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An Acyliminium Ion Approach Towards The Synthesis of β-Substituted 3,4-Dihydroisoquinolone Propionates

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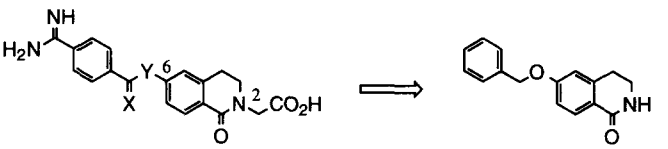
Abstract: A variety of α-methoxy amides were prepared either by selective reduction of the exocyclic carbonyl of a 2-acyl-3,4-dihydroisoquinolone and subsequent trapping of the resultant α-hydroxy amide with acidic methanol or by reacting the sodium salt of 3,4-dihydroisoquinolone with a functionalized α-chloro ether. These intermediates were reacted with 1-*tert*-butoxy-1-*tert*-butyldimethylsiloxy ethene in the presence of BF_3•Et_2O providing access to β-substituted isoquinolone propionates in good yield.

The development of Arg-Gly-Asp (RGD) mimics for use as antagonists of platelet glycoprotein (GP) IIb-IIIa has received considerable attention.[1] We have recently disclosed our efforts towards the design and optimization of a series of isoquinolone based Gly-Asp β-turn mimics with good activity towards GP IIb-IIIa.[2] Lead compounds **1** and **2** identified from these efforts required substitution of the isoquinolone nucleus at position 6 with an arginine isostere (benzamidine) and substitution at position 2 with an aspartate isostere (acetic acid).

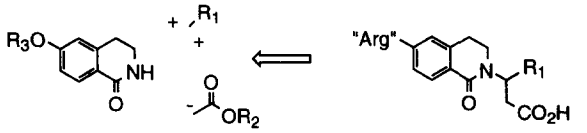


IC_{50} GP IIb-IIIa ELISA [3]

1 X = O, Y = NH 0.003 μM
2 X = H,H, Y = O 0.60 μM

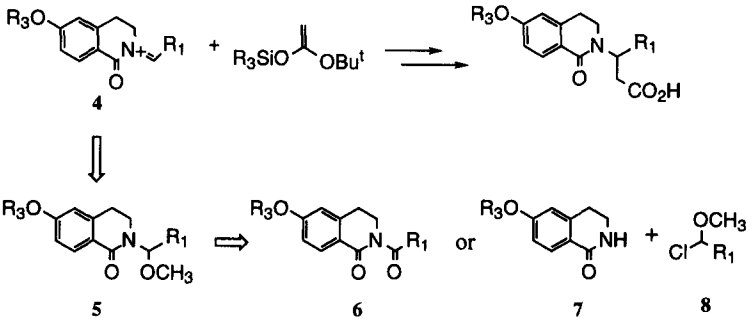
3

During the course of our efforts to further optimize the aspartate isostere, we required a method for the preparation of a variety of β-substituted isoquinolone propanoic acids. The ideal method would have made use of readily available isoquinolone **3**, thus necessitating the development of a protocol for the transformation of an amide into a β-substituted-β-amido propionate. Our retrosynthetic analysis of this problem is outlined in Scheme 1. Disconnection of the propionate residue from the isoquinolone nucleus at the carbon nitrogen bond provided an acid fragment which could be further simplified by disconnecting the bond between the α and β carbons.



