Zinc catalysed ester solvolysis. Application to the synthesis of tartronic acid derivatives†

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A novel synthesis of hydroxyglycine retropeptidic derivatives was achieved through a Passerini 3-component reaction of glyoxyl amides or esters, followed by an unprecedented environmentally benign zinc catalysed solvolysis.

The synthesis of retro- and retro-inverso peptides, peptide analogues in which one or more peptidic bonds are inverted, was shown to be an effective strategy for the development of peptidomimetic drugs with improved bioavailability and metabolic stability.[1] Tartronamide can be used as a retropeptidic surrogate of hydroxyglycine, which may be regarded as a stable transition state analogue of amide bond hydrolysis. Hence, non-symmetric tartronamides have been synthesised as inhibitors of matrix proteinases,[2] important pharmacological targets involved in tumour invasion and joint destruction processes. Peptidomimetic tartronamides have been also proposed as analogues of 15-desoxyspergualin, an immunosuppressive agent used to reduce graft rejection.[3]

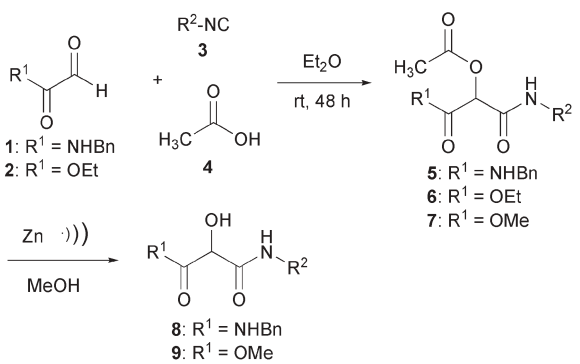
Multicomponent reactions (MCRs) are highly convergent processes that allow the efficient preparation of complex molecules from simple starting materials. MCRs of isocyanides, particularly the Ugi reaction, have been employed for the synthesis of peptide derivatives,[4] though, as far as we know, they have never been used in the synthesis of retropeptides. We envisaged that glyoxylamides (**1**), isocyanides (**3**) and a carboxylic acid, such as acetic acid (**4**), could be combined in a three component Passerini condensation[5] to give acylated tartronamide derivatives (**5**). Acyl hydrolysis would then transform adducts **5** into tartronamides (**8**; Scheme 1).

Ester hydrolysis usually requires rather acidic or basic conditions, which involve the use of corrosive reagents, leading to dangerous wastes. By contrast, in living systems many hydrolytic enzymes use Zn^{2+} to catalyse hydrolysis at physiological pH. The role of zinc in these enzymes may be two-fold, enhancing the electrophilic character of the substrate and also facilitating the formation of a nucleophilic hydroxyl anion.[6] Zn(II) complexes, often containing polydentate ligands, have been prepared as model compounds of hydrolytic metalloenzymes,[7] although their use in synthesis is generally impractical. We reasoned that cationic centres on the surface of finely divided zinc could be able to coordinate an alcoholic OH or a water molecule, activating them as nucleophiles in a solvolytic process. A heterogeneous catalytic system using Zn would have evident environmental and practical advantages in ester hydrolysis. We report here the results of the exploration of such catalytic system in the synthesis of tartronic acid derivatives.

In a first experiment we performed a Passerini condensation between benzylglyoxylamide (**1**),[8] cyclohexyl isocyanide (**3a**) and acetic acid (**4**). An equimolar mixture of the three components was stirred at rt in Et_2O for 3 days. The expected adduct **5a** precipitated from the reaction medium and was isolated by filtration, essentially pure, in a 68% yield.[9] We next attempted the hydrolysis of the ester **5a**, using ultrasonically activated Zn, in a mixture of saturated aqueous NH_4Cl and methanol. The reaction was followed by GC-MS until all the starting material was consumed. After 72 h, a single product was isolated from the reaction mixture, which according to its spectroscopic data was identified as the desired tartronamide **8a**. Remarkably, conversion was quantitative according to GC-MS data, and no hydrolysis of the amide group, or reduction to the corresponding malonodiamide[10] was detected.

We also investigated the effect of ultrasounds on the solvolysis.[11] Irradiation in an ultrasound bath significantly accelerated the reaction, which went to completion in just 6 h, in a methanolic solution with no added water.

