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A new method for the preparation of functionalized unnatural α-H-α-amino acid derivatives

David J. Hyett, Mara Didonè, Thierry J. A. Milcent, Quirinus B. Broxterman and Bernard Kaptein*

DSM Research, Life Sciences-Advanced Synthesis and Catalysis, PO Box 18, 6160 MD Geleen, The Netherlands

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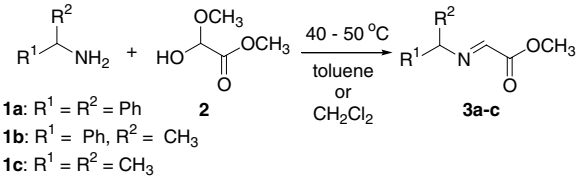
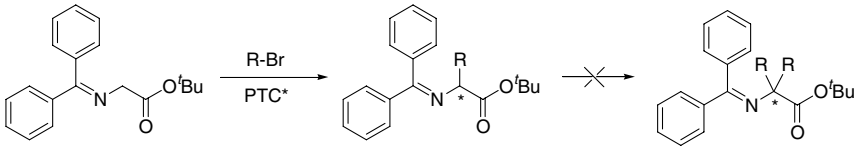
Abstract—A new method for the preparation of α-H-α-amino acids is reported based on the α-alkylation of iminoacetic acid esters or amides. These imines are readily available by the reaction of glyoxylic acid esters with branched primary amines. The subsequent reaction with methanolic ammonia gave the corresponding iminoacetic acid amides. α-Alkylation of these imines with various electrophiles under basic conditions, followed by an acidic hydrolysis, gave α-amino acids, esters, or amides in up to 93% yield. α-Alkylation under chiral PTC conditions resulted in mono-alkylated amino acids with 90% ee.

Of the various routes described to synthesize (enantiopure) α-H-α-amino acids, α-alkylation of glycine derivatives has gained an increasing interest in recent years. The method initially developed by O'Donnell has found widespread application in the laboratory, especially for the preparation of amino acids with functionalized side chains.[1–3] Thus glycine esters, activated as their benzophenone imines, can be selectively mono-alkylated as a result of an increase in the pK_a of the product after the first alkylation because of 1,3-allylic strain (Scheme 1).[4] A drawback of this procedure is the troublesome preparation of the benzophenone imine. A direct formation with benzophenone is a sluggish and low-yielding reaction requiring $BF_3{\cdot}Et_2O$ catalysis, whilst transimination using an expensive benzophenone imine is less attractive for a large-scale application.[1]

In order to develop an alternative to this alkylation process suitable for the industrial scale, we concentrated on activation using imines that are both easily prepared and derived from low-cost starting materials. We identified a good procedure using imines formed by reacting branched primary amines **1a–c** with glyoxylic acid ester derivatives, for example, hemi-acetal **2**.[5–7] These esters are readily available on a large scale (indeed some of them are produced annually on a multi-ton scale[8]) and react smoothly to form imines (e.g., **3a–c**) in 86–95% yields (Scheme 2).



Scheme 2. Imine formation by reaction of branched amines with methyl glyoxylate hemi-acetal.



Scheme 1. Selective (asymmetric) mono-alkylation of the benzophenone imine of glycine esters.

* Corresponding author. Tel.: +31 46 4767416; fax: +31 46 4767604; e-mail: bernard.kaptein@dsm.com