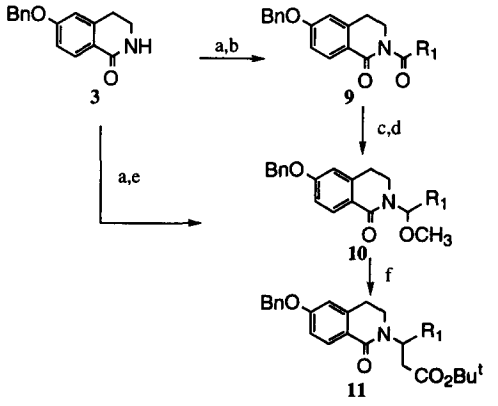
Scheme 1

This strategy afforded a variable "R" group situated between common ester and an amide fragments. We reasoned that this collection of subunits could be efficiently assembled from the reaction of acyliminium intermediate **4** with a silyl ketene acetal (Scheme 2).[4] The requisite acyliminium ion precursor (**5**) was envisioned to arise from either selective reduction of the exocyclic carbonyl of unsymmetrical imide **6** followed by trapping of the resulting α-hydroxy amide with a suitable alcohol, or by reacting amide **7** with an appropriately functionalized α-chloro ether **8**.[5] The former approach has seen extensive use in the preparation of cyclic α-alkoxy amides[6], but the literature provided scant guidance for the selective reduction of imides in which one acyl moiety is exocyclic.[7] Alkylation of amides with α-chloro ethers has precedent[8], but subsequent use of the formed α-alkoxy amide as an acyliminium ion precursor has, to the best of our knowledge, not been reported.[9]



Scheme 2

Synthesis efforts began with the condensation of the sodium salt of **3** with a variety of acid chlorides providing imides **9** in good yields (Scheme 3 and Table 1).[10] These constructs were then subjected to the action of DIBAH at -78°C followed by quenching with a slight excess of anhydrous HCl in methanol.[7b] The resulting



a) NaH; b) R_1COCl; c) DIBAH; d) HCl/MeOH; e) $R_1CH(OCH_3)Cl$;
f) 1-*tert*-butoxy-1-*tert*-butyldimethylsiloxy ethene - $BF_3{\bullet}Et_2O$

Scheme 3

slightly acidic reaction mixure was then allowed to warm to room temperature where it was *quickly* washed with H_2O to remove the aluminum residues and then washed extensively with saturated aqueous $NaHCO_3$. The crude α-methoxy amides **10** were stable to purification on silica gel. This reaction protocol generally afforded good yields of the desired exocyclic α-methoxy amides **10** with no detectable reduction of the endocyclic carbonyl.[11] Reaction by-products consisted of starting isoquinolone **3** and traces of aldehyde, both of which likely arise from incomplete quenching of the intermediate α-hydroxy amide or hydrolysis of the desired product during work-up.

We were unable to extend the above procedure to unsymmetrical imides in which the R group was phenyl. In this case, products isolated after sequential treatment with DIBAH and acidic methanol consisted of isoquinolone **3** and benzaldhyde. This suggested that the reduction was facile but trapping the intermediate α-hydroxy amide with methanol was inefficient. The desired phenyl substituted intermediates could however be prepared by reacting the sodium salt of **3** with the desired phenyl substituted α-chloro ethers (Table 2). This provided a convenient one step preparation of the desired materials.

Table 1. Yields[12] of products **9**[13], **10**[14], and **11**[15].

Entry	Acid chloride	Imide **9** Yield (%)	α–Methoxy amide **10** Yield (%)	β-Amido ester **11** Yield (%)
a	CH_3CH_2COCl	69	73	49
b	$CH_3(CH_2)_2COCl$	77	73	46
c	$CH_3(CH_2)_3COCl$	95	83	52
d	$CH_3(CH_2)_4COCl$	83	68	70
e	$CH_3(CH_2)_5COCl$	94	63	76
f	$CH_3CH_2O(CH_2)_3COCl$	64	83	78
g	$CH_3O(CH_2)_3COCl$	77	71	55
h	$CH_3O(CH_2)_2OCH_2COCl$	81	30	45
	α-Chloro Ether			
i	PhCH(OMe)Cl	-	68	63
j	4-I-PhCH(OMe)Cl	-	51	90

Treatment of a solution of α-methoxy amides **10** and excess 1-*tert*-butoxy-1-*tert*-butyldimethylsiloxy ethene (5 eq) in CH_2Cl_2 with one equivalent of $BF_3{\bullet}Et_2O$ at -78°C, followed by warming to room temperature provided modest yields of the desired β-substituted β-amido esters **11** after basic work-up. An excess of the ketene acetal was required for satisfactory yields, presumably due to competing decomposition of this intermediate in the presence of $BF_3{\bullet}Et_2O$. Use of other Lewis acids ($SnCl_4$, $TiCl_4$, TMSOTf) for acyliminium ion generation provided inferior results characterized by low yields and significant decomposition of both starting materials.

