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## Reformatsky reactions with SmI<sub>2</sub> in catalytic amount

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Abstract—A substoichiometric protocol for Reformatsky-type addition of  $\alpha$ -haloesters,  $\alpha$ -haloketones,  $\alpha$ -halonitriles, and  $\alpha$ -halophosphonates to carbonyl compounds has been developed.  $\beta$ -Hydroxyesters and  $\beta$ -hydroxynitriles were obtained in good to excellent yields.

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The reaction of  $\alpha$ -haloesters with carbonyl compounds in the presence of metallic zinc, to give  $\beta$ -hydroxy esters, represents a powerful synthetic tool for carbon-carbon bond formation. Since its discovery by Reformatsky, this reaction has been undergoing several improvements and its scope and selectivity have been considerably extended. Various parameters, such as metal activation, reaction temperature, solvent, properly designed reagents and educts have been extensively investigated. In addition, besides the classical zinc method, various other metals or metal derivatives have been tested.<sup>1</sup> To this concern, transition metals may offer important advantages in terms of milder conditions, higher reproducibility and stereoselectivity. A metal which has also proved quite useful is samarium(II) (used as SmI<sub>2</sub>), particularly for the remarkable stereoselectivity exhibited in intramolecular reactions, achieved through chelation control of the samarium intermediate in the transition state.<sup>2</sup> More recently we reported SmI<sub>2</sub>-mediated reactions of diethyl ( $\alpha$ -iodomethyl)phosphonate with carbonyl compounds to give  $\beta$ -hydroxyphosphonates.<sup>3a</sup> The same protocol was then extended to esters and lactones and applied to the synthesis of a precursor of the C-glycosyl analogue of thymidine 5'-( $\beta$ -L-rhamnosyl)diphosphate.3b

Unfortunately in these reactions, a 2.2–2.5 equiv of samarium(II) must be used to ensure reduction of the initially formed radical to an organosamarium; in addi-

tion, the use of the convenient, commercially available tetrahydrofuran solution of SmI2 is affected by low reproducibility when a stoichiometric protocol is used. To overcome these problems, we now report an  $SmI_2/$ Mg promoted Reformatsky-type reaction which allows the use of a substoichiometric amount of Sm(II) (10%), provided magnesium metal is present to carry out the reduction Sm(III)/Sm(II). We have optimised a similar protocol for Co(0)-mediated Reformatsky-type and aldol-type reactions of  $\alpha$ -halo esters, ketones and phosphonates with various electrophiles.<sup>4</sup> To our knowledge, few systems employing co-reductants for the catalytic use of SmI2 have been reported: for example Zn amalgam in the annulation of ketones to  $\gamma$ -lactones and in the radical cyclisation of unsaturated halides;<sup>5</sup> mischmetall in Reformatsky-type reactions;<sup>6</sup> Mg in pinacolic coupling of carbonyl compounds in the presence of trimethylsilyl chloride.<sup>7</sup>

The results are reported in Table 1 and deserve some comments.

The addition product was obtained in good to excellent yield when an  $\alpha$ -bromoester and a carbonyl compound (aldehyde or ketone) were used.  $\alpha$ , $\beta$ -Unsaturated carbonyls such as cinnamaldehyde gave the 1,2-addition product in excellent yield. Lower yields were obtained when an aromatic  $\alpha$ -bromoketone or  $\alpha$ -bromoacetonitrile was used.

The pinacolic coupling product was observed in appreciable amounts only with benzaldehyde (10-15%) depending on the run and on the addition order of the organic reagents to the samarium(II)).

Keywords: Catalysed Reformatsky reaction; Samarium(II) iodide.

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| Halogen compound                   | Electrophile  | Addition product (%)  | Pinacolic coupling product (%)            |
|------------------------------------|---|-----------------------|---|
| X EWG                              | $R \xrightarrow{Y} Y$<br>R' Y = O, NR"  | R<br>R'YH<br>YH       | R, K, |
| tert-Butyl-α-bromo acetate         | C <sub>6</sub> H <sub>5</sub> CHO   | 75 <sup>a</sup>       | 10  |
| tert-Butyl α-bromo acetate         | $(C_6H_5)_2CO$  | 77                    | _   |
| tert-Butyl α-bromo acetate         | $CH_3(CH_2)_5C(O)CH_3$  | 83                    | _   |
| tert-Butyl α-bromo acetate         | C <sub>6</sub> H <sub>5</sub> CH=CHCHO  | 91 <sup>a</sup>       | _   |
| tert-Butyl α-bromo acetate         | C <sub>6</sub> H <sub>5</sub> CH=NCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> | 24                    | 60.5                                      |
| tert-Butyl α-bromo acetate         | 2,3,5-Tri-O-benzyl-D-arabino-1,4-lactone  | $85^{a,b}$ d.r. = 2/1 | _   |
| Benzyl α-bromo acetate             | C <sub>6</sub> H <sub>5</sub> CHO   | 90 <sup>a</sup>       | _   |
| α-Bromo acetophenone               | C <sub>6</sub> H <sub>5</sub> CHO   | 38                    | _   |
| α-Bromo acetonitrile               | C <sub>6</sub> H <sub>5</sub> CHO   | 65                    | _   |
| Diethyl (a-iodomethyl) phosphonate | C <sub>6</sub> H <sub>5</sub> CHO   | 35°                   | _   |
| Diethyl (a-iodomethyl) phosphonate | (CH <sub>3</sub> ) <sub>3</sub> CHO   | 33                    |   |
| Diethyl (a-iodomethyl) phosphonate | (CH <sub>3</sub> ) <sub>2</sub> CHCHO   | 35                    | _   |

Table 1. Sm(II)-catalysed Reformatsky-type reactions

<sup>a</sup> Yields determined by NMR analysis.

