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Reactivities of mixed organozinc and mixed organocopper reagents, 2. Selective *n*-alkyl transfer in tri-*n*-butylphosphine-catalyzed acylation of *n*-alkyl phenylzincs; an atom economic synthesis of *n*-alkyl aryl ketones

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ABSTRACT

Tri-*n*-butylphosphine-catalyzed acylation of mixed *n*-alkyl phenylzincs with aromatic acyl halides in THF is efficient in selective transfer of *n*-alkyl groups to produce *n*-alkyl aryl ketones in good yields. This route provides an atom economic organocatalyzed alternative to transition metal-catalyzed acylation of di-*n*-alkylzincs.

Diorganozinc reagents (R_2Zn) are important organometallic compounds due to their high reactivity, ease of preparation and compatibility with many functional groups.[1] However, in their reactions, only one of the R groups is transferred to the electrophile. Mixed diorganozincs, R^1R^2Zn, in which one of the R groups has a lower rate of transfer than the other have been developed.[2] Ethyl and *tert*-butyl groups were found to react more slowly than other alkyl, vinyl and phenyl groups.[2a–e] Mixed diorganozincs, R_RR_TZn, which carry one transferable group (R_T) and one residual group (R_R) have recently proved to be synthetically useful.[3] Knochel showed that trimethylsilylmethyl (Me_3SiCH_2),[3a] neopentyl (*t*-$BuCH_2$) and neophyl ($PhMe_2CCH_2$) groups[3b] are excellent R_R groups.

Our literature survey has revealed that the dependence of transfer selectivity of the organyl groups in mixed diorganozincs, R^1R^2Zn, on the reaction parameters has not been investigated in detail. In continuation of our work on this subject, we recently reported that the relative transfer ability of organyl groups in *n*-butyl phenylzinc depends on the reaction conditions in their copper-catalyzed reaction with benzoyl chloride in THF.[4] We succeeded in controlling *n*-butyl or phenyl group transfer by using N- or O-donor cosolvents or an additive, such as tri-*n*-butylphosphine. In THF:*N*-methyl-2-pyrrolidinone (NMP) (3:1) and in THF:diethyleneglycol dimethyl ether (diglyme) (3:1), the *n*-butyl/phenyl group transfer ratio was 9:1 whereas only *n*-butyl group transfer was observed in THF:*n*-Bu_3P. The *n*-butyl/phenyl group transfer/ratio was 1:9 in THF: *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) (2:1).

It is remarkable that the copper-catalyzed chemoselective acylation of mixed alkyl arylzincs with an acyl halide can be carried out in THF:*n*-Bu_3P or in THF:TMEDA to yield alkyl ketones or aryl ketones in good yields, respectively.

In fact, acylation of organometallic compounds using acyl chlorides, which are cheap acylating agents provides a direct and convenient procedure for the synthesis of ketones[5] and also overcomes some typical drawbacks of Friedel–Crafts acylations such as reduced functional group tolerance and limitations due to substituent-directing effects. Diorganocuprates,[6] transition metal-catalyzed organolithiums,[7] Grignard reagents[8] and mono- and diorganozincs[1,9] are widely used organometallic species in acylation reactions. Protocols for the synthesis of ketones by acylation of Grignard reagents in the presence of a Lewis base (tri-*n*-butylphosphine[10a] or more recently, bis[2-(*N*,*N*-dimethylamino)ethyl]ether)[10b] and acylation of diorganozincs in the presence of a Lewis acid ($AlCl_3$[11]) have also been reported. Mixed diorganocuprates, R_RR_TCuM (M: Li, MgBr) with residual groups (R_R = RO, RS, R_2N, Me, RC≡C, $PhSO_2CH_2$) have been used for selective and effective transfer of R_T groups to acyl chlorides.[6a] However, there is no reported work on selective acylation of mixed diorganozincs, R_RR_TZn. We therefore decided to study the synthetic applicability of the acylation of *n*-alkyl arylzincs in more detail.

