Pergamon

Tetrahedron Letters, Vol. 38, No. 15, pp. 2733-2736, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00456-5

A Novel One-Pot Reformatsky Type Reaction Via Bismuth Salt In Aqueous Media

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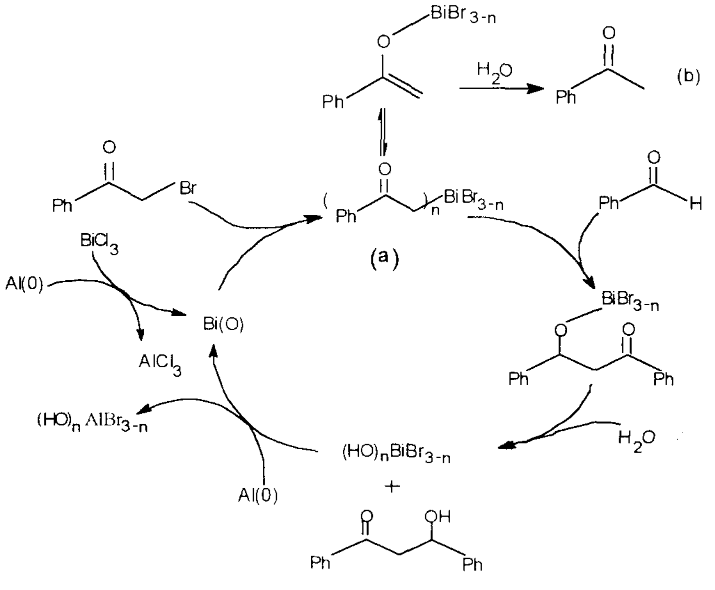
Abstract: In the presence of bismuth(Ⅲ)chloride-metallic aluminum, α-halo carbonyl compounds react with aldehydes in water under mild conditions to give β-hydroxy carbonyl compounds with stereoselectivity in good yields. © 1997 Elsevier Science Ltd.

The century old Reformatsky-type reaction has played an important role in carbon-carbon bond formation. After decades of stagnation, considerable progress has been achieved by continuously increasing the reactivity of the zinc, by application of various other metals or metal salts, and by the activation of the whole reaction system. All these reactions are carried out in organic solvents through a six-electron cyclic transition state [1]. Recently, a few reports dealed with Reformatsky type reactions which were carried out in aqueous media using zinc powder[2] or tin-aluminum couple[3]. To our knowledge, Reformatsky type reaction using bismuth has never been reported yet, and among group 5B elements, bismuth metal is cheaper and less toxic than arsenic or antimony[4,5]. Our interests both in extending the scope of the Reformatsky reaction and applying bismuth to modern organic synthesis have led us to investigate bismuth induced Reformatsky reaction.

Reported here is a new, simple and efficient method for the Reformatsky type reaction which is stereoselective. Typical procedures are as follows: Into a mixture of commercial grade Al powder(2 mmol) and $BiCl_3$(1 mmol) was added H_2O (5 mL), then an aldehyde (1 mmol) and an α-bromoketone (1.2 mmol) were added under nitrogen at room temperature. After stirring at the appropriate temperature for 4h, the reaction mixture was quenched with ether. The organic layer was separated , dried and evaporated to dryness, and the desired product was isolated by flash chromatography on silica gel. The results obtained are listed in Table 1.

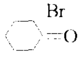
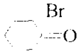
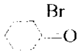
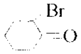
The reactions proceed in good yields with both aromatic and aliphatic aldehydes. The use of an excess amount of α-bromoketone raises the product yield, because the α-bromoketone may be partially consumed by protonation during the reaction (Scheme1), and the higher the reaction temperature, the more the protonated product (entries 5, 19). No real attempt has yet been made to determine if the reacting entity is a C or O metallated species, it is nevertheless probable that the reaction does not proceed via a stable bismuth enolate. It

Scheme 1



Presumed Mechanism of Catalytic $BiCl_3$-Al(0) Mediated Reformatsky Type Reaction

