Tetrahedron Letters, Vol. 33, No. 17, pp. 2383-2386, 1992
Printed in Great Britain

0040-4039/92 \$5.00 + .00
Pergamon Press Ltd

CONJUGATE ADDITION OF BENZYL COPPER REAGENTS TO α,β-ENOATES AND -ENONES.

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Abstract: Several benzylic copper reagents, BnCu(CN)MgCl, $Bn_2CuMgCl$, BnCu-TMSCl-HMPA, and BnCu-TMSCl-TMEDA, facilitate the conjugate addition of the benzyl ligand to α, β-enones, but only BnCu-TMSCl-TMEDA gave high yields with α, β-unsaturated esters.

While α, β-unsaturated ketones are excellent Michael acceptors in the conjugate addition of organocopper reagents[1-3], similar chemistry involving α, β-ethylenic esters is more difficult to perform and often requires the use of various additives. Yamamoto and his co-workers[2,4-6] have utilized a variety of alkyl and aryl copper reagents, $RCu \bullet BF_3$', which rely on the action of a Lewis acid to successfully mediate the transfer of the alkyl or aryl group to the enoate. Rapid and efficient conjugate additions to β-substituted enoates were effected by Lipshutz and his collaborators[1,3,7] *via* higher order mixed cuprates, $R_2Cu(CN)Li_2$. Besides promoting rates and enhancing yields in the addition of cuprates to α, β-unsaturated esters, the presence of trimethylsilyl chloride (TMSCl)[8-13] would presumably lead to trapping of an intermediate enolate as trimethylsilyl enol ether; in many instances this could be of considerable advantage for further synthetic transformations[12]. The Cu(I)- or Cu(II)- catalyzed conjugate addition of Grignard reagents to enoates is strongly accelerated by the addition of TMSCl with and without polar additives such as hexamethylphosphoric triamide (HMPA), tetramethylethylene diamine (TMEDA), and 4-dimethylaminopyridine (DMAP)[11,12,14-18]. Besides effecting an increase in the reactivity of the silyl halide, these compounds presumable serve to stabilize and solubilize the cuprates[12].

In contrast to the facile conjugate addition of alkyl-, aryl-, vinyl-, and allylic cuprates to a variety of α, β-ethylenic Michael acceptors, similar preparations and transfers involving the benzylic functionality are resticted to the addition of α -alkoxy benzylic[17]- and benzylic zinc organocuprates [19] to α, β - enones. Transfer of this highly reactive functionality has, however, not yet been reported for 1,4 -addition to α, β - unsaturated esters. Part of our synthetic programmes required the β-addition of a benzyl group to enoates and enones hence initiating investigation to the development of a general method towards the preparation of a variety of benzylic organocopper reagents and the subsequent transfer of this ligand to α, β-enones and specifically to -enoates.

Owing to the thermal instability of cuprates composed of benzylic ligands[17], we opted for the less reactive reagents prepared from organomagnesium compounds[3]. Thus, benzylic copper reagents (Table) were prepared by metal-halogen exchange between benzyl chloride and magnesium followed by transmetalation using various Cu(I)-species (CuI, CuCN, $CuBr\cdot Me_2S$). In contrast to benzyl bromide (BnBr) where Wurtz-like coupling led to the formation of bibenzyl, very little cross-coupling were observed when benzyl chloride were used in the Grignard reaction (*cf.* ref.20).

Treatment of cyclohexenone **1** and chalcone **2** with BnCu(CN)MgCl, $Bn_2CuMgCl$, $BnCu\cdot BF_3$, BnCu-TMSCl-HMPA, and BnCu-TMSCl-TMEDA (Table) gave moderate to excellent yields of