Herein, we report that acylation of *n*-alkyl phenylzincs with aromatic acyl chlorides in the presence of tri-*n*-butylphosphine

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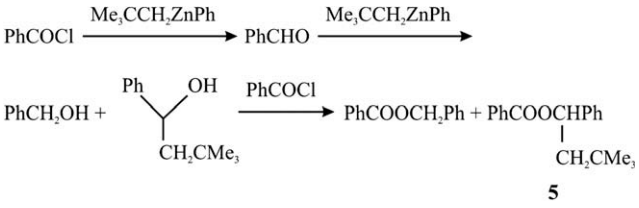
provides an alternative atom economic route for the synthesis of *n*-alkyl aryl ketones by acylation of di-*n*-alkylzincs in the presence of transition metal catalysts.

We first carried out copper-catalyzed acylation reactions of a number of alkyl arylzincs with benzoyl chloride to determine the transfer selectivity of alkyl or aryl groups in THF in the presence of the cosolvents NMP, diglyme or TMEDA. We prepared alkyl arylzincs by an in situ method, that is, arylzinc chloride, which was prepared by transmetallation of arylmagnesium bromide, was allowed to react with alkylmagnesium bromide. We determined the relative transfer ability of the organyl groups by calculating the GC yields of ketones using authentic samples in the acylation of the following R^1R^2Zn reagents: (R^1,R^2=*n*-Bu, 4-MeC_6H_4; *n*-Bu, 4-$MeOC_6H_4$; *n*-heptyl, Ph). The *n*-alkyl/aryl group transfer ratios were found to be about 8:1 in THF:NMP (3:1) and in THF: diglyme (2:1), and 1:9 in THF:TMEDA (2:1), which are not that different from those of *n*-BuPhZn. As observed, complete transfer of either the R^1 group or R^2 group does not take place. We also acylated neopentyl phenylzinc to check the transfer ability of a neopentyl group since this group was reported as a residual group in a number of reactions.[3a–c] However, neopentyl phenylzinc behaved similarly to other *n*-alkyl phenylzinc reagents in the acylation with benzoyl chloride under copper catalysis, that is, selective transfer of the neopentyl group took place, in THF: diglyme (2:1).

Thus, instead of further investigating the potential synthetic transfer of organyl groups in alkyl arylzinc reagents in THF in the presence of cosolvents, we carried out a detailed examination of *n*-Bu_3P catalysis for complete transfer of alkyl groups in alkyl arylzincs to acyl halides. As reported in our recent paper,[4] we found that selective transfer of the *n*-butyl group in the benzoylation of *n*-butyl phenylzinc could also be carried out in 86% yield in the presence of *n*-Bu_3P (1 equiv), but without CuI catalysis. We performed optimization experiments on the amount of *n*-Bu_3P required and the solvent. We found that possible catalytic formation of benzoyl tri-*n*-butylphosphonium chloride, $(PhCO)P^+(n\text{-}Bu)_3Cl^-$,[10a] in the presence of 10% *n*-Bu_3P also acylates the *n*-butyl group in *n*-butyl phenylzinc in a yield of 83%. Carrying out the *n*-Bu_3P-catalyzed benzoylation in the presence of THF:NMP (3:1) or THF:diglyme (2:1), which worked well for selective transfer of the *n*-butyl group did not increase the yield.

Having confirmed that the acylation of *n*-butyl phenylzinc with benzoyl chloride in THF in the presence of 10 mol % of *n*-Bu_3P results in selective transfer of the *n*-butyl group in good yield, we made a brief examination of the acylation of alkyl phenylzincs **1** with acyl halides **2** in the presence of *n*-Bu_3P **3**. The results are summarized in Table 1.