Surprisingly, when acetate **5a** was treated with $ZnCl_2$, solvolysis did not take place, and only starting material was recovered, even after 7 days stirring at rt. To rule out cleavage of the ester through reduction of the acyl group, we decided to perform the solvolysis of an ester large enough to allow a convenient analysis of the products by GC-MS. Therefore, aroyl ester **10**, synthesised by the Passerini reaction of benzylglyoxylamide (**1**), cyclohexyl isocyanide (**3a**) and *p*-toluic acid, was subjected to ultrasound irradiation in methanol, in the presence of an excess of Zn. GC-MS monitoring of the reaction revealed only the expected solvolysis products



Scheme 1 Synthesis of tartronodiamides and tartronoamidoesters.

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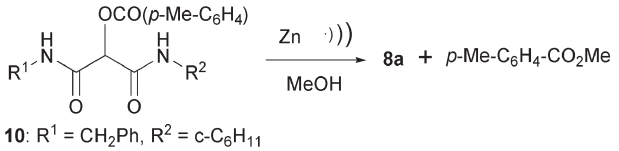
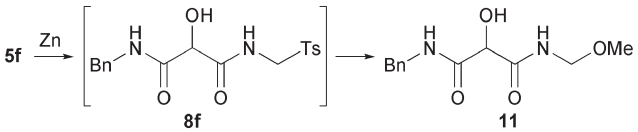
† Electronic supplementary information (ESI) available: Spectroscopic data of all new compunds. See DOI: 10.1039/b607358a



Scheme 2 Solvolysis of Passerini adduct **10**.



Scheme 3 Tandem solvolysis–β N–H elimination of adduct **5f**.

tartronamide **8a** and *p*-toluic acid methyl ester, but no *p*-methylbenzyl alcohol was detected (Scheme 2).

It is interesting to note that cleavage with Zn of acetate **5a** was significantly accelerated when a catalytic amount of $ZnCl_2$ was added. The reaction took place in methanol, in the presence of an excess of Zn and 10 mol% of $ZnCl_2$, in 6 h, or in just 3 h when ultrasonic irradiation was applied.[12] Apparently, a synergy between Zn^{2+} and the large surface of zinc metal account for the observed catalytic effect, as $ZnCl_2$ alone did not promote the solvolysis. In the absence of zinc chloride, Zn^{2+} is probably produced by the ultrasounds facilitated oxidation of the metal.[13]

We applied the optimised solvolysis conditions, using Zn and $ZnCl_2$ in methanol, to other biscarbamoylmethyl acetates (**5b–f**), obtained by the Passerini condensation of different isocyanides (**3b–f**). The results are shown in Table 1 (entries 1–5). Passerini reactions gave moderate to good yields of the adducts, and solvolysis was always quantitative as judged by GC-MS, although isolated yields varied between 77 and 99%.

In the case of the Passerini adduct **5f** (Table 1, entry 6), methanolysis was spontaneously followed by nucleophilic substitution of the tosyl group by a molecule of solvent, leading to methoxymethyl amide **11**. Although similar sulfone substituted amides are usually quite stable towards β N–H elimination,[14] in this case displacement of the tosyl group is probably facilitated by anquimeric assistance of the δ OH on intermediate **8f** (Scheme 3). Interestingly, tartronodiamide **11** contains two orthogonal protecting groups, which would allow, in principle, independent functionalisation of both amide groups.

Finally, amidoesters (**6**) obtained by the Passerini condensation of ethyl glyoxylate (**2**) have also been subjected to methanolysis in the same conditions used for the bisamides **5** (Scheme 1). In this case, the cleavage of the acetate was accompanied by transesterification of the ethyl ester. For the reaction of diester **6a**, a mixture of starting material, tartronoamidoester **9a** and the intermediate **7a** was detected by GC-MS. Longer reaction times led exclusively to **9a**, but significant decomposition was also detected. Nonetheless, tartronoamidoester **9d** was obtained in a moderate yield as the only product of the reaction of diester **6d**.

We also studied the possibility of recycling the catalyst. In five successive runs **5a** was hydrolysed to completion, in identical conditions, reusing the same Zn, which was separated by centrifugation and removal of the supernatant solution.

