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Reactivity of mixed organozinc and mixed organocopper reagents: **12.** Three component reaction of mixed (n-alkyl)(diaryl)zincates, chloroformates and phosphines for the synthesis of esters

Duygu Özkan, Ender Erdik*

Ankara University, Science Faculty, Beşevler, Ankara 06100, Turkey

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ABSTRACT

The reaction of mixed n-butyldiphenylzincate, n-BuPh$_2$ZnMgBr with ethyl chloroformate, ClCOOEt in the presence n-Bu$_3$P in THF takes place with quantitative yield and phenyl group transfer to give PhCOOEt. Ethoxycarbonylation of n-BuPh$_2$ZnMgBr is preferable to the reaction of PhMgBr forming ester and triphenylcarbinol and also to the reaction of triphenylzincate, Ph$_3$ZnMgBr for atom economy. Group selectivity in the phosphine catalyzed C–COOR coupling of n-BuPh$_2$ZnMgBr and n-Bu$_2$PhZnMgBr can be controlled by changing reaction parameters. n-Bu$_3$P catalyzed reaction of n-BuPh$_2$ZnMgBr with ClCOOEt takes place with phenyl selectivity whereas reaction of n-Bu$_2$PhZnMgBr with ClCOOPh results in n-butyl transfer. Catalysis by Ph$_3$P increases n-butyl group:phenyl group transfer ratio in the ethoxycarbonylation of both zincates. Selective transfer of aryl groups in n-Bu$_3$P catalyzed reaction of n-butyl(aryl)$_2$ZnMgBr reagents with ClCOOEt in THF provides a new procedure for the organometallic synthesis of arenecarboxylic acid ethyl esters at room temperature.

1. Introduction

Organozinc reagents [1–3] are widely used organometallic reagents in organic synthesis due to their increased reactivity in the presence of transition metal and/or organic catalysis, availability of a number of methods for their preparation and their compatibility with many functional groups compared with organolithium and Grignard reagents.

Triorganozincates, R$_3$ZnM (M = Li, MgX; X = Br, Cl) represent a class of organozinc reagents which are more reactive than diorganozincs, R$_2$Zn and organylzinc halides, RZnX. However, triorganozincates have not been used in organic synthesis [4–8] as extensively as organozinc halides and diorganozincs.

The serious drawback in the synthetic use of R$_2$Zn and R$_3$ZnM reagents is the transfer of only one of the R groups to the electrophile leading to the low atom-economy in their reactions. To avoid this problem, mixed diorganozincs R^{1}R^{2}Zn [9–12] and mixed triorganozincates R^{1}R$^2_2$ZnM [13,14] have been developed, in which one of the R groups has a higher transfer rate than the other one. Mixed diorganozincs. R$_R$R$_T$Zn [15–18] and triorganozincates, R$_T$(R$_R$)$_2$ZnM [19–25] are synthetically useful reagents.

In the group selectivity of mixed cuprates R^{1}R^{2}CuLi, the commonly accepted hypothesis is that the group in R^{1}R^{2}CuLi that has a stronger bond to Cu acts as the group of lower selectivity [1,26–28].

In our serial work on the reactivity and group selectivity control of mixed organozinc and copper reagents [29–39], we observed that the group transfer of an organyl group as R$_T$ in mixed diorganozincs R^{1}R^{2}Zn [29–31,34,35], diorganocuprates, R^{1}R^{2}CuM (M = MgBr [32,37,38], ZnCl [38]) and copper catalyzed mixed triorganozincates, R^{1}R$^2_2$ZnMgBr [33,37] can be controlled by changing reaction parameters, i.e. counter ion, M, leaving group of the electrophile, solvent, temperature, transition metal catalyst and organic catalyst. We hypothesized that in reactions of mixed reagents, R^{1}R^{2}Zn and R^{1}R^{2}CuM, R^1 group can change not only the transfer ability, but also the transfer rate of R^2 group leading to different reaction rate of mixed reagents than that of homo reagents R$^2_2$Zn and R$^2_2$CuM [33,36,39]. We also developed new atom-economic procedures for C-organyl [32–34,37], C–N [31] and C–COR [29,30,34] coupling reactions using mixed diorganozinc reagents, R$_R$R$_T$Zn. However, to the best of our knowledge, the reactivity and group selectivity in reactions of mixed organozincates R^{1}R$^2{}_2$ZnM (M = Li, MgBr) has not been intensively investigated.

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* Corresponding author.
E-mail address: erdik@science.ankara.edu.tr (E. Erdik).