Acylation of *n*-alkyl phenylzincs with benzoyl chloride occurs chemoselectively to afford *n*-alkyl aryl ketones **4** in high yields (entries 1–3). It was reported that *n*-alkyl carbanions produce excellent yields whereas α-branched carbanions provide lower yields of ketones due to the formation of side products.[10] Hence, we did not examine the acylation of *sec*- and *tert*-alkyl phenylzincs, but we did study the outcome of the benzoylation of hindered neopentyl phenylzinc (entry 4). GC analysis using authentic samples of neopentyl phenyl ketone and benzophenone showed that the neopentyl group was not acylated chemoselectively, instead the phenyl group was acylated in a low yield. However, GC–MS analysis showed the formation of **5** as a co-product produced from the Meerwein–Pondorf–Verley type reduction of benzoyl chloride with neopentyl phenylzinc (Eq. 1).[10]

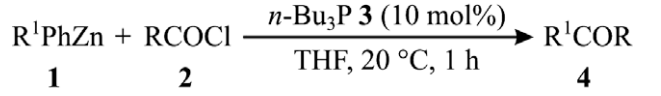


(1)

We also prepared a mixed 1,6-dizinc reagent by transmetallation of a 1,6-di-zinc reagent with 2 equiv of $ZnCl_2$ and then by reaction of the 1,6-di-Grignard reagent with 2 equiv of phenylmagnesium bromide. Acylation of $PhZn(CH_2)_6ZnPh$ gave the expected 1,6-diketone, $PhCO(CH_2)_6COPh$ in good yield (entry 5). 4-Acetoxy-1-butyl phenylzinc was also acylated successfully in a slightly lower yield (entry 6).

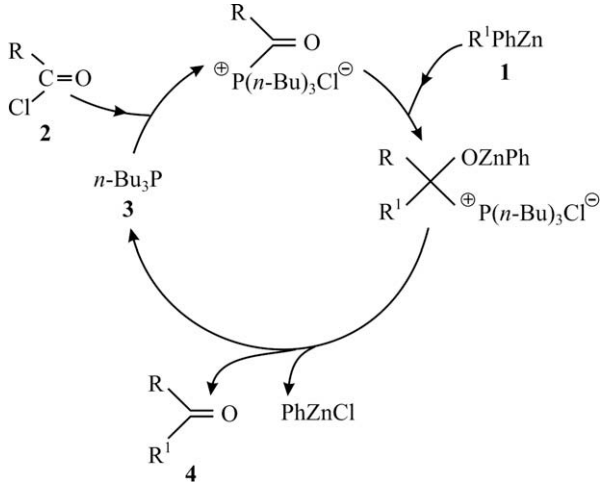
Acylation of *n*-butyl phenylzinc with 4-methylbenzoyl chloride produced a high yield of the expected ketone (entry 7). However, pivaloyl chloride did not acylate *n*-butyl phenylzinc chemoselectively in the presence of 10 mol % of *n*-Bu_3P. GC analysis using authentic samples of *n*-butyl *tert*-butylketone[10a] and phenyl *tert*-butylketone showed that both groups were acylated in low yields. However, in the presence of 1 equiv of *n*-Bu_3P, we were able to acylate the *n*-butyl group chemoselectively but only in low yield (entry 8). The use of succinoyl chloride for the acylation of *n*-butyl phenylzinc did not give acylated products but polymeric by-products instead. However, succinoyl chloride was also reported to give complex mixtures in the acylation of cuprates.[12]

Table 1
n-Bu_3P-catalyzed acylation of mixed *n*-alkyl phenylzincs in THF[a]



Entry	R^1	R	Yield[b] (%)
1	*n*-Bu	Ph	77
2	*n*-heptyl	Ph	80
3	*n*-decyl	Ph	90
4	Np	Ph	[c]
5	$PhZn(CH_2)_6$	Ph	67[d]
6	$MeCOO(CH_2)_4$[e]	Ph	54
7	*n*-Bu	4-MeC_6H_4	83
8	*n*-Bu	Me_3C	38[f]

[a] Compound **1** was prepared in situ by reacting PhZnCl with R^1MgBr in THF. See experimental, Ref. 13.
[b] Isolated yield. The products were fully characterized by ^1H NMR analysis.
[c] Side product **5** formed. See text.
[d] The product is the α,ω-diketone: $PhCO(CH_2)_6COPh$.
[e] Compound **1** (R^1=$MeCO(CH_2)_4$) was prepared in situ by reacting R1ZnBr with PhMgBr. See experimental, Ref. 13.
[f] GC yield in the presence of 1 equiv of *n*-Bu_3P.



