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THE USE OF THE REFORMATSKY REACTION FOR THE SYNTHESIS OF β-AMINO ACIDS

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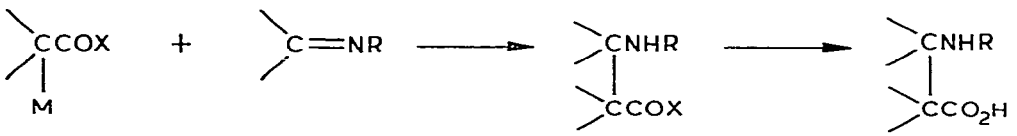
Summary

The salts of α-bromo acids react gently with imines in tetrahydrofuran in the presence of zinc; after acid hydrolysis, β-amino acids are directly obtained.

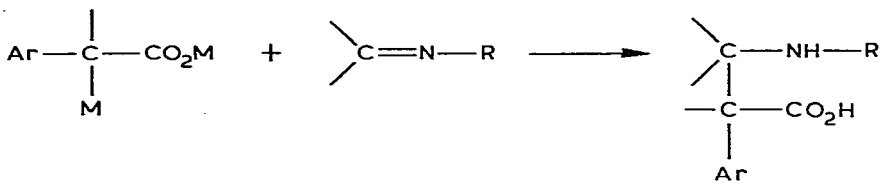
The classical methods for synthesis of β-amino acids from carboxylic acids derivatives are outlined in eq. 1 and 2.



(1)

(X = OR, NR_2;
M = ZnBr, Li)

Equation 1 depicts the Reformatsky reaction (M = ZnBr) on the imines [1,2] and the action of the lithiated ester on the imines [3], while of value for preparation of β-amino esters (or amides), these methods are less convenient for preparation of β-amino acids because of the need for subsequent hydrolysis of the esters (or amides).



(2)

(M = MgBr, Li, Na)

The Ivanov and related reactions (eq. 2) [3,4] lead directly to the β-amino

(Continued on p. 188)

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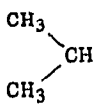
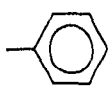
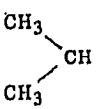
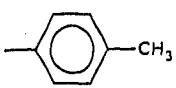
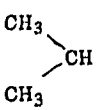
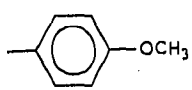
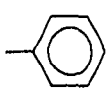
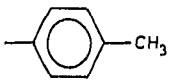
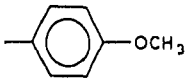
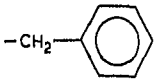
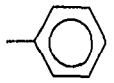
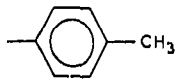
TABLE 1

β-AMINO ACIDS IV PREPARED: $PhCH(NHR^2)CHRCO_2H$ [a]

Compound	R^1	R^2	Yield (%) [b]	Molecular [c] formula	^1H NMR spectra (60 MHz, $CDCl_3$/TMS) δ (ppm)
IVa			65	$C_{18}H_{21}NO_2$ (283.36)	0.83—1.13 (m, 6H, $(CH_3)_2$); 1.70—2.40 (m, 1H, $CH(CH_3)_2$); 2.60 (m, 1H, $\succ CHCO_2H$); 4.58 (d, 1H, $\succ CHN\prec$); 5.93 (br s, 2H, $\succ NH + CO_2H$) [d]; 6.26—6.73 (m, 5H, $\succ NC_6H_5$); 6.83—7.30 (m, 5H, $-C_6H_5$).
IVb			67	$C_{19}H_{23}NO_2$ (297.38)	0.83—1.20 (m, 6H, $(CH_3)_2$); 2.15 (s, 3H, $CH_3C_6H_4$; 2.30—2.83 (m, 2H, $\succ CHCO_2H + CH(CH_3)_2$); 4.46—4.75 (m, 1H, $\succ CHN\prec$); 6.30—7.00 (m, 4H, C_6H_4); 7.18 (s, 5H, C_6H_5); 7.53 (s, 2H, $\succ NH + CO_2H$) [d]
IVc			41	$C_{19}H_{23}NO_3$ (313.38)	0.90—1.33 (m, 6H, $(CH_3)_2$); 1.85—2.40 (m, 1H, $CH(CH_3)_2$); 2.45—2.96 (m, 1H, $\succ CHCO_2H$); 3.73 (s, 3H, OCH_3); 4.60, 4.65 (d, d, 1H, $\succ CHN\prec$); 6.40—6.90 (m, 4H, C_6H_4), 7.28 (s, 5H, C_6H_5); 7.48 (s, 2H, $\succ NH + CO_2H$) [d]
IVd	$CH_3—CH_2$		70	$C_{17}H_{19}NO_2$ (269.33)	0.85 (t, 3H, CH_3); 1.20—1.97 (m, 2H, CH_2); 2.50—2.90 (m, 1H, $\succ CHCO_2H$); 4.50, 4.65 (d, d, 1H, $\succ CHN\prec$); 6.30—7.07 (m, 5H, $C_6H_5N\prec$); 7.18 (s, 5H, C_6H_5); 8.03 (s, 2H, $\succ NH + CO_2H$) [d]