<sup>b</sup> A diastereoisomeric mixture was obtained.

<sup>c</sup> Diethyl methyl phosphonate was obtained (25%).

The addition to the carbon-nitrogen bond present in the benzylimine of benzaldehyde was, in contrast, unsatis-factory: the main product was 1,2-diphenyl-1,2-diaminoethane (meso and racemate), arising from a pinacolic coupling reaction.

Once optimised, the protocol was applied to the lactone of 2,3,5-tri-*O*-benzyl– $\beta$ -D-arabinofuranose, as model compound for aldonolactones, useful precursors of *C*-glycosides and sugar-fused  $\beta$ -hydroxy and  $\beta$ -amino acids.<sup>8</sup> The reaction proceeded in very good yield (85%) and afforded the two diastereoisomeric products in 2/1 diastereoisomeric ratio.

To investigate whether an organomagnesium compound might be involved in the carbon-carbon bond formation, in some cases parallel experiments were performed (tert-butyl a-bromo acetate with transbenzvl cinnamaldehyde or with benzaldehyde;  $\alpha$ -bromoacetate with cinnamaldehyde or with 2,3,5-tri-O-benzyl-D-arabino-1,4-lactone). The bromoester and the electrophile were added at room temperature to two reaction flasks: one containing a substoichiometric amount of SmI<sub>2</sub> and magnesium in tetrahydrofuran, the other only magnesium in tetrahydrofuran. The amount of bromoester, electrophile, magnesium was the same in the parallel experiments and so were the other experimental parameters (molarity, speed of addition of the reagents, stirring and time of reaction). In the magnesium-only experiments, appreciable amounts of reagents were recovered unchanged. Further experiments evidenced that longer times and/or heating were required for the Mg-only reactions, which were, however, less reproducible and strongly dependent on the experimental parameters, most of all magnesium activation. An added advantage, when Sm(II) is present, is the colour of the solution that continuously changes during the addition of the organic reagents and that allows a visualisation of the course of the reaction.

This substoichiometric protocol was also tested for the reaction of diethyl ( $\alpha$ -iodomethyl)phosphonate with various aldehydes: the addition product,  $\beta$ -hydrox-yphosphonate, was formed, but only in modest yields (33–35%) and was accompanied by appreciable amounts of diethyl methylphosphonate (20–25%). Furthermore the reaction required, to proceed, the addition of an equimolar amount of trimethylsilyl chloride/bromide.

In a typical procedure, a solution of the carbonyl compound (1 mmol) and the halo compound (1 mmol) in tetrahydrofuran (2.0 mL) was added portion-wise at room temperature and under vigorous stirring to a mixture of samarium iodide (0.1 M solution in THF, 1.0 mL) and activated (with 1,2-dibromoethane) magnesium turnings (0.15 g) in THF (1.0 mL). The course of the reaction was monitored by observing the colour of the solution which turned blue to yellow and then back to blue for several times during the addition of the organic reagents.9 At the end of the reaction, monitored by thin layer chromatography (silica; eluting with n-hexane/ethylacetate), the reaction mixture was filtered. The remaining magnesium turnings were washed with tetrahydrofuran and reused. The organic phase was diluted with ethyl acetate and poured into crushed ice. The aqueous phase was extracted three times with ethyl acetate  $(3 \times 6 \text{ mL})$ . The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure, to afford a crude material, which was purified by column chromatography on silica gel.

In conclusion we have developed a new protocol for the synthesis of  $\beta$ -hydroxyesters and  $\beta$ -hydroxynitriles via samarium-mediated Reformatsky-type reactions, with some advantages with respect to the corresponding stoichiometric reactions: reduction of the samarium and the solvent (tetrahydrofuran) amounts; greater reproducibility; easier monitoring of the course of the reaction and timely visualisation of the end point, with consequent minimisation of the side products. The results ob-

tained in the samarium(II)-mediated reactions are comparable with those obtained in the Co(0) mediated reactions;<sup>4</sup> however, samarium does not require a phosphine to stabilise its low oxidation state, which has a double advantage: one reagent (the phosphine) is saved and the waste does not contain phosphine or phosphine oxide. In addition, in the Co-mediated procedure, when the solid triphenylphosphine is used, a chromatography is required to purify the product from triphenylphosphine or triphenylphosphine oxide. Chromatography can be avoided when the volatile trimethylphosphine is used, but this reagent is more toxic and less easy to handle. Last but not least, samarium derivatives are in general less toxic. Glyconolactones can be used as electrophiles, thus providing an entry to sugar-fused- $\beta$ hydroxy acids and C-glycosides. The protocol can be also applied to the synthesis of  $\beta$ -hydroxyphosphonates but in only modest yields and in the presence of trimethylsilylchloride as an additive.

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