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DIRECT FORMATION OF FUNCTIONALIZED KETONES VIA THE COUPLING OF FUNCTIONALIZED ORGANOCOPPER REAGENTS WITH ACID CHLORIDES

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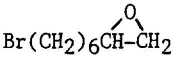
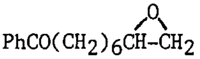
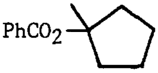
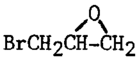
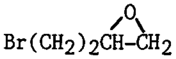
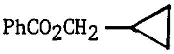
Summary: Highly reactive copper solutions have been prepared by the lithium naphthalide reduction of a copper(I) iodide/triphenyl-phosphine complex. These copper solutions react rapidly with functionalized alkyl halides to give organocopper reagents which have been effectively trapped with acid chlorides giving functionalized ketones in good yields. Ester, nitrile, chloride, remote epoxide, and, to some degree, ketone groups can be tolerated by this approach.

The coupling of acid halides with organometallic reagents is among the most widely used methods for the synthesis of ketones.[1,2] Previous reports from our laboratory have described the formation of ketones directly from the coupling of acid halides with organic halides mediated by highly reactive nickel[2a,2b,3] and cadmium[3,4] metal powders. In a continuation of our previously reported research involving highly reactive copper[5], we wish to report the formation of functionalized ketones by the reaction of acid halides with highly functionalized organocopper reagents. Significantly, the organocopper species can be prepared directly from the reaction of functionalized organic halides with highly reactive copper. This approach allows for the preparation of organocopper reagents with functionality not tolerated by the typical preparations involving the reaction of an organolithium or Grignard reagent with a copper(I) salt.[6] The lithium naphthalide reduction of a mixture of copper(I) iodide and triphenylphosphine in THF under an argon atmosphere gives a dark red-black solution of highly reactive copper. The copper reacts with functionalized alkyl bromides very rapidly (< 10 min) at -35 °C, giving stable alkylcopper species which can be effectively trapped with an excess of an acid chloride to give good yields of functionalized ketones.[7,8] Ester, nitrile, chloride, remote epoxide, and, to some degree, ketone functionalities are compatible with the reaction conditions (Table I).

The choice of phosphine is quite significant in the formation of the organocopper species. Homocoupling of the alkyl bromide does not occur when PPh_3 is used as the ligand for CuI. The use of other ligands such as PBu_3, PEt_3, tris(dimethylamino)phosphine (HMPT), or tricyclohexylphosphine (PCy_3) has been shown in previous results[5a] to give the homocoupled product in yields varying from 10 to 30%. This homocoupling is believed to result from the reaction of the newly formed organocopper species with unreacted alkyl bromide. Reactions with alkyl iodides, however, give some homocoupled product when PPh_3 is used as the ligand and considerably more homocoupling using the other more highly donating ligands. Therefore, the results suggest that the "nucleophilicity" of the organocopper reagent (as well as the reactivity of the copper solutions) increases with the increasing donor ability of the ligand.[9] Although they are less nucleophilic, the PPh_3-derived organocopper species, nonetheless, give better yields in the cross-coupling reactions with acid chlorides since none of the starting alkyl bromide is lost as the homocoupled product. In addition, product isolation is convenient in reactions using PPh_3 as ligand since most of the copper(I) halide/ligand complex is insoluble in diethyl ether which is used for extraction of the crude reaction mixtures.

An excess of the acid chloride must be used to trap the organocopper reagent since the acid

Table I. **Reactions of Functionalized Organocopper Reagents With Acid Chlorides.**

Entry	Alkyl Halide (equiv.)		Acid Chloride (equiv.)		Product[a,b]	% Yield[c]
1	$Br(CH_2)_7CH_3$	(0.20)	PhCOCl	(1.33)	$PhCO(CH_2)_6CH_3$	83
2	$Br(CH_2)_3CO_2Et$	(0.20)	PhCOCl	(0.55)	$PhCO(CH_2)_3CO_2Et$	93 (81)
3	$Br(CH_2)_3CN$	(0.20)	PhCOCl	(0.57)	$PhCO(CH_2)_3CN$	-- (79)
4	$Br(CH_2)_6Cl$	(0.20)	PhCOCl	(0.56)	$PhCO(CH_2)_6Cl$	83 (77)
5	 $Br(CH_2)_6\overset{O}{CH-CH_2}$	(0.21)	PhCOCl	(0.59)	 $PhCO(CH_2)_6\overset{O}{CH-CH_2}$	59 (58)[d]
6 7	p-$IC_6H_4CO_2Et$	(0.20) (0.20)	PhCOCl	(1.01) (0.58)	p-$EtO_2CC_6H_4COPh$	85 69
8	$Br(CH_2)_2CO_2Et$	(0.20)	PhCOCl	(0.53)	$PhCO(CH_2)_2CO_2Et$	79 (66)
9	$Br(CH_2)_3CO_2Et$	(0.21)	$MeO_2C(CH_2)_2COCl$	(0.64)	$MeO_2C(CH_2)_2CO(CH_2)_3CO_2Et$	49[d]
10	$Br(CH_2)_3CN$	(0.20)	$CH_3(CH_2)_2COCl$	(0.57)	$CH_3(CH_2)_2CO(CH_2)_3CN$	61
11	$Br(CH_2)_4COCH_3$	(0.20)	PhCOCl	(0.57)	$PhCO(CH_2)_4COCH_3$	19
					+ 	46
12	 $BrCH_2\overset{O}{CH-CH_2}$	(0.19)	PhCOCl	(0.53)	$PhCO_2CH_2CH{=}CH_2$	-- (66)
13	 $Br(CH_2)_2\overset{O}{CH-CH_2}$	(0.20)	PhCOCl	(0.64)		88 (77)[d]