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Ester functionality is one of the most common functional groups and can be prepared using a number of metal free and metal catalyzed methods [40,41]. However, to the best of our knowledge, the use of C—COOR coupling of organolithium, -magnesium and -zinc reagents and diorganocuprates is very limited [42,43]. Due to the importance of a selective acylation procedure for carbanions, we focused our interest on the applicability of mixed R^1R^2Zn and $R^1(R^2)_2ZnMgBr$ reagents for organometallic synthesis of esters.

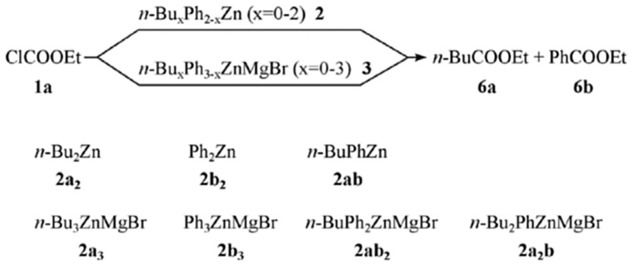
Here, we report our progress on the control of group selectivity of (*n*-alkyl)(aryl)$_2$zincates in acylation with chloroformate esters, ClCOOR and achieving a protocol for the conversion of C_{aryl}—Zn bond to C_{aryl}—COOR bond.

2. Results and discussion

As a model reaction to investigate the group selectivity of mixed R^1R^2Zn (**2**) and $R^1(R^2)_2ZnMgBr$ (**3**) reagents with chloroformates, we chose *n*-butyl and phenyl groups in these reagents to transfer to ethyl chloroformate, ClCOOEt (**1a**) in THF (Scheme 1). We also investigated the reaction of homo diorganozincs and homo triorganozincates to compare with mixed reagents for atom-economy in the synthetic application.

We used magnesium-based diorganozincs and triorganozincates. For the preparation of mixed diorganozinc **2ab**, PhZnCl was allowed to react with *n*-BuMgBr in a one pot procedure [30]. The same procedure can be also applied by reacting *n*-BuZnCl with PhMgBr. Mixed triorganozincates **3ab$_2$** and **3a$_2$b** were also prepared easily using *n*-butyl- and phenylzinc reagents and *n*-butyl- and phenyl Grignard reagents [34].

The original attachment of *n*-Bu or Ph groups to Zn or Mg does not make a change on the transfer ability of these groups in mixed diorganozincs and triorganozincates [34].



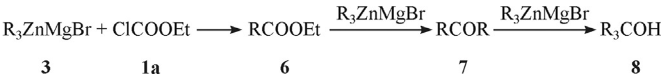
Scheme 1. Ethoxycarbonylation of homo and mixed diorganozincs, $n\text{-}Bu_xPh_{2-x}Zn$ (x = 0–2) (**2**) and mixed triorganozincates, $n\text{-}Bu_xPh_{3-x}ZnMgBr$ (x = 0–3) (**3**).

First, we determined the effect of the reaction parameters on the group selectivity of mixed triorganozincates, $n\text{-}BuPh_2ZnMgBr$ (**3ab$_2$**) and $n\text{-}Bu_2PhZnMgBr$ (**3a$_2$b**) in their reaction with ethyl chloroformate (**1a)** in THF. In the initial study, we determined the background yields using homozincates, tri*n*-butylzincate (**3a$_3$**) and triphenylzincate (**3b$_3$**).

Table 1 summarizes the yields and group selectivities, i.e. *n*-Bu group: Ph group transfer ratios in the ethoxycarbonylation of homo zincates, **3a$_3$** and **3b$_3$** and mixed zincates, **3ab$_2$** and **3a$_2$b**. Transfer abilities of organyl groups were found by calculating the GC yields of ketones using authentic samples of **6a** and **6b**. The reaction temperature and time was optimized to be 25 °C and 1 h, respectively. The reaction of **3a$_3$** gave the product ester **6a** in 43% yield whereas **3b$_3$** afforded the ester **6b** in a lower yield of 22% (entries 1 and 2).

Ethoxycarbonylation of mixed zincate **3ab$_2$** resulted in a good total yield of 76% with a **6a**:**6b** ratio of 10:90 (entry 3). For the reaction of mixed zincate **3a$_2$b**, a total yield of 48% was obtained with a **6a**:**6b** ratio of 25:75 (entry 4).

