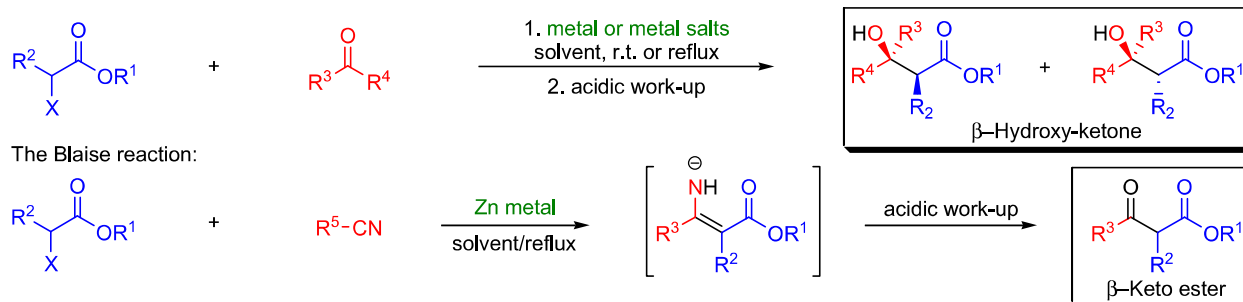


## REFORMATSKY REACTION

(References are on page 661)

**Importance:**[Seminal Publication<sup>1</sup>; Reviews<sup>2-19</sup>; Modifications & Improvements<sup>20-37</sup>; Theoretical Studies<sup>38-40</sup>]

In 1887, S. Reformatsky, reported that in the presence of zinc metal, iodoacetic acid ethyl ester reacted with acetone to yield 3-hydroxy-3-methylbutyric acid ethyl ester.<sup>1</sup> Since this initial report, the classical *Reformatsky reaction* was defined as the zinc-induced reaction between an  $\alpha$ -halo ester and an aldehyde or ketone. The scope of the reaction, however, extends far beyond this original definition, and today, the metal-induced reaction of  $\alpha$ -carbonyl halides with a wide range of electrophiles are referred to as the *Reformatsky reaction*. The reaction is a two stage process: first the activated zinc metal inserts into the carbon-halogen bond, and this is followed by the reaction of the zinc enolate (Reformatsky reagent) with the carbonyl compound in an *aldol reaction*. The general features of the *Reformatsky reaction* are:<sup>5,7,9</sup> 1) the reaction is most commonly carried out in a single step by addition of the  $\alpha$ -halo ester and the carbonyl compound to the suspension of the activated zinc, but performing the organozinc reagent prior to the addition of the electrophile is also possible; 2) most often ether solvents are used such as diethyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane, but mixtures of these solvents with aromatic hydrocarbons and more polar solvents such as acetonitrile, dimethyl formamide, dimethyl sulphoxide, and hexamethylphosphoric triamide are also used; 3) organozinc reagents can be formed from 2-bromoalkanoates,  $\alpha$ -bromo ketones, alkyl 2-bromomethyl-2-alkenoates,<sup>41</sup> and alkyl 4-bromo-2-alkenoates<sup>42</sup>; and 4) in addition to aldehydes and ketones, *Reformatsky reagents* also react with esters,<sup>43</sup> acid chlorides,<sup>44</sup> epoxides,<sup>43</sup> nitrones,<sup>45</sup> aziridines,<sup>46</sup> imines,<sup>47</sup> and nitriles<sup>48</sup> (*Blaise reaction*). The scope of the *Reformatsky reaction* was considerably extended by the development zinc-activation procedures. Activated zinc metal can be formed in two ways:<sup>7</sup> 1) by removal of the deactivating zinc oxide layer from the metal surface employing reagents such as iodine, 1,2-dibromoethane, copper(I) halides, mercuric halides or by using zinc-copper or zinc-silver couple;<sup>2,5,7,9,12</sup> and 2) by reduction of zinc halides in solution by various reducing agents such as potassium<sup>49</sup> (*Rieke zinc*), sodium<sup>50</sup> or lithium naphthalide<sup>51</sup> and potassium-graphite laminate<sup>52</sup> (C<sub>8</sub>K) to form finely dispersed zinc metal. Metals other than zinc were also used including lithium,<sup>22</sup> magnesium,<sup>20</sup> cadmium,<sup>28</sup> barium,<sup>37</sup> indium,<sup>21,34</sup> germanium,<sup>36</sup> nickel,<sup>31</sup> cobalt,<sup>35</sup> and cerium.<sup>24</sup> A major breakthrough in the *Reformatsky reaction* was the application of metal salts with favorable reduction potentials, the most important ones being samarium(II) iodide,<sup>23,32,33</sup> chromium(II) chloride,<sup>29</sup> and titanium(II) chloride.<sup>25</sup> These reactions often can be carried out under mild conditions and afford the products with high stereoselectivity. In addition to these metal salts, cerium(III) halides,<sup>30</sup> disodium telluride,<sup>30</sup> trialkylantimony/iodine,<sup>26,27</sup> and diethylaluminum chloride<sup>26,27</sup> can also be employed. The main advantages of the *Reformatsky reaction* over the classical *aldol reaction* are the following: 1) the reaction succeeds even with highly substituted ketone substrates; 2) the ester enolate can be formed in the presence of highly enolizable aldehyde and ketone functionalities; and 3) the reaction is uniquely suited for intramolecular reactions.



X = Cl, Br, I; R<sup>1</sup> = alkyl; R<sup>2</sup> = H, alkyl, aryl; R<sup>3</sup>, R<sup>4</sup> = H, alkyl, aryl; R<sup>5</sup> = alkyl, aryl; solvent: Et<sub>2</sub>O, THF, 1,4-dioxane, DME, benzene, toluene, MeCN, DMF, DMSO; metal: Zn, Mg, Cd, Ba, In, Ge, Co, Ni, Ce; metal salt: SmI<sub>2</sub>, CrCl<sub>2</sub>, TiCl<sub>2</sub>, CeX<sub>3</sub>, Na<sub>2</sub>Te, R<sub>3</sub>SnLi, R<sub>3</sub>Sb/I<sub>2</sub>, Et<sub>2</sub>AlCl;

**Mechanism:** <sup>53-57</sup>

Spectroscopic<sup>53,56</sup> and crystallographic<sup>54,55</sup> studies of Reformatsky reagents derived from  $\alpha$ -halo esters showed that the enolate is present in the C-enolate form and in ether solvents they form dimers. Enolates derived from  $\alpha$ -halo ketones prefer the O-metal enolate form.<sup>57</sup> It is assumed, based on theoretical calculation,<sup>38</sup> that the zinc enolate dimers are dissociated by the action of the carbonyl compound and converted to the corresponding O-zinc enolates. Subsequently, the reaction goes through six-membered chairlike transition state.