[a] Reactions were done at -35 °C, then were typically warmed to room temperature for 30 min prior to workup. The organocopper species in entries 11-13 did not give the expected cross-coupled ketone as the major products. [b] All products gave consistent IR, ^1H and ^{13}C NMR, and high resolution mass spectral data. [c] GC yields based on calibrated chromatographically pure isolated samples. Isolated yields (after column and usually preparative thin layer chromatography) are given in parentheses. [d] Approximately 10-15% of the starting alkyl halide was also observed in these reactions.

chloride can also react with the unreacted copper still present. Previous results from our laboratory[10] have shown that the copper solution reacts rapidly with benzoyl chloride to form cis-stilbene diol dibenzoate (**1**) in very good yield. Indeed, each of the reactions employing benzoyl chloride gave a substantial amount of (**1**), which was readily separated from the desired ketones by silica gel chromatography.

The stabilization of organocopper species containing epoxide and ketone functionalities is highly dependent upon the number of carbons in the chain between the copper and epoxide or ketone moieties. For certain cases, intramolecular cyclization can occur.[11,12] As shown by work currently in progress[13], the epoxide functionality must be located in such a position that intramolecular epoxide attack by the organocopper species cannot occur. Carbon chain lengths which allow formation of ring sizes from 3 thru 6 will undergo intramolecular cyclization, either by attack at the terminal or internal carbon of the epoxide (Table I, entry 13). For larger rings, intramolecular cyclization is not appreciable and the intermediate epoxide-containing organocopper species can be efficiently trapped with an acid chloride to give the epoxyketone product (Table I, entry 5). Attempts to form a stable organocopper species in the α-position relative to an epoxide were unsuccessful, giving only an eliminated alkoxide which is trapped with benzoyl chloride (Table I, entry 12).

The formation of a stable organocopper species containing a methyl ketone group was only partially successful (Table I, entry 11). After benzoyl chloride trapping, only a low yield of the desired diketone product was observed. The major product resulted from intramolecular attack of the carbonyl by the copper species.[11d] The resulting alkoxide is then trapped with benzoyl chloride. It is expected that control of this competing cyclization reaction may be possible if the length of the carbon chain between the carbonyl and bromide is such that intramolecular cyclization would lead to an unfavorable ring size, just as with the bromoepoxides described earlier. The cyclization described above occurs with a methyl ketone. It is unsure whether other, more sterically demanding, ketones will undergo similar intramolecular carbonyl attack. This will be studied in future reactions to determine the scope and potential utility of this cyclization procedure.

In summary, active copper solutions prepared using PPh_3 react rapidly with alkyl bromides giving organocopper species which couple effectively with acid chlorides giving ketones in good yields. The organocopper species can contain considerable functionality previously unavailable, thereby increasing the utility of organocopper reagents for ketone synthesis.

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References and Notes

1. Shirley, D.A. Org. React. (N.Y.) 1954, 8, 28.

2. Among the many reagents used for this reaction are organomagnesium, -zinc, -cadmium, -mercury, -tin, -copper, -iron, -nickel, -boron, -aluminum, -silicon, -zirconium, -rhodium, -manganese, and -palladium reagents as well as other related catalytic systems. (a) Inaba, S.; Rieke, R.D. J. Org. Chem. 1985, 50, 1373. (b) Inaba, S.; Rieke, R.D. Tetrahedron Lett. 1983, 24, 2451. (c) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.; Miller, J.A.; Stoll, A.T. Tetrahedron Lett. 1983, 24, 5181. (d) Grey, R.A. J. Org. Chem. 1984, 49, 2288. (e) Posner, G.H.; Whitten, C.E. Org. Synth. 1976, 55, 122. Each of these references also cite numerous metal-mediated ketone syntheses.

3. Rieke, R.D.; Burns, T.P.; Wehmeyer, R.M.; Kahn, B.E. In "High Energy Processes in Organometallic Chemistry"; Suslick, K.S., Ed.; ACS Symposium Series 333: American Chemical Society: Washington DC, 1987; pp 223-245.