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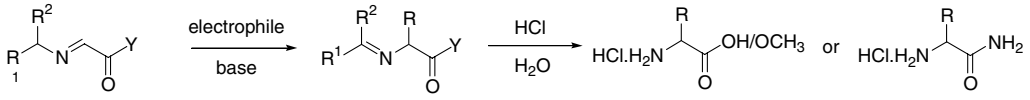
Although iminoacetates have been frequently used as electrophiles for the addition of organometallic reagents[6] or as dienophiles in Diels–Alder reactions,[7] to our knowledge deprotonation and use as nucleophilic reagents has never been described. The alkylation of imines **3a–c** with various electrophiles, using either PTC conditions[9] or, for example, with KO^{t}Bu as base, gave imines **5a–i** of α-mono-alkylated α-amino acid methyl esters in 56–91% unoptimized yields (Table 1).[10] Different electrophiles were tested, varying from activated species such as allylic, propargylic or benzylic chlorides and bromides through 1,4-acceptors, such as acrylonitrile and crotonitrile, to unactivated *n*-butyl iodide. Our initial attempts focused on the use of *N*-benzhydrylimines in order to obtain mono-alkylation. However, the use of other branched primary amines also resulted in selective mono-alkylation. The application of (racemic) *N*-1-phenylethyl- or *N*-*i*-propyl-imino substrates (**3b/3c**, respectively) proved to be advantageous from an industrial perspective; the corresponding amines are cheap, readily available and have a lower molecular weight than benzhydrylamine. As a result of this lower molecular weight, the intermediate imines contain a higher weight percentage of 'amino acid end-product'. Thus a higher productivity is possible since (assuming identical molar yields) less kgs of intermediate imine would have to be processed in order to produce 1 kg of end-product.

The acidic hydrolysis of mono-alkylated imines **5a–i** with dilute hydrochloric acid gave the hydrochloride salts of the corresponding mono-alkylated amino acids **6** or amino acid methyl esters **7**, depending on the hydrolysis conditions.[1]

In addition to the alkylation of methyl esters **3a–c**, we also studied the alkylation of amides **4a–c**, which could be readily formed by the reaction of **3a–c** with methanolic NH_3 (Scheme 3). Amide **4a** could be mono-alkylated in high yields and the subsequent acidic hydrolysis of the imines resulted in amino acid amides **8a–n** (Table 1). Amides **4b** and **4c** resisted alkylation under the reaction conditions studied, most likely because of higher pK_a values.

The remarkably fast amidation reaction of methyl esters **3a–c** to amides **4a–c** is most likely the result of the inductive effect of the imino functional group. Using 7 M NH_3 in methanol at an ambient temperature, the amidation was complete within 30 min. The alternative explanation for this fast reaction, namely initial (mixed) aminal formation followed by an intramolecular amida-

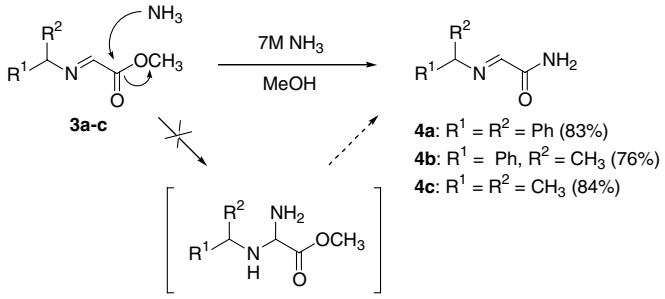
Table 1. Alkylation of the imines of glyoxylic acid esters **3a–c** and amide **4a**



