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Chemistry of ketone α,β-dianions. Acylation reactions of dianion cuprates by acid chlorides

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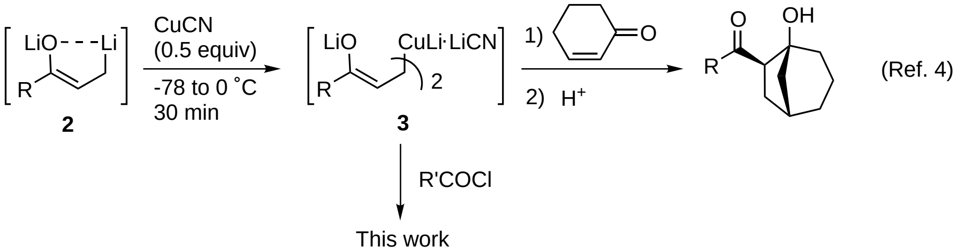
Abstract—The cross-coupling reaction of dianion cuprates, generated from ketone α,β-dianions and copper salts, with acid chlorides, was studied. The reaction gave good to moderate yields of unsymmetrical 1,4-diketones. The consecutive treatment of a dianion cuprate with cyclohexanecarbonyl chloride and methyl iodide or two different acid chlorides gave 2-methyl-substituted 1,4-diketone or triketone, respectively. © 2002 Elsevier Science Ltd. All rights reserved.

In spite of the rapid growth of the anion chemistry in organic synthesis,[1] the potential of dianions as synthetic intermediates has yet to be fully explored. Of particular interest to us is the use of ketone dianions (enolate anions having another carbanion function) as a platform for the construction of a ketone framework and, related to this, we have previously reported on the generation of ketone α,β-dianions **2** and their reactions with electrophiles.[2,3] Dianion cuprates **3**[4] are unique, since, in contrast to dianion zincates,[5] which undergo a normal mode of conjugate addition to enones to give unsymmetrical 1,6-diketones, they undergo formal [3+2] cycloadditions with enones to give bicyclic alcohols (Scheme 1). Since the reaction of organocuprate reagents with acid halides is one of the most popular reactions available for the synthesis of unsymmetrical ketones,[6] this fact led us to examine the reaction of dianion cuprates with acid chlorides. In this communication, we report that (i) the desired cross-coupling reaction takes place even with the case of dianion cuprates, thus providing a new route to unsymmetrical 1,4-diketones, and (ii) the consecutive addition of an acid chloride and methyl iodide or two different acid chlorides gave the corresponding three-component assembled products.

The formation of ketone α,β-dianions **2** and their conversion to the corresponding cuprates **3** were carried out according to our previously reported protocol and involved the direct reaction of β-dichlorobutylstannyl ketones **1** with *n*-BuLi.[4] Typically, dianion cuprates **3**, which were prepared by the consecutive treatment of **1** (1 mmol) with *n*-BuLi (4 mmol) and CuCN (0.5 mmol) in THF, were then treated with acid chlorides (0.5



Scheme 1.

