The First Isolation of Crystalline Ethyl Bromozincacetate, Typical Reformatsky Reagent: Crystal Structure and Convenient Preparation

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Abstract: The highly reproducible preparation of ethyl bromozincacetate was achieved by a convenient procedure in which an excess amount of zinc powder was subjected to activation by chlorotrimethylsilane, followed by dropwise addition of ethyl bromoacetate. From the resultant solution of this Reformatsky reagent, crystalline ethyl bromozincacetate was isolated and its crystal structure was elucidated as its tetrahydrofuran-coordinated dimer (BrZnCH$_2$CO$_2$Et·THF), by X-ray crystal structure analysis. Although it had a dimeric structure similar to the tert-butyl bromozincacetate crystal, the two had different stereochemistry in the zinc-containing eight-membered ring (ZnCH$_2$CO)$_2$. The crystalline reagent obtained possessed satisfactory reactivity and stability for practical use. On the other hand, by preparing the tetrahydrofuran-free ethyl bromozincacetate in such solvents as 1,2-dimethoxyethane or cyclopentyl methyl ether, unintended crystallization could be successfully prevented.

Key words: Reformatsky reagent, ethyl bromozincacetate, isolation, tetrahydrofuran-coordinated dimer, convenient preparation

Ethyl bromozincacetate$^1$ (Figure 1) is a classical and typical Reformatsky reagent, versatile for reactions with not only aldehydes and ketones, but also nitriles, azomethines, carboxylic acid chlorides, and others.

![Figure 1](image)

Figure Dekker et al.$^2$ reported the crystal structure of tert-butyl bromozincacetate as its tetrahydrofuran-coordinated dimer (BrZnCH$_2$CO$_2$t-Bu·THF)$_2$ by X-ray crystal structure analysis. They also studied ethyl and tert-butyl bromozincacetates in solution by association measurements and NMR spectroscopy, concluding the reagents were dimeric in all but the most polar solvents.$^3$ However, ethyl bromozincacetate could not be obtained in crystalline form and its crystal structure remained ambiguous.$^4$ That is, in the article of Dekker et al., it was described that the two bulky tert-butyl groups of the tert-butyl bromozincacetate dimer preferred tetrahydrofuran-coordination over Zn–Br–Zn bridging, which would cause association to higher aggregates.$^2$ It was also described that ethyl bromozincacetate was isolated as its solvent-free form from a solution of dimethoxymethane, but tert-butyl bromozincacetate prepared in tetrahydrofuran still contained one tetrahydrofuran molecule per zinc atom.$^{2b}$ Hence a difference may remain in solvent coordination or aggregation degree between the ethyl derivative and the tert-butyl derivative, and so the crystal structure of the ethyl derivative was of interest.

On the other hand, we needed to establish a large-scale preparative method for ethyl bromozincacetate for the production of new drug candidates. Thereupon attempts to prepare this reagent in tetrahydrofuran avoiding highly inflammable diethyl ether were made, but this resulted in low reproducibility, where the reaction may or may not begin, or if it began a rapid reaction occurred that got out of control, or the yield of the Reformatsky reaction product may become extremely low. Although the pre-treatment of zinc powder by hydrochloric acid$^5$ was also tried, it showed no remarkable improvement. There were many reports concerning the Reformatsky reaction, but few focused on the reproducibility and exothermic behavior. It was even confusing that there were variations in the reaction conditions such as the presence or absence of carboxyl compounds, relative amounts of the materials, and the choice of the reaction solvent; a definitive method for the reproducible synthesis of ethyl bromozincacetate in tetrahydrofuran could not be found in literature.

