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ß-AMINO ESTERS VIA THE REFORMATSKY REACTION: RESTRAINING EFFECTS OF THE *ortho*-METHOXYPHENYL SUBSTITUENT.

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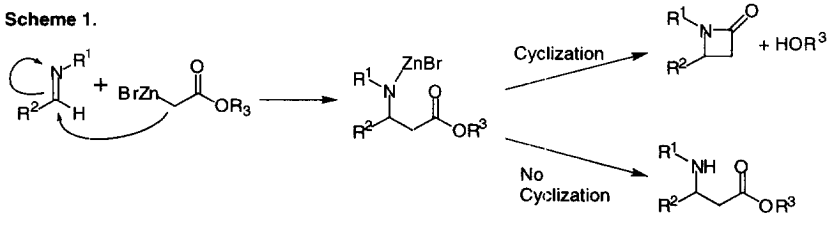
Abstract: ß-Amino esters are, in most cases, the *only* products of the Reformatsky reaction in CH_2Cl_2 between (methoxycarbonyl)methyl zinc bromide (prepared *in-situ*) and imines prepared from either an aryl or alkyl aldehyde and *o*-anisdine (Scheme 2). Restraining properties of the *ortho*-methoxyphenyl group, which lead to sole formation of the ß-amino ester, are ascribed to the inductive effect of the *ortho*-methoxy substituent.

ß-Amino acids, although far less abundant in nature than their α-analogues, nevertheless hold an important place in pharmacology.[1] The best known class of medicinally important ß-amino acid derivatives are the ß-lactam antibiotics for which ß-amino acids can serve as synthetic intermediates or precursors.[2] Recently, attention has been focused on the ability of peptides composed of ß-amino acids to adopt predicable and reproducible folding patterns similar to those observed for α-amino acid peptides.[3]

A straightforward and convenient preparation of ß-amino esters is the addition of a Reformatsky reagent to an aldimine.[4] A complication of this method can often be the formation of the related ß-lactam (Scheme 1). This reaction, first reported by Gilmann and Speeter to afford ß-lactams in refluxing benzene,[5] was later shown by Mohan and co-workers to be sensitive to the electron-withdrawing nature of the nitrogen substituent of the imine. They reported the formation of "resinous material" when R^1 was a *para*-nitrophenyl substituent.[6] Dardoize and co-workers studied this addition in ether solvents and reported that ß-lactams or ß-amino esters were formed in ratios which were temperature dependent.[7]

Scheme 1.



In order to explain the observation that this reaction affords both ß-lactams and ß-amino esters, we proposed a mechanistic working model which proceeds through a common zinc amide intermediate (Scheme 1). In developing a predictable Reformatsky-imine addition we reasoned that a mildly electronegative R^1 substituent should reduce the nucleophilicity of the nitrogen, thus reducing the tendency toward cyclization. Ideally, such a group should also be spectroscopically simple and easily removed. In this paper we report the restraining effects

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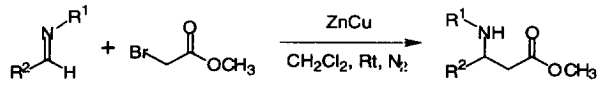
of the *ortho*-methoxyphenyl group

Scheme 2.



As illustrated in Scheme 2, if R^1 is an *ortho*-methoxyphenyl group then ß-amino esters are, in most cases, the only products. The scope of this reaction was explored and the results are presented in Table 1. Entries 1-8 clearly indicate that the outcome of this reaction is generally independent of the identity of R^2. The electronic influence of R^2 was examined in entries 5 (donating) and 6 (withdrawing). Imines with alkyl R^2 substituents (entries 7 and 8) are equally selective .

We ascribe the restraining effects of the *ortho*-methoxyphenyl nitrogen substituent to an inductive effect arising from the close proximity of the electronegative oxygen of the methoxy group to the nitrogen-zinc bond, thus reducing its nucleophilic character. The dual substituent parameter treatment developed by Taft and co-workers[8] attributes substituent effects to an additive blend of inductive and resonance effects. Taft[8] and later Yoder,[9] have demonstrated that the inductive effect dominates over the resonance effect for *ortho* substituents by a factor of nearly two to one, while for many *para* substituents the reverse is the case. Entry 9 tests our "basicity" hypothesis. The reaction of an imine derived from 2-chloroaniline under these conditions affords the ß-amino ester as the sole product. In this case, the inductive effect dominates the resonance effect by a factor of nearly 2.5 to one.[8,9] Internal consistency would predict that a *para*-methoxyphenyl R^1 substituent (entry 12) should promote lactam formation. In agreement with both our prediction and the literature,[10] we observed a product ratio of 55:45 ester:lactam.

The possibility of either chelation or steric effects retarding cyclization were tested by entries 10 and 11, respectively. Both experiments resulted in similar mixtures of lactam and ester products. These data coincide with previous observations for Reformatsky-imine additions at room temperature[7] and they also indicate that neither possible chelation[11] nor steric effects are sufficient to prevent lactam formation.

