to give phenyl(thienyl)ketones in high yields (entries 8-9).

$$ArB(OH)_2 + PhCOCl \xrightarrow[Na_3CO_3,\ Me_2CO\text{-}H_2O,\ 20\,^{\circ}C]{PdCl_2} \underset{76\text{-}96\%}{PhCOAr}$$

Ar = *o*-, *m*-, *p*-MeC_6H_4, 4-Me-3-$NO_2C_6H_3$, 5-bromo-2-thienyl, 5-formyl-3-thienyl

Table 2. Cross-Coupling Reactions of RCOCl with $ArB(OH)_2$[a]

Entry	**Ar**	**Time, h**	**Yield,[b] %**
1	*o*-MeC_6H_4	2	80
2	*m*-MeC_6H_4	1.5	95
3[c]	*m*-MeC_6H_4	72	59
4[d]	*m*-MeC_6H_4	3.5 days	79
5[e]	*m*-MeC_6H_4	10 days	79
6	*m*-MeC_6H_4	2	79
7		1	96
8[8]		1	85
9[9]		1.5	76

a) Reactions were carried out in acetone-water (3:1) at 20°C using $ArB(OH)_2$ (1.05 mmol), PhCOCl (1 mmol), Na_2CO_3 (1.63 mmol) and $PdCl_2$ (0.01 mmol) under argon unless otherwise noted. b) Isolated yield. c) 1 mol.% $PdCl_2(PPh_3)_2$. d) In dry acetone. e) In dry THF.

In conclusion, we have found that phosphine-free palladium-catalyzed reaction of organoboranes with acyl chlorides proceeds readily in aqueous or nonaqueous media to give the corresponding ketones in high yields under extremely mild conditions. Further studies of mechanism and scope of this reaction are in progress.

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5. *Nonaqueous procedure:* Na_2CO_3 *(1.5 mmol), acyl chloride (1 mmol) and* $Pd(OAc)_2$ *(0.01 mmol) were added to a stirred solution of* $NaBAr_4$ *(0.25 mmole) in acetone (9ml) under argon. The reaction mixture was stirred at 20°C for the period indicated in the Table 1. The products were isolated by TLC over silica gel.*
6. *Aqueous Procedure: Benzoyl chloride (1mmol) and aqueous 0.1 M* $PdCl_2$ *(0.1 ml, 0.01mmol) were added to a stirred mixture of* $ArB(OH)_2$ *(1.05 mmol) [or* $NaBAr_4$ *(0.25 mmol)], aqueous 1.63 M* Na_2CO_3 *(1 ml, 1.63 mmol),* H_2O *(1 ml) and 6 ml of acetone under argon. The reaction mixture was stirred at 20°C for the period indicated in the Table 2. The products were isolated by TLC over silica gel.*
7. ^{1}H NMR data (400 MHz, acetone-D_6): 8.57(dd, 1 H, $J=1$ Hz, $J=5$ Hz, thiophene ring), 8.48(dd, 2 H, $J=1.5$ Hz, $J=7$ Hz, *o*-H, Ph), 8.31(dd, 1 H, $J=1$ Hz, $J=3.5$ Hz, thiophene ring), 8.26(t, 1 H, $J=4$, thiophene ring), 8.12(t, 2 H, $J=7.5$, *m*-H, Ph), 7.86(dd, 1 H, $J=3.5$ Hz, $J=5$ Hz, *p*-H, Ph).
8. ^{1}H NMR data (400 MHz, acetone-D_6): 8.2(m, 3 H), 7.8(m, 1 H), 7.65(m, 3 H).
9. ^{1}H NMR data (400 MHz, acetone-D_6): 10.09(br s, 1 H, CHO), 8.62(br s, 1 H, thiophene ring), 8.38(br s, 1 H, thiophene ring), 7.91(d, 2 H, $J=7$ Hz, *o*-H, Ph), 7.70(t, 1 H, $J=7.5$ Hz, *p*-H, Ph), 7.59(t, 2 H, $J=7.5$ Hz, *m*-H, Ph).