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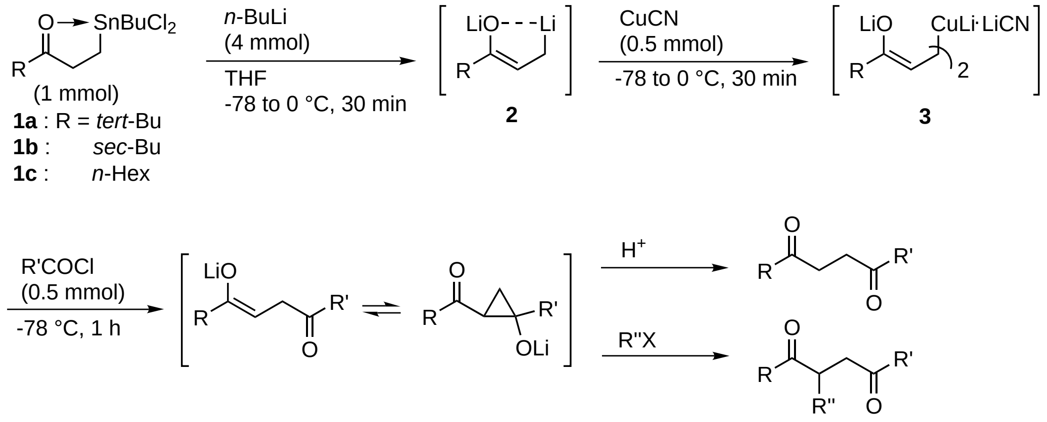
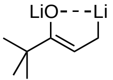
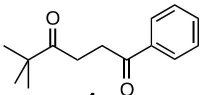
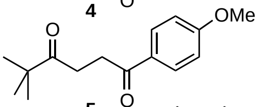
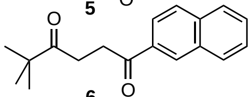
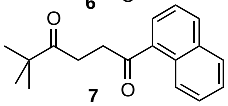
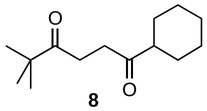
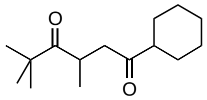
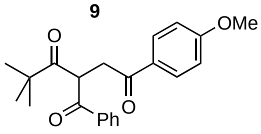
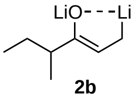
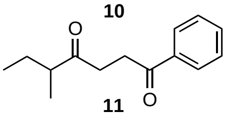
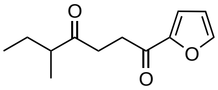
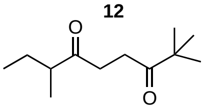
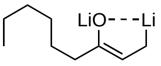
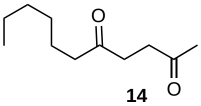


Scheme 2.

Table 1. Reaction of dianion cuprates **3** with acid chlorides[a]

run	α,β-dianion **2**	reagents (conditions)	product	isolated yield[b]
1	 **2a**	1) CuCN (-78 to 0 °C) 2) PhCOCl (-78 °C)	 **4**	58%
2		1) CuCN (-78 to 0 °C) 2) *p*-MeOPhCOCl (-78 °C)	 **5**	64%
3		1) CuCN (-78 to 0 °C) 2) 2-NaphthylCOCl (-78 °C)	 **6**	54%
4		1) 2-ThienylCu(CN)Li (1 equiv, -78 °C) 2) 1-NaphthylCOCl (-78 °C)	 **7**	40%
5		1) CuCN (-78 to 0 °C) 2) CyclohexylCOCl (-78 °C)	 **8**	53%
6		1) CuCN (-78 to 0 °C) 2) CyclohexylCOCl (-78 °C) 3) MeI (5 equiv, -78 to -45 °C with HMPA)	 **9**	41%
7		1) CuCN (-78 to 0 °C) 2) *p*-MeOPhCOCl (-78 °C) 3) PhCOCl (4 equiv, -78 to -40 °C)	 **10**	59%[c]
8	 **2b**	1) CuCN (-78 to 0 °C) 2) PhCOCl (-78 °C)	 **11**	76%
9		1) CuCN (-78 to 0 °C) 2) 2-FurylCOCl (-78 °C)	 **12**	68%
10		1) 2-ThienylCu(CN)Li (1 equiv, -78 °C) 2) *t*-ButylCOCl (-78 °C)	 **13**	43%
11	 **2d**	1) CuCN (-78 to 0 °C) 2) MeCOCl (-78 °C)	 **14**	49%

[a] For a general procedure, see footnote 6. [b] Flash chromatography on silica gel was performed for isolation. [c] 2,4,4-Trimethyl-1-phenyl-1,3-pentanedione was formed as a principal byproduct.

mmol) at −78°C for 1 h. Aqueous workup and purification of the crude mixture by silica gel chromatography gave 1,4-diketones (Scheme 2).[7] As summarized in Table 1, both aromatic and aliphatic acid chlorides undergo the expected cross-couplings at −78°C, to give good to moderate yields of 1,4-diketones. Mixed cuprates comprised of α,β-dianions and 2-thienylCu(CN)Li were also found to give unsymmetrical ketones, albeit in rather modest yields (runs 4 and 10). It should be noted that, in the case of 1:1 reactions, we frequently observed the formation of a symmetrical 1,6-diketone as a byproduct, which is likely formed via the dimerization of lithioxyallylcopper(I), arising from the first acylation of the cuprates **3**.[8]