Now, after trial and error, a highly reproducible method for the formation of ethyl bromozincacetate was achieved using a convenient procedure in which excess zinc powder was subjected to activation by chlorotrimethylsilane,$^6$ followed by dropwise addition of ethyl bromoacetate (Equation 1).$^7$ For the zinc powder, technical grade$^8$ could be used without any pretreatment, and commercial tetrahydrofuran containing stabilizers could also be used as it was. Initiation could be recognized by a rise in temperature accompanying the exothermic reaction.$^9$ This preparative method was favorable to scale-up, because there was no time lag between bromoacetate addition and reaction progress, and the reaction progress could be controlled according to the dropwise addition rate.$^{10}$

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\text{Zn powder} \xrightarrow{(5 \text{ mol} \%)} \text{TMSCI} \quad \text{BrCH$_2$CO$_2$Et} \xrightarrow{(0.3–1.0 \text{ equiv})} \text{BrZnCH$_2$CO$_2$Et}
\]

Equation 1
From the obtained solution of the Reformatsky reagent, presumably being of improved chemical purity,11,12 crystalline precipitates of the ethyl bromozincacetate readily developed. The crystal structure of this product was determined by X-ray crystal structure analysis as the tetrahydrofuran-coordinated dimer (BrZnCH₂CO₂Et·THF)₂ analogous to the case of tert-butyl bromozincacetate (Figure 2). Therefore, the ethyl derivative did not differ from the tert-butyl derivative in its degree of aggregation. However, the stereochemistry of the eight-membered ring was different from the tert-butyl derivative.2 That is, the two bromo groups and the two tetrahydrofuran ligands each have the cis-configuration, in contrast to the trans-configuration in the tert-butyl derivative. In addition, the conformation of the eight-membered ring was boatlike, in contrast to the chairlike conformation in the tert-butyl derivative.13 These structural distinctions were considered to be derived from the difference in steric bulk of the ethyl and tert-butyl groups. Figure 3 illustrates the stereoview of the dimeric molecular structure.

The isolated crystalline ethyl bromozincacetate showed good reactivity14 in Reformatsky reactions. We have already reported that the yield and selectivity were significantly improved for the reaction of crystalline ethyl bromozincacetate with p-benzoquinone compared to the classical Reformatsky procedure.15 It also turned out this crystalline reagent possesses satisfactory stability for practical use and can be stored in the refrigerator for at least six months (Table 1). Although the stability in the solution state was more important, it was anticipated that this crystalline reagent might contribute, more or less, to improved convenience in conducting the Reformatsky reaction.

From the above results and literature, it was presumed that the crystallinity of bromozincacetates was influenced by ligand species and, at least, the tetrahydrofuran coordination facilitated crystallization. We prepared the ethyl bromozincacetate in such solvents as 1,2-dimethoxyethane or cyclopentyl methyl ether to prevent unintended crystallization in large-scale production. The resultant tetrahydrofuran-free solution remained uncrystallized.16 Moreover, the crystalline reagent could be prepared by adding tetrahydrofuran to this ‘uncrystallizable’ solution. This was considered to be the reason why Orsini et al. and Dekker et al. formerly failed to isolate the crystals, because not only the purity of the reagent was not sufficiently high,15 but also the ‘tips’ on crystallinity and ligand species could not be recognized well merely from the information at that time.

As mentioned above, typical Reformatsky reagent ethyl bromozincacetate was successfully prepared in a convenient and easily exotherm-controlled manner. Further, crystalline ethyl bromozincacetate was isolated for the first time and its crystal structure was resolved by X-ray crystal structure analysis.17 By the isolation of this versatile reagent in good purity, it was anticipated that it would become easy to design reactions including asymmetric syntheses.

NMR data were collected on a Bruker DPX-300 with TMS as an internal standard. IR spectral measurements were carried out by Take-da Analytical Research Laboratories, Ltd.

Table 1 Stability Evaluation of Crystalline Ethyl Bromozincacetate

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Time (d)</th>
<th>BrZnCH₂CO₂Et (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25</td>
<td>0</td>
<td>89</td>
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<tr>
<td></td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>0–5</td>
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<td>89</td>
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<td>60</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>93</td>
</tr>
</tbody>
</table>

* Relative amount of BrZnCH₂CO₂Et to the degradation product EtOAc, calculated on the basis of ³H NMR.
Crystalline Ethyl Bromozincacetate (BrZnCH₂CO₂Et·THF)₂
Under an inert atmosphere TMSCl (5 mL, 39.4 mmol) was added to Zn powder (52.3 g, 0.8 mol) in THF (200 mL). The mixture was stirred at 20–25 °C for 30 min, ethyl bromoacetate (44.4 mL, 0.4 mol) in THF (500 mL) was then added dropwise at 22–45 °C and the mixture was stirred at 32–45 °C for 1 h. After cooling spontaneously to 25 °C, residual Zn was filtered off and washed with THF (150 mL). The combined filtrates were concentrated in vacuo to ca. 150 mL, at which point crystallization began; it was stirred over ice to give a crystalline product that was collected by pressure filtration, washed with THF (20 mL), and dried (N₂ stream) to yield ethyl bromozincacetate as a white crystalline powder; yield: 88.9 g (73%).