4. Burkhardt, E.R.; Rieke, R.D. J. Org. Chem. 1985, 50, 416.

5. (a) Wehmeyer, R.M.; Rieke, R.D. J. Org. Chem. 1987, 52, 5056. (b) Wu, T.-C.; Wehmeyer, R.M.; Rieke, R.D. J. Org. Chem. 1987, 52, 5057. (c)Ebert, G.W.; Rieke, R.D. J. Org. Chem. 1984, 49, 5280. (d) Rieke, R.D.; Rhyne, L.D. J. Org. Chem. 1979, 44, 3445.

6. Among the numerous excellent reviews in Cu chemistry are: (a Posner, G.H. Org. React. (N.Y.) 1972, 19, 1. (b) Posner, G.H. Org. React. (N.Y.) 1975, 22, 253. (c) Posner, G.H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980. (d) Lipshutz, B.H. Synthesis 1987, 325. (e) Lipshutz, B.H. Tetrahedron 1984, 40, 5005. (f) Normant, J.F. Synthesis 1972, 63. (g) "Comprehensive Organic Chemistry", Barton, D. and Ollis, W.D., Ed.; Pergamon Press: Oxford, 1979, Vol. 3, Chapter 15. (h) "Gmelin Handbook of Inorganic Chemistry: Organocopper Compounds", Springer-Verlag: Berlin, Part 1, 1985; Part 2, 1983. (i) "Comprehensive Organometallic Chemistry", Wilkinson, G; Stone, F.G.A., Abel, E.W., Ed.; Pergamon Press: Oxford, 1982; Vol. 2, pp 709-763; Vol. 7, pp 685-722.

7. In a typical reaction, Li (10.20 mmol) and naphthalene (12.39 mmol) in freshly distilled THF (10 mL) are stirred under argon until the Li is consumed (approx. 2 h). CuI (9.19 mmol) and PPh$_3$ (11.13 mmol) in THF (15 mL) are stirred for 30 min giving a thick white slurry which is transferred via cannula to the dark green solution of lithium naphthalide at 0 °C. (Later experiments show that slightly better results are obtained if the lithium naphthalide solution is added to the CuI/PPh$_3$ mixture.) The resultant reddish-black solution of active copper is stirred for 20 min at 0 °C. Ethyl 4-bromobutyrate (1.88 mmol) and GC internal standard n-decane (1.10 mmol) are added neat via syringe to the active copper solution at -35 °C. The solution is allow to stir for 10-15 min at -35 °C followed by addition of benzoyl chloride (5.07 mmol) neat to the organocopper solution at -35 °C. The reaction is allowed to stir 1 h 30 min at -35 °C followed by warming to room temperature for 30 min. (GC analysis shows the reaction to be essentially complete after stirring at -35 °C.) The reaction is then worked-up by pouring into saturated aqueous ammonium chloride, extracting with diethyl ether, and drying over anhydrous sodium sulfate. (For compounds not sensitive to base, the ether layer is also washed with 5% aqueous sodium hydroxide solution.) Silica gel chromatography (hexanes followed by mixtures of hexanes/ethyl acetate) and further purification by preparative thin-layer chromatography (2 mm plate) provides the keto-ester product in 81% isolated yield (93% GC yield after quantitation using the isolated product for the preparation of GC standards).

8. A small amount of benzophenone is typically also observed when benzoyl chloride is used as a reagent. Whether this could arise due to some lithium naphthalide promoted cleavage of the PPh$_3$ P-C bond or whether it results from the direct reaction of active copper with benzoyl chloride is uncertain.

9. Background for the steric and electronic effects of phosphine ligands in transition-metal catalyzed reactions has been summarized in several papers and references included therein. (a) Tolman, C.A. J. Am. Chem. Soc. 1970, 92, 2953, 2956. (b) Tolman, C.A. Chem. Reviews 1977, 313. (c) "Comprehensive Organic Chemistry", Barton, D. and Ollis, W.D., Ed.; Pergamon Press: Oxford, 1979, Vol 2, Chapter 10.

10. Wu, T.-C.; Rieke, R.D. J. Org. Chem. 1988, 53, 2381.

11. Many examples of similar intramolecular cyclization have been reported using other metals. (a) Cooke, M.P.; Houpis, I.N. Tetrahedron Lett. 1985, 26, 3643, (b) Cooke, M.P.; Houpis, I.N. Tetrahedron Lett. 1985, 26, 4987, (c) Molander, G.A.; Etter, J.B. Tetrahedron Lett. 1984, 25, 3281 and references included therein. Intramolecular cyclization has also been reported for a vinylcopper species (d) Corey, E.J.; Kuwajima, I. J. Am. Chem. Soc. 1970, 92, 395.

12. The epoxide and ketone cyclizations occur very rapidly (<10 min) at -35 °C. The study of the effects of lower temperature, solvent, etc., on these cyclizations is in progress for the intramolecular epoxide reactions[13] and will be made at a later date for the ketone cyclizations.

13. Wu, T.-C.; Rieke, R.D., submitted for publication.

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