Table 1: $BiCl_3$-Al(0) Mediated Synthesis of β-Hydroxy Carbonyl Compounds

Entry	α-Bromoketones[a]	Aldehydes	Reaction Temp.(°C);Time(h)	Yield(%)[b] (erythro:threo)[c]	Dehalogenated Products(%)
1	$PhCOCH_2Br$	PhCHO	60; 4	63[d]	32
2	$PhCOCH_2Br$	PhCHO	60; 4	82	28
3	$PhCOCH_2Br$	PhCHO	60; 48	80[e]	25
4	$PhCOCH_2Br$	$p\text{-}ClC_6H_4CHO$	60; 4	86	25
5	$PhCOCH_2Br$	$p\text{-}ClC_6H_4CHO$	85; 4	41	63
6	$PhCOCH_2Br$	$p\text{-}ClC_6H_4CHO$	60; 12	85	25
7	$PhCOCH_2Br$	$p\text{-}MeOC_6H_4CHO$	70; 4	61	46
8	$PhCOCH_2Br$	$n\text{-}C_5H_{11}CHO$	60; 4	73	38
9	$PhCOCH_2Br$	$n\text{-}C_6H_{13}CHO$	60; 4	77	36
10	$PhCOCH_2Br$	$n\text{-}C_8H_{17}CHO$	60; 4	81	31
11	$p\text{-}BrC_6H_4COCH_2Br$	PhCHO	60; 4	83	25
12	$p\text{-}BrC_6H_4COCH_2Br$	$p\text{-}ClC_6H_4CHO$	60; 4	89	23
13	$p\text{-}BrC_6H_4COCH_2Br$	$p\text{-}MeOC_6H_4CHO$	60; 4	65	46
14	$p\text{-}BrC_6H_4COCH_2Br$	$n\text{-}C_5H_{11}CHO$	60; 4	72	38
15	$p\text{-}BrC_6H_4COCH_2Br$	$n\text{-}C_6H_{13}CHO$	60; 4	75	38
16	$p\text{-}BrC_6H_4COCH_2Br$	$n\text{-}C_8H_{17}CHO$	60; 4	84	30
17		PhCHO	60; 4	80 (84:16)	32
18		$p\text{-}ClC_6H_4CHO$	60; 4	90 (86:14)	25
19		$p\text{-}ClC_6H_4CHO$	85; 4	50 (50:50)	58
20		$p\text{-}ClC_6H_4CHO$	60; 12	89 (56:44)	26

a) α-Bromoketone (1.2 mmol), carbonyl compound(1 mmol), $BiCl_3$(1 mmol), Al(2 mmol) were employed. b) Isolated yields by flash column chromatography (petroleum: ethyl acetate = 9:1), based on aldehydes . c) The ratio of the diastereo isomers (erythro and threo) was determined by 500 MHz ^1H NMR[6]. d) α-Bromoketone (1.0 mmol) was employed. e) $BiCl_3$(0.1 mmol) and Al(0.2mmol) were used.

is noteworthy that only a catalytic amount of $BiCl_3$ was needed to effect the reaction (entry 3), and a catalytic cycle can be presumed in which some acylbismuth reagent (a) is formed through the oxidative addition of α-bromocyclododecanone to Bi (0) generated by the reduction of $BiCl_3$ with Al(0). Although the reaction mechanism is not yet clear, we propose that the reaction involves an acyclic transition state rather than a conventional cyclic one[7] or a SET mechanism[8]. This hypothesis is based on the following observations. Firstly, we obtained preponderant erythro products from the reaction (entries 17, 18), and the cyclic mechanism of the reaction would lead to threo aldols predominantly; Secondly, we found no usual side products from self-condensation of the aliphatic aldehydes expected from metal enolate chemistry in aqueous media (entries 8-10, 14-16); Thirdly , this reaction did not take place in the absence of $BiCl_3$ or Al(0), and hardly any expected product was obtained when the aldehyde was added to a mixture of α-bromoketone and metals in water. Further studies of the mechanism and the application of this reaction are in progress in our laboratory.

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(*Received in China* 4 *October* 1996; *revised* 6 *December* 1996; *accepted* 31 *January* 1997)