Scheme 1. A possible catalytic role for *n*-Bu_3P in *n*-Bu_3P-catalyzed acylation of *n*-alkyl phenylzincs.

Depending on the formation of acyl *n*-butylphosphonium ions as acylating reagents,[10a] we propose a possible sequence of reactions that enables *n*-Bu_3P to function in a catalytic mode for the *n*-Bu_3P-catalyzed chemoselective acylation of *n*-alkyl phenylzincs to give *n*-alkyl ketones (Scheme 1).

In conclusion, we have shown that selective acylation of *n*-alkyl groups in *n*-Bu_3P-catalyzed reactions of mixed *n*-alkyl phenylzincs reagents with aromatic acyl halides in THF is an efficient method for the synthesis of *n*-alkyl arylketones.[13] This route provides a simple and atom economic alternative to transition metal-catalyzed acylation of di *n*-alkylzinc reagents. Further studies concerning the functional group selectivity of mixed diorganozincs in acylation and C–C and C–heteroatom coupling reactions are underway.

Acknowledgement

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13. *Typical procedure for the acylation of n-alkyl phenylzincs*: All reactions were carried out in oven-dried glassware under a positive pressure of nitrogen using standard syringe-septum cap techniques. GC analyses were performed on a Thermo Finnigan gas chromatograph equipped with a ZB-5 capillary column packed with phenylpolysiloxane using the internal standard technique.[14] Phenylzinc chloride was prepared by addition of 1 equiv of phenylmagnesium bromide to a solution of 1 equiv of $ZnCl_2$ in THF at −20 °C and stirring at that temperature for 15 min. 4-Acetoxy-1-butylzinc chloride was prepared by direct LiCl promoted insertion of Zn into 4-acetoxy-1-iodobutane.[15] A two-necked flame-dried flask was charged with $ZnCl_2$ (10 mmol) in THF (10 ml) and cooled to −20 °C. Phenylmagnesium bromide (10 mmol) was added at −20 °C with stirring. To freshly prepared phenylzinc chloride, *n*-alkylmagnesium bromide (10 mmol) was added and the mixture was stirred at that temperature for 15 min. For the preparation of mixed 4-acetoxy-1-butyl phenylzinc, 4-acetoxy-1-butylzinc chloride was mixed with phenylmagnesium bromide. To the mixed *n*-alkyl phenylzinc and *n*-Bu_3P (1 mmol, 0.2 ml), acyl halide (10 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. The mixture was hydrolyzed by addition of 1M HCl and subsequently extracted with Et_2O. The combined ethereal solutions were washed with aq $NaHCO_3$ solution, dried, concentrated by rotary evaporation and subjected to silica gel column chromatography with hexane:EtOAc (1:1) as eluent to give *n*-alkyl aryl ketones. ^1H NMR spectroscopic data of the acylation products of selected reactions.
(Table 1, entry 2) ^1H NMR (400 MHz ,$CDCl_3$) δ: 0.88 (t, 3H, J = 7.2 Hz), 1.26–1.36 (m, 8H), 1.74 (m, 2H), 2.95 (t, 2H, J = 7.2 Hz), 7.43–7.47 (m, 2H), 7.52–7.56 (m, 1H), 7.94–7.96 (m, 2H).
(Table 1, entry 5) ^1H NMR (400 MHz, $CDCl_3$) δ: 1.43 (m, 4H), 1.75 (m, 4H), 2.97 (t, 4H, J = 7.2 Hz), 7.45 (m, 4H), 7.55 (m, 2H), 7.95 (dd, 4H, J = 7.6 Hz, J = 1.4 Hz).
(Table 1, entry 6) ^1H NMR (400 MHz, $CDCl_3$) δ: 1.70–1.84 (m, 4H), 2.03 (s, 3H), 3.01 (t, 2H, J = 7.2 Hz), 4.01 (t, 2H, J = 7.2 Hz), 7.45 (m, 2H), 7.55 (m, 1H); 7.95 (m, 2H).
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