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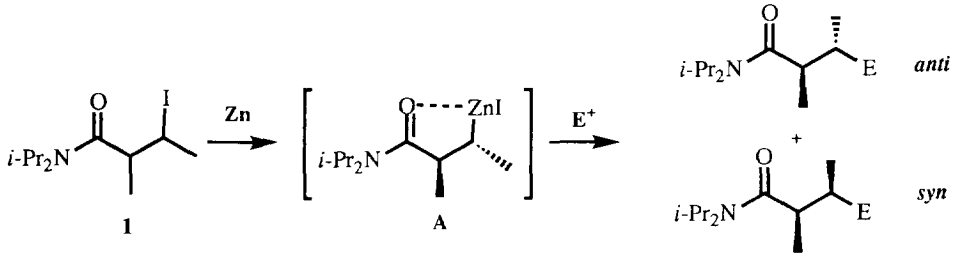
Complementary Diastereoselective β-Acylation of α-Methylbutanamide

Takashi Houkawa, Tsuyoshi Ueda, Satoshi Sakami, Morio Asaoka,* and Hisashi Takei

Department of Life Chemistry, Tokyo Institute of Technology, Midoriku, Yokohama 226, Japan

Abstract: Both the *syn*- and *anti*-diastereomers of 4-aryl-2,3-dimethyl-4-oxobutanamides were respectively synthesized in a highly diastereoselective manner.

The stereocontrol with enolates or allylic organometallic reagents is well documented.[1] In contrast, the stereochemical aspects of organometallic reagents with sp^3 carbon centers bound to the metal groups have not yet been fully explored.[2] As part of our continuing studies in the field of stereocontrol with sp^3 carbanions,[3] the diastereocontrol in the reactions of β-iodozinc derivative of α-methylbutanamide **A** with some electrophiles under various conditions was examined (Scheme 1).

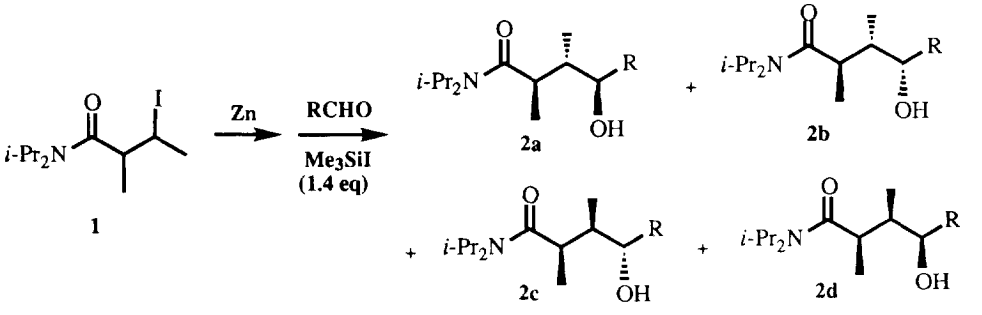


Scheme 1

After conversion of **1** into the iodozinc reagent **A**,[4] reaction with benzaldehyde in the presence of 1.4 equivalent of Me_3SiI in dichloromethane gave a mixture of three diastereomers (**2a** : **2b** : **2c** = 66 : 33 : 1) in 49% yield (Scheme 2; Table 1, entry 1). Though the diastereoselectivity between C3 and C4 was modest (*anti* : *syn* = **2a+2c** : **2b** = 2 : 1), the diastereoselectivity between C2 and C3 was excellent (*anti* : *syn* = **2a+2b** : **2c** = 99 : 1). Encouraged by the above results, we investigated this reaction in detail. Use of acetonitrile as a solvent increased the yield and the level of C3-C4 diastereoselectivity (*anti* : *syn*=4 : 1). The reactions with some other aromatic aldehydes were also carried out to give the expected adducts with almost exclusive C2-C3 *anti*-stereochemistry. These results are listed in Table 1.

The structure of **2a** (R=Ph) was assigned, after conversion into the corresponding γ-butyrolactone derivative, by comparison of the coupling constants of ^{1}H-nmr with those of the reported analog (R=Me).[5] The relative stereochemistry between C3 and C4, thus assigned on the lactone, was consistent with that

speculated from the coupling constant of the benzylic protons of acyclic precursors [R=Ph: *anti* : **2a** J=8.9 Hz; **2c** J=8.9 Hz, *syn* : **2b** J=2.0 Hz]. The cis relationship of the C2 and C3 hydrogens was also confirmed by NOE experiments on the lactone. For the compounds **2b** and **2c**, the relative stereochemistry between C2 and C3 was confirmed by the oxidation of their hydroxy groups (*vide infra*). The structures of the other derivatives were assigned on the basis of analogy with these results.