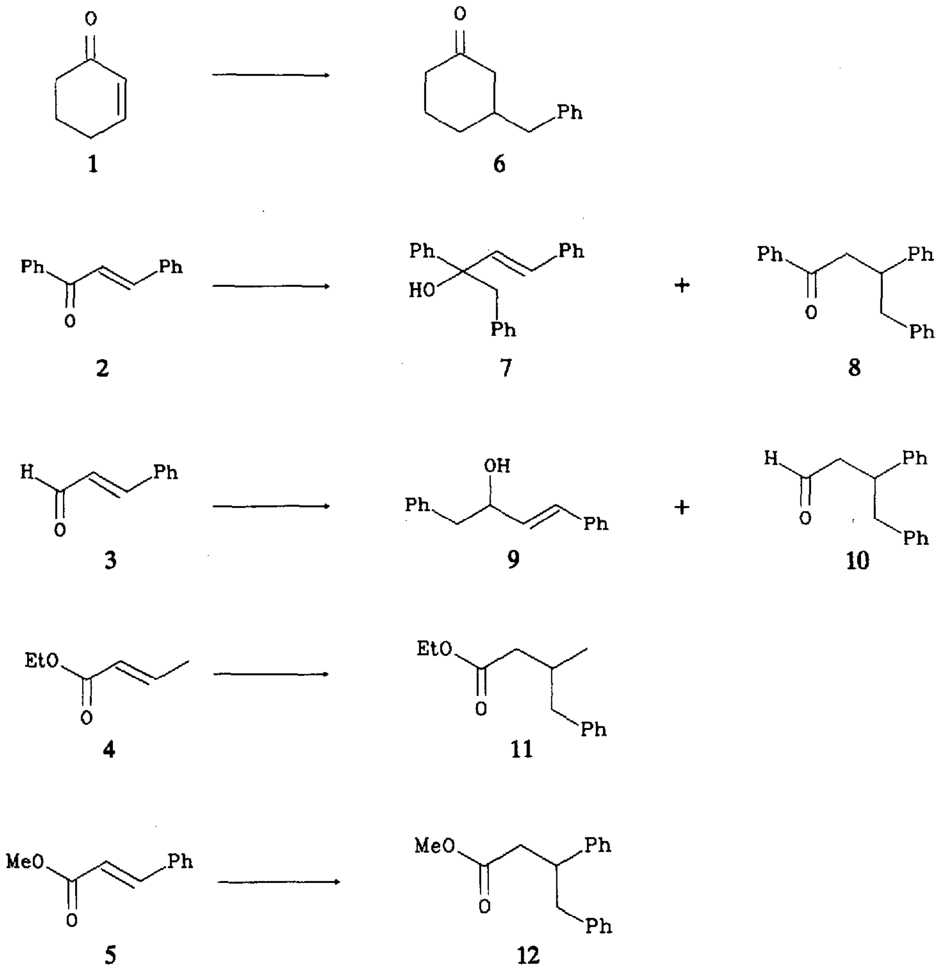

Table: Conjugate addition of benzyl copper reagents to α,β-enones and - enoates

Entry	Substrate	Copper Reagent[a]	Conditions °C/Hour	Products[b]	Ratio	Yield %
1	**1**	A (4 eq.)	-78/1	**6**	-	95
2	**2**	A "	-78 → -70/1	**8**	-	61
3	**3**	A "	"	**9, 10**	2 : 1	46
4	**4**	A "	-78 → 0/24	-	-	c
5	**5**	A "	"	-	-	c
6	**2**	B (4 eq.)	-78 → −70/1	7, 8	1 : 1.7	90
7	**3**	B "	"	9, 10	1.7 : 1	67
8	**4**	B "	-78 → 0/24	11	-	24
9	**5**	B "	"	12	-	2
10	**2**	C (4 eq.)	-78 → -60/2	**7, 8**	1 : 2	61
11	**3**	C "	-78 → -40/3	**9**	-	20
12	**4**	C "	-78 → 0/24	-	-	c
13	**5**	C "	"	-	-	c
14	**1**	D (2 eq.)	-78 → -70/1	**6**	-	93
15	**2**	D "	-78 → -60/2	**7, 8**	1 : 4	62
16	**3**	D "	-78 → -40/3	**9, 10**	1 : 16	62
17	**3**	E (0.05 eq)	-78 → -50/2	**9, 10**	3.5 : 1	66
18	**4**	E "	-78 → -50/6	**11**	-	36
19	**5**	E "	"	**12**	-	16
20	**2**	F (2 eq.)	-78 → -60/2	**7, 8**	1 : 5	63
21	**3**	F "	-78 → -40/4	**9, 10**	10 : 1	63
22	**4**	F "	-78 → -40/24	**11**	-	73
23	**5**	F "	"	**12**	-	86

[a] Reagents: A - BnMgCl (4 mmol, 1 eq)/CuCN (1 eq)/Et_2O (*cf.* ref. 23). B - BnMgCl (4 mmol, 2 eq)/$CuBr\cdot Me_2S$ (1 eq)/Et_2O (*cf.* ref. 23). C - BnMgCl (2 mmol, 1 eq)/$CuBr\cdot Me_2S$ (1 eq)/$BF_3\cdot OEt_2$ (1 eq)/Et_2O (*cf.* ref. 23). D - BnMgCl (1.1 mmol, 1 eq)/CuI (1 eq)/TMSCl (5 eq)/HMPA (1.2 eq)/THF (*cf.* ref. 15). E - BnMgCl (1.1 mmol, 1 eq)/5 mol % $CuBr\cdot Me_2S$/TMSCl (1.8 eq)/HMPA (1.2eq)/THF (*cf.* ref. 15). F - BnMgCl (2 mmol, 1 eq)/CuI (1 eq)/TMSCl (2.5 eq)/TMEDA (1.1 eq)/THF (*cf.* ref. 17).

[b] All new compounds gave satisfactory micro-analysis or accurate mass values.

[c] No Reaction.

predominantly the 1,4-addition products (entries 1, 2, 14, 15, and 20), the only exceptions being the more reactive Gilman- ($Bn_2CuMgCl$) and BF_3-activated reagents where 1,2-addition became prominent (entries 6 and 10 *vs* 2, 15, and 20). In reaction with cinnamaldehyde **3**, however, all the reagents exhibited a tendency towards 1,2-addition but for BnCu-TMSCl-HMPA, which effected a considerable percentage of 1,4-addition. Such a preference for 1,2-addition may presumably be interpreted as a steric complement to the α-effect[21] by the bulky TMSCl-HMPA complex[22]. The α, β- unsaturated esters **4** and **5** were unreactive towards BnCu(CN)MgCl and, surprisingly, also to the Yamamoto reagent ($BnCu \bullet BF_3$) which is reputed for the transfer of ligands to esters. Excellent yields (73 - 86 %) were, however, possible through utilization of TMSCl with the copper(I) stabilizing additive[12], TMEDA, which proved to be superior to HMPA for benzylic transfer to enoates.

We have thus established a method for the facile preparation and transfer of the highly reactive benzyl ligand to a variety of α, β-enones and especially -enoates. This protocol should usefully complement existing methodologies of copper catalyzed conjugate addition in synthetic organic chemistry.

Useful proposals as to the preparation and purification of copper reagents by Prof. B.H. Lipshutz, as well as Financial support by the Foundation for Research Development and the Sentrale Navorsingsfonds of this University are greatfully acknowledged.

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(Received in UK 11 February 1992)