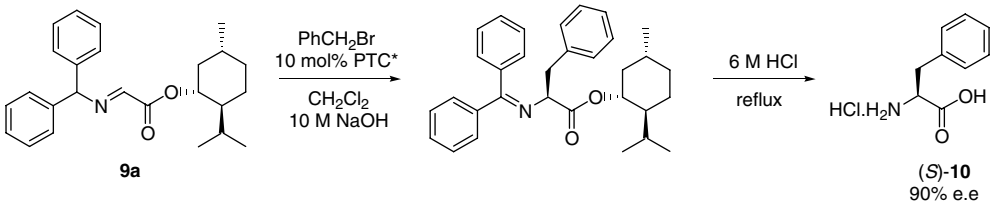
Entry	Substrate	R^1	R^2	Y	Method[a]	Electrophile (R–X)[b]	Yield (%)
1	**3a**	Ph	Ph	OCH_3	A	H_2C=CH–CH_2–Br	88 **5a**
2	**3a**	Ph	Ph	OCH_3	A	HC≡C–CH_2–Br	73 **5b**
3	**3a**	Ph	Ph	OCH_3	B	H_2C=CH–CN	90 **5c**
4	**3b**	Ph	CH_3	OCH_3	A	H_2C=CH–CH_2–Br	56 **5d**
5	**3b**	Ph	CH_3	OCH_3	B	H_2C=CH–CN	64 **5e**
6	**3b**	Ph	CH_3	OCH_3	B	CH_3–CH=CH–CN	68 **5f** (60:40)
7	**3c**	CH_3	CH_3	OCH_3	A	H_2C=CH–CH_2–Br	90 **5g**
8	**3c**	CH_3	CH_3	OCH_3	A	*n*-C_4H_9–I	85 **5h**
9	**3c**	CH_3	CH_3	OCH_3	A	Ph–CH_2–Br	91 **5i**
10	**4a**	Ph	Ph	NH_2	C	H_2C=CH–CH_2–Br	88 **8a**
11	**4a**	Ph	Ph	NH_2	C	HC≡C–CH_2–Br	85 **8b**
12	**4a**	Ph	Ph	NH_2	D	H_2C=CH–CH_2–Br	93 **8a**
13	**4a**	Ph	Ph	NH_2	D	PhCH_2–Br	89 **8c**
14	**4a**	Ph	Ph	NH_2	D	3-F–$C_6H_4CH_2$–Br	65 **8d**
15	**4a**	Ph	Ph	NH_2	D	3-MeO–$C_6H_4CH_2$–Br	81 **8e**
16	**4a**	Ph	Ph	NH_2	D	4-Br–$C_6H_4CH_2$–Br	78 **8f**
17	**4a**	Ph	Ph	NH_2	D	4-CN–$C_6H_4CH_2$–Br	66 **8g**
18	**4a**	Ph	Ph	NH_2	D	4-NO_2–$C_6H_4CH_2$–Br	62 **8h**
19	**4a**	Ph	Ph	NH_2	D	4-Ph–$C_6H_4CH_2$–Cl	62 **8i**
20	**4a**	Ph	Ph	NH_2	D	1-Napht–CH_2–Cl	73 **8j**
21	**4a**	Ph	Ph	NH_2	D	2-Napht–CH_2–Br	71 **8k**
22	**4a**	Ph	Ph	NH_2	D	9-Anthr–CH_2–Cl	72 **8l**
23	**4a**	Ph	Ph	NH_2	D	3-Py–CH_2–Br	77 **8m**
24	**4a**	Ph	Ph	NH_2	D	Ph_2CH–Br	80 **8n**

[a] Reaction at ambient temperature of a solution of 1 equiv of **3/4** and 1.1–1.2 equiv of electrophile; method A, in MTBE by the addition of 1.1 equiv of KO^{t}Bu; method B, in MTBE by the addition of 0.1–0.3 equiv of KO^{t}Bu; method C, in CH_2Cl_2 by the addition of 1.2 equiv of KO^{t}Bu; method D, PTC conditions: CH_2Cl_2/10 M NaOH solution/5–10 mol % Bu_4NHSO_4.

[b] All reactions proceeded via an S_N2 mechanism, except for entries 3, 5 and 6, which gave the 1,4-addition products **5c**, **5d** and **5f**. Compound **5f** was obtained in a 60:40 diastereomeric ratio according to ^{1}H NMR.



Scheme 3. Amidation reaction of iminoacetic acid methyl esters **3a**–**c**.



Scheme 4. Asymmetric PTC alkylation of L-menthyl *N*-benzhydryliminoacetate **9a** using the Lygo PTC* catalyst *N*-(9-anthracenylmethyl)cinchonidinium chloride.

tion, seems unlikely because only primary amides were formed. A mixed aminal mechanism would be expected to lead to product mixtures containing both primary amides (resulting from intramolecular amidation by $-NH_2$) and substituted amides (resulting from intramolecular amidation by $-NH^iPr$, $-NHCH(CH_3)Ph$ or $-NHCHPh_2$). The amidation of **3a**–**c** can also be performed with primary amines but secondary amines reacted very sluggishly (results not shown).