In conclusion, we have developed a novel and convenient synthesis of tartronic acid derivatives through a sequence of a Passerini 3-component condensation and a mild solvolysis catalysed by Zn. Solvolysis is performed in neutral aqueous or alcoholic solution, conditions that are compatible with many different functional groups and in accordance with the principles of green chemistry. Furthermore, Zn can be recycled and reused in successive hydrolyses with no significant loss of catalytic activity. This procedure may be easily adapted for the preparation of partially modified retropeptides with possible pharmacological interest. Experiments are currently underway in our laboratory.‡

Table 1 Results of the passerini and solvolysis reactions

Entry	R^1	R^2	Passerini[a] (%)	Solvolysis[b] (%)
1	$PhCH_2NH$	C_6H_{11}	**5a** (68)	**8a** (99)
2	$PhCH_2NH$	^{t}Bu	**5b** (70)	**8b** (97)
3	$PhCH_2NH$	$PhCH_2$	**5c** (55)	**8c** (77)
4	$PhCH_2NH$	2,6-Me_2Ph	**5d** (61)	**8d** (99)
5	$PhCH_2NH$	^{t}BuO$_2$CCH$_2$	**5e** (65)	**8e** (94)
6	$PhCH_2NH$	4-MePhSO$_2$CH$_2$	**5f** (87)	**11** (77)
7	CH_3CH_2O	C_6H_{11}	**6a** (45)	**9a** (12)[c]
8	CH_3CH_2O	2,6-Me_2Ph	**6d** (61)	**9d** (51)[c]

[a] *Representative procedure for the Passerini condensation*: 5 mmol of each acetic acid (**4**), *N*-benzyl glyoxylamide (**1**) or ethyl glyoxylate (**2**) and the corresponding isocyanide (**3**) were stirred for 72 h in 5 mL of Et_2O at rt. The precipitate was filtered and washed with *i*-PrOH (5 mL) and *i*-Pr_2O (5 mL). [b] *Representative procedure for the solvolysis*: A mixture of **5** or **6** (0.3 mmol), Zn dust (3 mmol) and $ZnCl_2$ (0.03 mmol) in MeOH (12 mL) was irradiated in a sonication bath for 3–4 h. The reaction mixture was decanted from the Zn and concentrated, and the product was purified by column chromatography (15 cm × 2.5 cm Ø, SiO_2, hexane–EtOAc 7 : 3 to 1 : 1). [c] Reaction time: 7 h.

Notes and references

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9 Data for (benzylcarbamoyl)(cyclohexylcarbamoyl)methyl acetate (**5a**): (68%) white solid; mp 175–177 °C; IR (cm^{-1}) 3272, 1747, 1679, 1659, 1543; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5 H), 6.65 (d, 1 H, J = 7.8 Hz), 5.59 (s, 1 H), 4.46 (m, 2 H), 3.75 (m, 1 H), 2.25 (s, 3 H), 2.00–1.10 (m, 10 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.52 (C), 164.62 (C), 163.51 (C), 137.25 (C), 128.69 (CH), 127.55 (CH), 72.20 (CH), 48.68 (CH), 43.53 (CH_2), 32.57 (CH_2), 25.29 (CH_2), 24.60 (CH_2), 20.67 (CH_3); MS (FAB) *m/z* (%) 333 (M^+ + 1, 100), 291 (11); HRMS calcd for $C_{18}H_{25}N_2O_4$: 333.1813. Found: 333.1814.
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12 Data for N^1-benzyl-N^3-cyclohexyl-2-hydroxymalonamide (**8a**): (99%) white solid; mp 142–144 °C; IR (cm^{-1}) 3279, 1644, 1542; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (br s, 1 H), 7.35–7.10 (m, 5 H), 7.13 (br d, 1 H, J = 7.6 Hz), 4.64 (br s, 1 H), 4.47 (m, 3 H), 3.75 (m, 1 H), 2.0–1.10 (m, 10 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.72 (C), 167.30 (C), 137.21 (C), 128.71 (CH), 127.62 (CH), 127.50 (CH), 70.26 (CH), 48.70 (CH), 43.60 (CH_2), 32.65 (CH_2), 25.31 (CH_2), 24.58 (CH_2); MS (EI) m/z (%) 290 (M^+, 7), 209 (2), 165 (41), 106 (35), 91 (100); HRMS calcd for $C_{16}H_{22}N_2O_3$: 290.1630. Found: 290.1642.
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