IVe	CH_3-CH_2		66	$C_{18}H_{21}NO_2$ (283.36)	0.87 (t, 3H, CH_3CH_2); 1.17–2.00 (m, 2H, CH_2); 2.15 (s, 3H, CH_3) 2.42–2.97 (m, 1H, $\succ CHCO_2H$); 4.50, 4.60 (d, d, 1H, $\succ CHN\prec$); 6.27–6.97 (m, 4H, C_6H_4); 7.20 (s, 5H, C_6H_5); 7.94 (s, 2H, $\succ NH + CO_2H$) [d]
IVf	CH_3-CH_2		51	$C_{18}H_{21}NO_3$ (299.36)	0.86 (t, 3H, CH_3CH_2); 1.20–2.16 (m, 2H, CH_2); 2.36–2.93 (m, 1H, $\succ CHCO_2H$); 2.63 (s, 3H, OCH_3); 4.43, 4.56 (d, d, 1H, $\succ CHN\prec$); 6.26–6.76 (m, 4H, C_6H_4); 7.23 (s, 5H, C_6H_5); 7.75 (s, 2H, $\succ NH + CO_2H$) [d]
IVg	CH_3-CH_2		38	$C_{18}H_{21}NO_2$ (283.36)	0.87 (t, 3H, CH_3); 1.20–1.90 (m, 2H, CH_2CH_3); 2.53–3.02 (m, 1H, $\succ CHCO_2H$); 3.85–4.05 (d, d, 1H, $\succ CHN\prec$); 6.30 (br s, 2H, $CH_2N\prec$); 7.35, 7.45 (s, s, 10H, 2-C_6H_5); 9.55 (s, 2H, $\succ NH + CO_2H$) [a]
IVh	CH_3-CH_2	CH_3-CH_2	35	$C_{13}H_{19}NO_2$ (221.29)	0.70–1.20 (m, 6H, $2CH_3$); 1.33–2.20 (m, 4H, $2CH_2$); 2.33–2.73 (m, 1H, $\succ CHCO_2H$); 4.68, 4.88 (d, d, 1H, $\succ CHN\prec$); 7.23–7.30 (s, s, 5H, C_6H_5); 8.95 (s, 2H, $\succ NH + CO_2H$) [d]
IVi	$-CH_3$		48	$C_{16}H_{17}NO_2$ (255.30)	1.12 (d, 3H, CH_3); 2.70–3.15 (m, 1H, $\succ CHCO_2H$); 4.52, 4.80 (d, d, 1H, $\succ CHN\prec$); 6.35–7.20 (m, 5H, $C_6H_5N\prec$); 7.30 (s, 5H, C_6H_5); 8.05 (s, 2H, $\succ NH + CO_2H$) [d]
IVj	$-CH_3$		40	$C_{17}H_{19}NO_2$ (269.43)	1.10 (d, 3H, $CH_3CH\prec$); 2.15 (s, 3H, CH_3); 4.45, 4.75 (d, d, $\succ CHN\prec$); 6.30–7.03 (m, 4H, C_6H_4); 7.27 (m, 5H, C_6H_5); 8.07 (s, 2H, $\succ NH + CO_2H$) [d]