In conclusion, we have demonstrated that α-methoxy amides **10** can be prepared by selective reduction of the exocyclic carbonyl contained in unsymmetrical imides **9** or by reaction of the sodium salt of **3** with various phenyl substituted α-chloroethers. These α-methoxy amides serve as precursors to acyliminimum ion intermediates which can be trapped with a silyl ketene acetal ultimately providing β-substituted isoquinolone propionates. Efforts toward generalizing this method for the preparation of other β-substituted-β-amido propionates are underway.

Acknowledgments: The authors wish to thank Steve Kaldor for helpful discussions and advice.

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3. This value represents the concentration required to reduce the binding of fibrinogen to purified human GP IIb-IIIa by 50%. For details see reference 2.
4. An alternative approach for the construction β-amido esters would employ the Michael addition of amide anions to acrylates. Interesting protocol for this type of transformation has been recently disclosed. Ahn, K.H.; Lee, S.J. *Tetrahedron Lett.* **1994**, *35*, 1875-1878.
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9. Iminium salts have been prepared by the reaction of an α-chloro ether with an amine. See: Jahn, U.; Schroth W. *Tetrahedron Lett.* **1993**, *34*, 5863-5866.
10. All new compounds provided satisfactory spectroscopic and analytical data.
11. The selectivity observed for this reduction is probably dictated by the fact that the approach to the endocyclic carbonyl is more sterically demanding and/or that its reactivity is likely reduced by conjugation with the C_6 benzyloxy group.
12. All reported yields are unoptimized.
13. Representative procedure for the reduction of imides **9**: A solution of the imide (1.0 mmol) and THF (5 mL) was treated at -78°C with DIBAH (1.3 mmol) and the resulting solution was allowed to stir for 1h. The reaction mixture was then quenched by the addition of a methanolic solution of anhydrous HCl (0.6N, 5.2 mmol). The resulting solution was allowed to warm to room temperature over the course of 5 minutes where it was diluted with EtOAc (50 mL) and quickly washed with H_2O (2 x 15 mL) and then saturated aqueous $NaHCO_3$. The solution was then dried ($MgSO_4$) and concentrated. Chromatography on silica gel, eluting with hexanes/EtOAc, provided intermediates **10** in good yield.
14. Representative example for alkylation of isoquinolone **3** with phenyl-substituted α-chloro ethers: A mixture of **3** (1.0 mmol) and THF (15 mL) was treated with NaH (1.2 mmol) and the resulting solution was maintained at reflux for 1h. The heterogeneous mixture was then allowed to cool to room temperature where it was treated with the desired α-chloro ether (1.1 mmol). The resulting mixture was stirred at room temperature for 4h. This mixture was diluted with EtOAc (50 mL) and washed with H_2O. The organic material was then dried ($MgSO_4$) and concentrated. Chromatography on silica gel, eluting with hexanes/EtOAc, provided phenyl substituted intermediates **10** in good yield.
15. Representative procedure for the preparation of β-substituted isoquinolone propionates **11**: A mixture of α-methoxy amide **10** (1.0 mmol), 1-*tert*-butoxy-1-*tert*-butyldimethylsiloxy ethene (5.0 mmol) and CH_2Cl_2 (10 mL) was treated with freshly distilled BF_3•Et_2O (1.0 mmol) at -78°C. The resulting solution was allowed to warm to room temperature and was thus maintained for an additional 3h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The crude product was purified on silica gel eluting with hexanes/EtOAc which provided the desired products in moderate to good yield.

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