The inherent difficulty in the reaction of organozincate reagents **3** with chloroformate ester **1a** is possible formation of ketones **7** and tert-alcohols **8** as side products (1). However, in the reaction of homo and mixed zincates, ketones were not detected and the yield of ter-alcohols, $n\text{-}Bu_3COH$ and Ph_3COH did not exceed 10%.



$$\underset{\mathbf{3}}{R_3ZnMgBr} + \underset{\mathbf{1a}}{ClCOOEt} \longrightarrow \underset{\mathbf{6}}{RCOOEt} \xrightarrow{R_3ZnMgBr} \underset{\mathbf{7}}{RCOR} \xrightarrow{R_3ZnMgBr} \underset{\mathbf{8}}{R_3COH} \qquad (1)$$

As seen, much lower ethoxycarbonylation yields of *n*-Bu group, i.e. 8% and 12% were obtained using mixed zincates **3ab$_2$** and **3a$_2$b** respectively, compared to the yield obtained in the reaction of homozincate **3a$_3$**, i.e. 43%. However, we were excited by the ethoxycarbonylation yields of Ph group, i.e. 68% and 36% using mixed zincates **3ab$_2$** and **3a$_2$b**, respectively, which are higher than the yield obtained in the reaction of homozincate **3b$_3$**, i.e. 22%. Next, expecting a change in *n*-Bu group or Ph group transfer, we investigated the effect of transition metal catalysis and organic catalysis on the group selectivities in the ethoxycarbonylation of **3ab$_2$**. As transition metal catalysts, a range of Cu, Ag, Ni and Pd salts were screened (Table 1). The use of CuI as a catalyst lowered the total yield to 24% in the reaction of **3ab$_2$** (entry 5) and the yield was further decreased to 12% in the presence of CuCN and $CuBr.Me_2S$. The use of AgI or $AgOCOCF_3$ as a catalyst in the reaction of **3ab$_2$** led to a modest yield of about 40% (entries 6 and 7) with phenyl selective coupling. $NiCl_2(PPh_3)_2$ catalysis did not give a yield higher than 18% (entry 8). Ethoxycarbonylation in the presence of $PdCl_2$ did not proceed to completion with a yield of 44% (entry 9) and catalysis with $Pd(OAc)_2$ or PEPPSI-iPr resulted in inferior yields of 36% and 4%, respectively with phenyl selectivity. Unreacted ethyl chloroformate **1a** was mostly recovered in transition metal-free and catalyzed reactions of zincates.

The reaction of homodiorganozincs, di*n*-butylzinc (**2a$_2$**), diphenylzinc (**2b$_2$**) and mixed *n*-butylphenylzinc (**2ab**) in ethoxycarbonylation with **1a** did not take place and gave dramatically low yields of 7–10% in the presence of CuI catalysis.

In studying the effects of organic catalysis on the group selectivity of mixed triorganozincates in their reaction with **1a,** we used donor solvents as cosolvents in THF and Lewis bases as additives. In ethoxycarbonylation of **3ab$_2$** in THF, we used donor solvents, NMP, diglyme, DMF and also TMEDA as cosolvents. The results showed that increasing polarity of the solvent prevented the organyl groups from transferring to C=O group resulting in yields lower than 5%. The recovery of ethyl chloroformate **1a** only in 20–40% yield suggests a possible reaction between these N-donor and O-donor solvents and **1a**. In fact, it is known that tert-amines react with chloroformate esters to give carbamates under appropriate conditions [44]. However, we did not turn our attention to a possible reaction of donor solvents with **1a**.

We already found $n\text{-}Bu_3P$ and Ph_3P as successful additives to carry out the acylation of *n*-BuPhZn (**2ab**) in high yield with complete *n*-Bu group transfer and developed a phosphine catalyzed acylation of mixed (*n*-alkyl)phenylzincs with aromatic acyl chlorides for the synthesis of *n*-alkylarylketones [30]. In acylation of Grignard reagents [45] and diorganozincs [30] possible *in situ* formation of acylphosphonium salts, $(RCO)P^{\oplus}R_3Cl^{\ominus}$ have been reported [30,45]. So expecting formation of a similar phosphonium salt, $(EtOOC)P^{\oplus}R_3Cl^{\ominus}$ from ClCOOEt (**1a)** and R_3P, we tried phosphine catalysis to see if the yield increases and/or group selectivity changes in ethoxycarboylation (Table 2). We observed that $n\text{-}Bu_3P$ catalysis proceeded the reaction with a quantitative yield and complete phenyl selectivity (entries 1 and 2) compared with