The formation of the racemic amino acid amides **8a**–**n** is especially attractive because it can be combined with the enzymatic resolution process developed at DSM Research some years ago. For example, the resolution of amides **8a** and **8b** using the L-aminopeptidase from *Pseudomonas putida* ATCC 12633 has been described previously.[11]

Initial studies into an asymmetric alkylation procedure have been performed using iminoacetate **9a**, obtained in a 98% yield as a colourless solid from commercially available L-menthyl glyoxylate hydrate[8] and benzhydrylamine **1a**. Although the asymmetric induction by the chiral menthyl ester moiety upon alkylation with benzyl bromide using KO^tBu in CH_2Cl_2 (method C, ee 10% (*S*)) or achiral PTC alkylation conditions (method D, ee 18% (*S*)) is rather limited, the combination of this moiety and a chiral PTC catalyst resulted in good ees. Using the phase transfer catalyst *N*-(9-anthracenylmethyl)cinchonidinium chloride, developed by Lygo,[12] benzylation in CH_2Cl_2/10 M NaOH solution at 0 °C gave (*S*)-phenylalanine **10** in an 81% yield and 90% ee (Scheme 4). The enantiopurity of this material was improved to 98% ee by crystallization from aqueous 2-propanol.

Since the use of the chiral PTC catalyst with methyl ester **3a** or amide **4a** gave low ees, it can be postulated that the menthyl moiety provides a comparable steric interaction to that of a *tert*-butyl ester (which has been used successfully in related reactions, see Scheme 1).[3,12] The menthyl ester is preferred in this case because *tert*-butyl glyoxylate is not readily available on an industrial scale.

In conclusion, a new method for the preparation of α-H-α-amino acid derivatives by the selective α-mono-alkylation of iminoacetic acid esters or amides has been identified.[13] The benefit of this method results from the availability of the starting materials and an easy preparation of the iminoacetic acid derivatives compared to the *N*-benzhydrylidene-glycine esters. The formation and alkylation of the iminoacetic acid derivatives proceeds in high yields and gives access to enantiopure amino acids, either by asymmetric PTC alkylation or by enzymatic resolution of the racemic amino acid amides.

Acknowledgements

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5. The iminoacetic acid esters are readily prepared by addition of 1 equiv of the primary amine to a solution of the hemi-acetal or hydrate of glyoxylic acid esters in an inert solvent (toluene, CH_2Cl_2, MTBE, etc.). After stirring

for 1 h at 40–50 °C, the water and alcohol by-products were removed by partial evaporation of the solvent. The solution can be used directly for further reaction (optionally after drying over Na_2SO_4) or the solvent can be removed to obtain the pure imine as a (coloured) oil. Trituration with heptane gave methyl *N*-(diphenylmethyl)iminoacetate **3a** as a stable white solid, mp 63–66 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.70 (s, 1H, N=C*H*), 7.20 (m, 10H, $2C_6H_5$), 5.60 (s, 1H, Ph_2CH), 3.79 (s, 3H, OCH_3). The imines that are liquid and do not solidify, tend to decompose slowly. For the imine formation, it is not necessary to start with the free glyoxylic acid esters as is often described in the literature.[6,7]

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8. Methyl glyoxylate methyl hemi-acetal and L-menthyl glyoxylate hydrate are produced by DSM Pharma Chemicals annually on multi-ton scale.
9. PTC conditions: organic solvent (toluene, CH_2Cl_2 or methyl *t*-butyl ether)/10 M NaOH or KOH solution/5–10 mol Bu_4NHSO_4.
10. Typical example: To a solution of **3c** (1.00 g, 7.74 mmol) and allyl bromide (1.12 g, 9.29 mmol) in MTBE (30 ml) was added KO^{t}Bu (0.95 g, 8.5 mmol) in small portions over 30 min. The suspension was stirred at room temperature for 15 min and then the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and the remaining undissolved salt (KBr) was removed by filtration through decalite. The organic filtrate was washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to give **5g** as a brown oil (1.18 g, 7.0 mmol, 90%). ^{1}H NMR ($CDCl_3$), δ (ppm): 5.78 (m, 1H, C*H*=CH_2), 5.10 (m, 2H, CH=CH_2), 4.17 (m, 1H, α-C*H*), 3.72 (s, 3H, OCH_3), 2.66 and 2.48 (2m, 2H, β-CH_2), 2.09 and 1.88 (2s, 6H, $(CH_3)_2$C=N).
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