IR (ATR method): 3512, 2983, 2897, 1736, 1695, 1589, 1446, 1371, 1286, 1244, 1070, 1022, 918, 858, 769 cm⁻¹.

1H NMR (pyridine-d₅): δ = 1.10 (t, J = 7.1 Hz, 6 H), 1.20 (s, 4 H), 1.74–1.82 (m, 8 H), 3.54–3.66 (m, 8 H), 3.84 (q, J = 7.1 Hz, 4 H).

13C NMR (pyridine-d₅): δ = 17.77, 67.3, 57.5, 25.4, 19.6, 15.0.

1H NMR (pyridine-d₅): δ = 1.57–1.69 (m, 8 H), 3.59–3.72 (m, 8 H), 4.07 (q, J = 7.1 Hz, 4 H).

13C NMR (pyridine-d₅): δ = 179.4, 67.6, 58.0, 25.6, 18.7, 14.7.

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References
(3) In the strongly coordinating solvent DMSO, the reagent was interpreted to be monomeric.
(4) Both Orsini et al. (ref. 12) and Dekker et al. (ref. 2) clearly described that they failed to obtain the crystals of this reagent.
(6) Picotin, G.; Migniac, P. J. Org. Chem. 1987, 52, 4796; in this report, ethyl bromoacetate was reacted with zinc in the presence of a carbonyl substrate and Et₂O was used as solvent.
(7) Consulting the literature relating to Mg activation, I₂ and 1,2-dibromoethane were also examined, but TMSCl was most preferable. Indeed when I₂ was utilized for Zn activation in Et₂O, sometimes there was an induction period and heating was needed for reaction to be initiated: Zitsman, J.; Johnson, P. Y. Tetrahedron Lett. 1971, 12, 4201.
(8) Metallic zinc ca. 96–97% (impurities: Pb, Cd, Fe), particle size 6 µm (average), Honjo Chemical Corporation.
(9) Heat values calculated from the adiabatic reaction in a Dewar vessel were as follows: heat of reaction ΔHₜₐₐ = 2.47 × 10³ J/mol, adiabatic temperature increase ΔTₜₐₐ = 81 °C.
(10) Figure 4 shows the influence of the addition period of ethyl bromoacetate on the exothermic behavior of the reaction mixture. Fundamentally, the appropriate addition rate varies depending on the reaction scale, cooling capacity, stirring efficiency, etc., and, therefore, should be carefully determined on the basis of suitable safety evaluations.
(11) Although we attempted to analyze impurities by an NMR study of the concentrated residue of the obtained ethyl bromozincacetate–THF solution, useful information could not be obtained due to residual THF and other complicated constituents; there was no trace of side products such as...
ethyl acetoacetate in the NMR spectrum of the isolated crystals. On the other hand, we observed molecular ion peaks of ethyl acetoacetate, diethyl succinate, and other unknown compounds in the GC-MS of the hydrolytically quenched THF soln; adequate GC methods for quantitative analysis of the reagent solution could not be set up.

(12) Orsini et al. reported that the ethyl bromozincacetate in THF that they prepared, was contaminated by ethyl acetoacetate; Orsini, F.; Pelizzoni, F.; Ricca, G. *Tetrahedron Lett.* 1982, 23, 3945.

(13) The ethyl derivative was rotationally symmetric, while the tert-butyl derivative was point symmetric.

(14) We have been concerned that the reactivity of the reagent itself, not its reactivity in slurry state, was inhibited by irreversible changes during crystallization. However, there were no problems with this crystalline reagent.


(16) Even when these solutions were concentrated, crystallization did not occur. On the other hand, the crystallization could not be prevented when DME or another solvent was added after preparing the reagent as the THF solution.


(18) The crystallographic data have been deposited at the Cambridge Crystallographic Data Center; deposition number CCDC 656586.