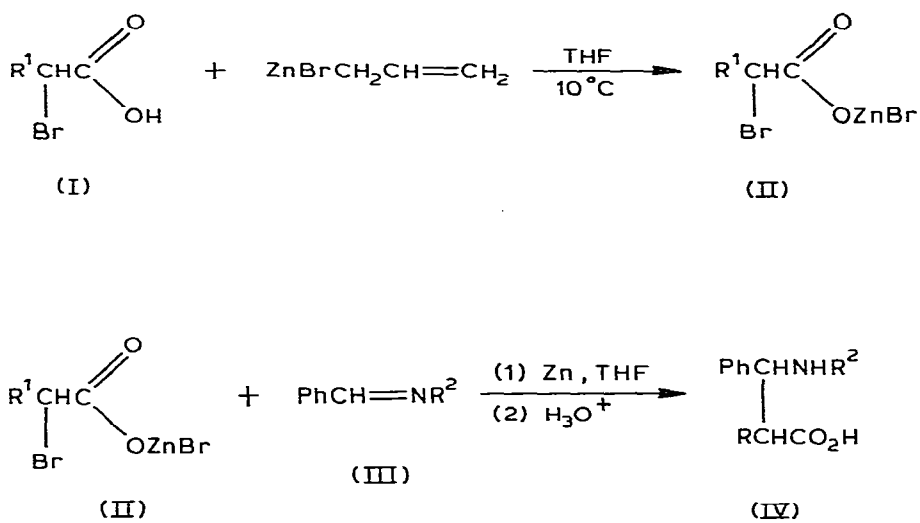
[a] All products are obtained as a mixture of diastereoisomers. [b] Yield of isolated product based on I. [c] All products gave satisfactory microanalyses (C ±0.25, H ±0.35, N ±0.45%). [d] The peak disappears with shaking in D_2O.

acids, but have the disadvantage that only aromatic carboxylic acids have been used. The reactions have not, to our knowledge, been extended to aliphatic acids.

We now report a new method for direct synthesis of β-amino acids using the Reformatsky reaction. This new method has the advantages of the earlier routes (eq. 1, 2) without their disadvantages.

We previously described the use of α-bromocarboxylic salts II in the Reformatsky reaction, and showed that these reagents are of value for the preparation of β-hydroxy acids [5], ketones [6] and γ-lactones [7]. In continuation of these studies, we have found that these salts II react with imines III, as in the classical Reformatsky reaction, to give β-aminoacids IV in fairly good yields. We have investigated the scope and importance of this reaction.

The organozinc salts II are easily prepared by action of allylzinc bromide on the α-bromocarboxylic acid in tetrahydrofuran (THF). The reagent II is then heated with imine III in the presence of zinc to give, after acid hydrolysis, the corresponding β-aminoacid IV (Scheme 1).



SCHEME 1

The simplicity of the method and the satisfactory yields obtained (see Table 1) mean that this new route provides a good method for the one-step synthesis of β-amino acids.

Preparation of the α-bromosalt II

The allylzinc bromide was prepared as described in ref. 8 from zinc (6.5 g, 0.1 g-atom), allylbromide (12.1 g, 0.1 mol), and dry tetrahydrofuran (60 ml) at 10°C for 1 h and during 15 min 0.08 mol of α-bromocarboxylic acid I was added to the solution at 0°C during 15 min.

Reaction of II with imine III: preparation of β-amino acids IV. General procedure

To the organozinc reagent II prepared as described above, are added the imine III (0.08 mol), zinc (0.08 g-atom, 5.2 g), HgI_2 (a few mg as catalyst) and dry tetrahydrofuran (30 ml). The mixture is then heated at 65°C with stirring until the zinc has disappeared (2—3 h). The mixture is then added to a mixture of hydrochloric acid (30 ml of concentrated HCl) and crushed ice. After extraction with ether (3 × 100 ml) the organic layer is washed five times with water to remove $ZnBr_2$. (Compounds IVg and IVh (Table 1) have to be extracted with chloroform and washed once with water since they are very soluble in this latter.) In order to remove the unchanged imine III from the β-amino acid IV, the washed organic layer is treated with aqueous sodium hydroxide (10 g of NaOH in 100 ml of water). The aqueous layer is then acidified with an excess of hydrochloric acid and extracted many times with ether. The ethereal layer is washed with satured aqueous sodium chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent under vacuum gives the crude product IV, which is purified by recrystallisation from petroleum ether.

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