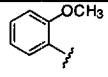
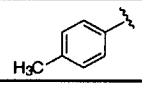
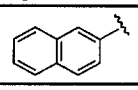
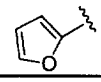
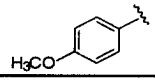
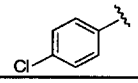
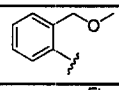
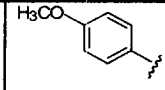
We found that the mode of preparation of the Zn-Cu couple played an important role. The Zn-Cu couple, prepared according to the method of Santaniello and Manzocchi,[12] was the most active. Zinc dust was found to be the most reactive, although zinc granules were also active. The activated Zn-Cu couple was stable in the air and remained active for about six months.

A few reports of Reformatsky reactions in halogenated solvents have appeared in the literature.[13] We found that our reactions could be conducted in either CH_2Cl_2 (distilled from P_2O_5 or CaH) or the more traditional ether solvent, THF. However, reaction times in THF were typically four to ten times longer. This is expected since there is increased solvation of the zinc enolate by the Lewis basic solvent, THF.[14]

The *ortho*-methoxyphenyl *N*-substituent is easily removed by cerium ammonium nitrite (CAN)[15] to afford the unmasked ß-amino ester. For example, methyl 3-(2-methoxyphenyl)amino-3-phenylpropionate (Entry 1 product) was deprotected to afford methyl 3-amino-3-phenylpropionate in 84% yield.

We have described a highly predictable, efficient, and gentle (CH_2Cl_2, room temperature) method for the preparation of ß-amino esters based on the Reformatsky reaction. Experiments to exploit the two-point binding potential of this system in an asymmetric fashion are on-going and will be reported in due course.

Table 1. Reaction Results of Representative Aldimines with Methyl Bromoacetate (Scheme 2).

Entry	R^1	R^2	Solvent	Time[a]	Ester Yield[b]	Lactam Yield[c]
1			CH_2Cl_2	1h	89%	None
2	"		CH_2Cl_2	3h	80%	None
3	"		CH_2Cl_2	1.5h	78%	<5%
4	"		CH_2Cl_2	15h	92%	None
5	"		CH_2Cl_2	1h	84%	<5%
6	"		CH_2Cl_2	3.5h	93%	None
7	"		CH_2Cl_2	15h	66%	None
8	"		CH_2Cl_2	17h	51%	None
9			CH_2Cl_2	3.5h	91%	None
10		"	CH_2Cl_2	4h	78%[c]	22%
11		"	CH_2Cl_2	1.5h	80%[c]	20%
12		"	CH_2Cl_2	3.5h	55%[c]	45%

All compounds afforded satisfactory spectroscopic data. For typical reaction conditions see reference 16. a) Completion time based on TLC analysis; b) Isolated yields; c) Percentages based on ^{1}H-NMR analysis of the crude product mixture.

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11. While these experiments do not rule out the possibility that zinc chelation could well retard cyclization, these results seem to imply that chelation does not contribute significantly. However, we are currently conducting further experiments to test the influence of chelation.
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16. Typical experimental: **Methyl 3-(2-methoxyphenyl)amino-3-phenylpropionate** (Entry 1). To a stirred solution of the aldimine (0.22 g, 1.0 mmol) and methyl bromoacetate (0.37 g, 2.4 mmol) in 3 mL of CH_2Cl_2 under N_2 was added the Zn-Cu (dust, 0.20 g, 3.0 mmol). Reaction progress was followed by TLC, after 1 h the reaction mixture was decanted into 15 mL of 1 M HCl, shaken and separated. The aqueous phase was extracted once with 10 mL of CH_2Cl_2. The combined organics were washed with sat. $NaHCO_3$, water, brine, dried with $MgSO_4$ and concentrated *in-vacuo* to afford 0.31 g of an oily tan, crystalline solid which was recrystallized from isopropyl alcohol to afford 0.25 g (89%) as clear, colorless needles: mp 107-108 °C; Rf = 0.24 (SiO_2 40% hexane/CH_2Cl_2); IR (Thin film) 3415, 2993, 2862, 1733, 1600, 1513, 1456, 1436, 1349, 1251, 1226, 1174, 1123, 1026, 739, 703 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.43-7.25 (m, 5H), 6.81-6.62 (m, 3H), 6.46 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz), 5.07 (d, 1H, J = 7.0 Hz), 4.89 (q, 1H, J = 7.0 Hz), 3.89 (s, 3H), 3.67 (s, 3H), 2.88 (m, 2H); 50 MHz ^{13}C-NMR ($CDCl_3$) δ 171.3, 146.8, 142.2, 136.4, 128.6, 127.2, 126.0, 120.9, 116.7, 111.0, 109.3, 55.2, 54.4, 51.5, 42.6; Anal. calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.49; H, 6.74; N, 4.97.