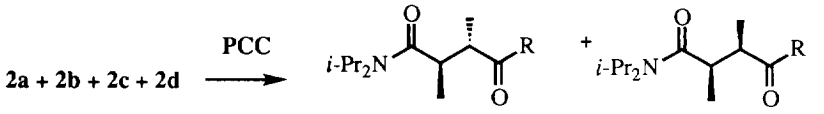
Scheme 2

Table 1. **Reaction of organozinc reagent A with aromatic aldehydes**

Entry	R	Solvent	Time (h)	Yield (%)	Ratio 2a : 2b : 2c : 2d
1	Ph	CH_2Cl_2	2.5	49	66 : 33 : 1 : 0
2	Ph	CH_3CN	2	64	70 : 28 : 1 : 1
3	*p*-Tol	CH_3CN	2	68	76 : 22 : 1 : 1
4	*p*-MeO-C_6H_4	CH_3CN	2	63	82 : 16 : 1 : 1
5	*o*-MeO-C_6H_4	CH_3CN	2	63	73 : 23 : 2 : 2
6	*o*-Tol	CH_3CN	2	47	59 : 34 : 5 : 2

A typical procedure: To activated zinc[6] (2.6 mmol) were added **1** (2 mmol, a 1:1 mixture of diastereomers) in acetonitrile (4 ml) and chlorotrimethylsilane (0.2 mmol) at room temperature, and the mixture was stirred for 1 h. To the mixture were added an aromatic aldehyde (2.4 mmol) and iodotrimethylsilane (2.8 mmol). After 2 h stirring, the reaction mixture was stirred with 2M HCl (5 ml) for 10 min. Usual work-up and purification by column chromatography gave a mixture of **2a-2d**. The ratio was determined by ^{1}H-nmr and/or HPLC.

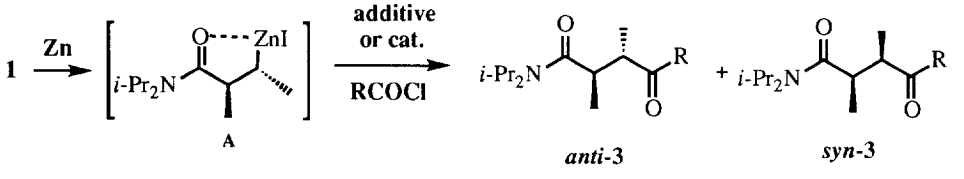
The oxidation of the above mixtures of diastereoisomers with PCC proceeded without isomerization of the chiral center to give the expected *anti*-keto amides in good yields (Scheme 3).



		anti-3		*syn*-3
R = Ph	**82 %**	**99**	:	**1**
***p*-Tol**	**94 %**	**98**	:	**2**
***p*-MeO-C_6H_4**	**84 %**	**98**	:	**2**

Scheme 3

Direct acylation of organozinc reagent **A** with acid halides was also investigated. Since organozinc reagent **A** was almost inert to acid halides, benzoylation with benzoyl chloride was carried out after transmetalation to a copper reagent.[7] A mixture of *anti*- and *syn*-isomers was produced in a ratio of 74 : 26 (Table 2, entry 1; Scheme 4). By a nickel-catalyzed acylation, preferential formation of *syn*-diastereomer (*anti* : *syn* = 36 : 64) was observed (entry 2). An exclusive formation of *syn*-isomer was achieved by a Pd(0)-catalyzed acylation[8] (entry 3). Among some reaction conditions examined, the combination of dioxane as solvent with 5 mol % of Pd[(*o*-tol)3P]4 as catalyst was the best choice. In a similar manner, other aromatic acid chlorides reacted to give *syn*-isomers almost exclusively.



anti-3 *syn*-3

Scheme 4

A typical procedure: To a mixture of **1** (1 mmol) and activated zinc (1.3 mmol) in dioxane (1 ml) was added chlorotrimethylsilane (0.1 mmol) at room temperature. After 1 h stirring, to the mixture were added Pd[(*o*-tol)3P]4 (66 mg, 0.025 mmol, 5 mol %) in dioxane (1 ml) and an acid chloride (0.7 mmol). The mixture was stirred for 14 h at room temperature. Usual work-up and purification by column chromatography gave **3**. Determination of the diastereo ratio was carried out on both the crude and purified products by ^{1}H-nmr and/or HPLC .

Table 2. Acylation of organozinc reagent A with acid chlorides

Entry	R	Additive or catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)	Ratio *anti*-3 : *syn*-3
1	Ph	CuCN-2LiCl (1 eq)	THF	-78-rt	13.5	50	74 : 26
2	Ph	$NiCl_2(PPh_3)_2$	dioxane	rt	16	26	36 : 64
3	Ph	$Pd(PPh_3)_4$	THF	rt	13	52	1 : 99
4	Ph	$Pd(PPh_3)_4$	dioxane	rt	13	51	2 : 98
5	Ph	$Pd[(o\text{-tol})_3P]_4$	dioxane	rt	15	90	1 : 99
6	*p*-Tol	$Pd[(o\text{-tol})_3P]_4$	dioxane	rt	13.5	73	4 : 96
7	*p*-MeO-C_6H_4	$Pd[(o\text{-tol})_3P]_4$	dioxane	rt	13	56	1 : 99
8	*o*-MeO-C_6H_4	$Pd[(o\text{-tol})_3P]_4$	dioxane	rt	19	33	7 : 93

Though the mechanism of the above reactions remains unelucidated, we have demonstrated for the first time that a complementary 1,2-diastereoselective acylation of sp^3 carbon center is possible.

Further studies with various electrophiles are currently in progress.

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