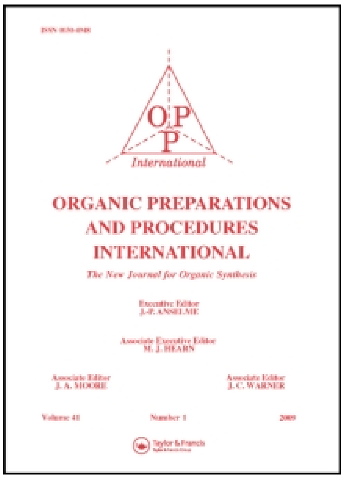

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G. B. Bennett[a]; J. Nadelson[a]; L. Alden[a]; A. Jani[a]
[a] Research and Development Division, Sandoz, Inc., East Hanover, New Jersey

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SYNTHESIS OF t-BUTYLKETONES BY USE OF PHENYLTHIO(t-BUTYL)CUPRATE (POSNER'S REAGENT)

G. B. Bennett*, J. Nadelson, L. Alden and A. Jani
Research and Development Division
Sandoz, Inc.
East Hanover, New Jersey 07936

In connection with other work, an efficient synthesis of bis-t-butylketones was required. A recent article[1] describes the reaction of t-alkyl Grignard reagents with acyl halides in the presence of cuprous salts to provide such sterically hindered ketones. The difficulties in preparing these hindered Grignard reagents, including incomplete formation and losses during filtration and transfer, as well as their failure to react with certain acyl halides (e.g. oxalyl chloride) led us to seek an alternate approach.

t-Butoxyl-t-alkylcuprates[2] and certain other mixed cuprates[3] have been shown to be effective in C-C bond formation without the related instability and low yields obtained with other organocopper(I) reagents.[4] Of these and several other[5] possible approaches to the desired t-butylketones, the use of a mixed cuprate reagent, in particular phenylthio(t-butyl)cuprate (I)[6] appeared the most promising. Treatment of oxalyl

$$t\text{-BuCu(Li)SPh} \quad + \quad \text{RCOCl} \quad \longrightarrow \quad t\text{-BuCOR}$$

I

chloride with two equivalents of I gave a 100% yield of 2,2,5,5-tetramethyl-3,4-hexanedione[7] (See Table 1 for a summary of analytical data). With malonyl chloride, which possesses acidic methylene protons and hence the possibility of side reactions, a 78% yield of the desired 2,2,6,6-tetramethyl-3,5-heptanedione[8] was realized.

In order to gain some understanding of the scope, limitations and synthetic utility of this coupling reaction, the unsaturated compounds fumaryl chloride and maleic anhydride, and the aromatic compounds, phthaloyl and terephthaloyl chloride were treated with cuprate I. Fumaryl chloride afforded a 58% yield of E-2,2,7,7-tetramethyl-4-octene-3,6-dione.[9] With terephthaloyl chloride, a 55% yield of p-dipivaloylbenzene[10] was obtained. When only one equivalent of cuprate I was employed, equivalent amounts of starting diacid chloride and p-dipivaloylbenzene were isolated. No mono adduct was observed. Phthaloyl chloride provided the corresponding o-dipivaloylbenzene in 58% yield. Due to some disparity between our PMR and mp data and those reported for the latter compound,[11] the CMR and uv spectra[12] were recorded. Both helped in substantiating our structural assignment. In none of the reactions thus far discussed were any side products observed.

Whereas copper-catalyzed conjugate addition reactions in the presence of saturated ketones, esters and lactones are well documented,[3] cases involving anhydrides, as well as conjugate addition to unsaturated anhydrides, have not been reported. Treatment of maleic anhydride with one equivalent of reagent I gave on the usual[6] work-up, a crude oil consisting of three major components. Chromatography over silica gel (30:1) with $CHCl_3$-toluene (1:3) (300 ml) gave a 19% yield of

5,5-dimethyl-2-t-butyl-4-oxohexanoic acid.[13] Further elution with $CHCl_3$-toluene (1:1) provided 2-t-butyl-3-carbomethoxypropionic acid[14,15] in 44% yield. With the exception of the starting maleic anhydride, which could be isolated on further elution ($CHCl_3$), no unsaturated products could be detected, even in the crude product mixture. One of two possible explanations could account for the reactivity of maleic anhydride. Either the reaction rate of cuprate I with anhydrides is sufficiently slow to allow initial 1,4-conjugate addition or the cisoid configuration as in the case of maleic anhydride is particularly susceptible to 1,4-addition reactions with cuprate reagents. Treatment of succinic anhydride with two equivalents of cuprate I under identical reaction conditions led primarily to the recovery of starting anhydride. Only a minor amount of 5,5-dimethyl-4-oxohexanoic acid[16] could be isolated. Dimethyl maleate on treatment with 2 equivalents of reagent I, afforded after chromatography over silica gel (30:1), dimethyl fumarate(10%) and dimethyl maleate(16%) followed by an inseparable mixture of more polar materials, several of which contained saturated t-butyl groups.