We also attempted to trap the resulting enolates, which would lead to three-component coupling reactions. Thus, the consecutive treatment of dianion cuprate **3** with cyclohexanecarbonyl chloride (1 mol equiv.) and MeI (5 mol equiv., with HMPA) gave the predicted 2-methylated 1,4-diketone **9** in 41% yield (run 6). An experiment using two different acid chlorides was also successful and gave triketone **10** in 59% yield, in which the second reagent underwent *C*-acylation of the enolate portion (run 7).

In summary, we have shown that the cross-coupling reaction of organocuprate **3** with acid chlorides gives unsymmetrical 1,4-diketones in good to moderate yields. The resulting enolate can be further methylated at the α-position or acylated with a different acid chloride to give the corresponding three-component coupling products. Efforts to extend ketone dianion chemistry to other useful processes are now underway and will be reported in due course.

Acknowledgements

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7. A typical procedure for the reaction of cuprates with acid chlorides (run 8): To a cooled solution (−78°C) of β-dichlorobutylstannyl ketone **1b** (360 mg, 1 mmol) in THF (10 mL) was added *n*-BuLi (2.59 mL, 1.54 M solution in hexane, 4 mmol) dropwise over a period of 5 min under an atmosphere of argon. This solution was allowed to warm to 0°C followed by stirring for 30 min. To a suspension of copper cyanide (45 mg, 0.5 mmol) in THF (2 mL) was added a precooled solution (−78°C) of the resulting α,β-dianion **2b** (1 mmol, 10 mL in THF) via a cannula at −78°C. The reaction mixture was allowed to warm to 0°C over a 20 min period and was stirred for 10 min at 0°C. After cooling to −78°C, benzoyl chloride (54 μL, 0.5 mmol) was added to this homogeneous solution of lithium cuprate **3b**. Stirring was continued for 1 h at −78°C, and the resulting dark purple solution was then treated with a mixture of saturated aqueous NH_4Cl and concentrated NH_4OH solutions (1:1, 2 mL) at −78°C. The reaction mixture was warmed to ambient temperature and poured into saturated aqueous NH_4Cl (40 mL). The aqueous layer was separated and extracted with Et_2O (40 mL×3), and the organic phases were combined, dried, and concentrated in vacuo. Purification by flash chromatography (elution with hexane/Et_2O, 8:1) provided the desired 1,4-diketone **11** (83 mg, 76%) as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, 3H, $J=7.6$ Hz), 1.13 (d, 3H, $J=6.8$ Hz), 1.44 (m, 1H), 1.76 (m, 1H), 2.57 (m, 1H), 2.94 (t, 2H, $J=6.4$ Hz), 3.27 (t, 2H, $J=6.4$ Hz), 7.45–7.56 (m, 3H), 7.98 (d, $J=6.8$ Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.6, 15.9, 26.0, 32.2, 34.8, 48.0, 128.0, 128.5, 133.0, 136.8, 198.7, 213.2; EIMS m/z (relative intensity, %) 218 (M^+, 10), 161 ($M^+-C_4H_9$, 100), 105 (38), 77 (Ph, 21), 57 (C_4H_9, 21); IR (neat, cm^{-1}) 1712 ($\nu_{C=O}$), 1689 ($\nu_{C=O}$); HRMS calcd for $C_{14}H_{18}O_2$: 218.1307. Found: 218.1305; anal. calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.96; H, 8.37.
8. This was tested in a separate experiment. A THF solution involving dianion copper(I), separately generated from dianion **2a** and an equimolar amount of copper cyanide at −78°C, when warmed to 0°C, gave the symmetrical 1,6-diketone in 45% yield after proton quenching. For examples of homo-coupling reactions observed in the related allyl cuprate reagents, see: (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. *J. Org. Chem.* **1989**, *54*, 4977; (b) (with dioxygen) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276; (c) (with dioxygen) Whitesides, G. M.; SanFilippo, J., Jr.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302.