Thus it would appear that cuprate I undergoes conjugate 1,4-addition to unsaturated anhydrides at a rate faster than that for 1,2-addition to the anhydride carbonyl moiety, yet at a rate considerably slower than that for coupling with acid chlorides. It should be noted that in all cases, the cited yields are for distilled analytically pure material. In most instances the crude yields including starting material were of the order of 90-100%. Only with maleic anhydride was more than a single product formed during the reaction. In all cases the procedure of Posner[6] was followed. The pertinent data are summarized in Table 1.

TABLE 1

				PARTIAL SPECTPA DATA	
SM	Product	mp (bp)[a]	Yield [b]	PMR[c]	ir[d]
ClCOCOCl	$Me_3CCOCOCMe_3$	(109-16/150)[e]	100	1.21(s,18H)	1705
$ClCOCH_2COCl$	$Me_3CCOCH_2COCMe_3$	(75-80/12)[f]	78	1.24(s,18H), 3.76(s,1H)[g], 5.78(s,0.5H)[g], 16.27(broad s,0.5H)[g]	1758, 1716, 1605
ClCOCH=CHCOCl	$Me_3CCOCH=CHCOCMe_3$	109-10[h]	58	1.18(s,18H), 7.41(s,2H)	1685
p-$(ClCO)_2C_6H_4$	p-$(Me_3CCO)_2C_6H_4$	80-81.5	55	1.44(s,18H), 7.65(s,4H)	1680
o-$(ClCO)_2C_6H_4$	o-$(Me_3CCO)_2C_6H_4$	160-1[i] (97-101/2.5)	58	1.30(s,18H), 7.43,7.48(ABq,4H)	1685
Maleic anhydride	$Me_3CCOCH_2CH(Me_3C)COOH$	78-81[j]	18.9	1.02(s,9H), 1.15(s,9H), 1.75-3.14 (m,3H)	1710(w)
	and;				
	$MeO_2CCH_2CH(Me_3C)COOH$	(110-5/0.025)[k]	43.9	1.02(s,9H), 2.30-2.94(m,3H), 3.66(s,3H)	1735, 1710
Succinic anhydride	$Me_3CCO(CH_2)_2COOH$	-[l]	<5	1.19(s,9H), 2.41-2.95(m,4H)	---

(a) Expressed in °C and (°C/mmHg). (b) Isolated yields, not optimized. (c) Recorded on either a Varian T-60 or XL-100 spectrometer; expressed in δ relative to TMS. (d) Recorded on a Perkin-Elmer Model 257 or 457 Spectrometer, expressed in cm^{-1}. (e) Lit[7] bp (67-8°/12); yields 50-93%. (f) Lit[1] bp (86°/11); yield 77%. (g) Keto/Enol: 1/1. (h) Lit[9] mp 110-11°; no yield reported. (i) Lit[11] mp 145°; no yield reported. (j) Lit[13] mp 81-82.5°; yield 30%. (k) See Ref. 15 for physical data of the corresponding diacid. (l) Lit[16] mp 65-6°.

EXPERIMENTAL

General Procedure. Preparation of 2,2,5,5-tetramethyl-3,4-hexanedione.- To a suspension of cuprous thiophenolate (7.09g, 41 mmol) in anhydrous THF (140 ml) at -20° under N_2 was added dropwise a solution of t-BuLi (33.0 ml of 1.23 M, 40.5 mmol) in pentane. After stirring at -20° for 5 minutes the mixture was cooled to -70° and oxalyl chloride (2.54g, 20 mmol) was added dropwise. The stirring was continued at -70° for 1 hour after which MeOH (14 ml) was added and the mixture was allowed to warm to RT. Saturated NH_4Cl solution (50 ml) was added and the precipitate removed by filtration thru celite. The aqueous phase was washed with Et_2O and the organic phases were combined, dried over Na_2SO_4 and the solvent removed at reduced pressure. Distillation (109-16°/150mm) afforded 3.40g (100%) of the desired t-butyl ketone.

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Found: C,77.8; H, 9.4

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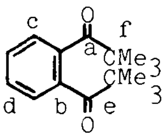
12.


CMR: 212.304 (a), 140.735 (b), 129.137 (c), 126.869 (d), 44.140 (e), 27.958 (f).

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Found: C, 57.3; H, 8.4

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