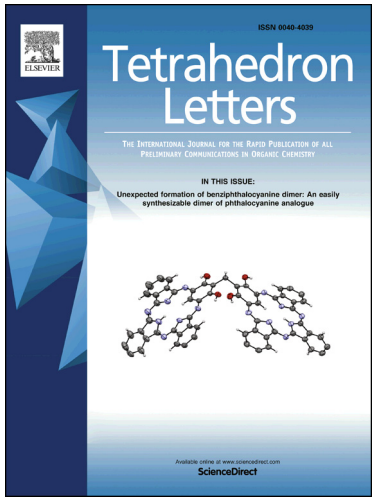

Selective alkylation/oxidation of *N*-substituted isoindolinone derivatives: synthesis of *N*-phthaloylated natural and unnatural α-amino acid analogues

Pravin C. Patil, Frederick A. Luzzio, Jarrid M. Ronnebaum

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Selective alkylation/oxidation of *N*-substituted isoindolinone derivatives: synthesis of *N*-phthaloylated natural and unnatural α-amino acid analogues

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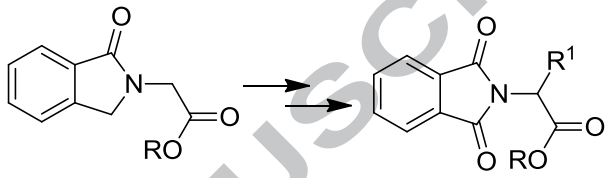

R=ethyl, *tert*-butyl
R^1=alkyl, allyl, propargyl, aryl

Alkylations: 51-93%
Oxidations: 65-98%

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Selective alkylation/oxidation of *N*-substituted isoindolinone derivatives: synthesis of *N*-phthaloylated natural and unnatural α-amino acid analogues

Pravin C. Patil , Frederick A. Luzzio∗ and Jarrid M. Ronnebaum

Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky 40292 USA

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ABSTRACT

The interchangeability of the isoindolinone group as a nitrogen protecting group for amino acid intermediates is demonstrated by the preparation of several natural and unnatural α-amino acid derivatives using a two-carbon *N*-isoindolinone (phthalimidine) scaffold. Using a selective benzylic oxidation, the *N*-isoindolinone group is then converted to the *N*-phthaloyl group for convenient removal (65-98%). For preparation of the isoindolinone products which were to be the substrates for benzylic oxidation, a range of side chains were installed on the isoindolinone-protected glycine equivalent on deprotonation to demonstrate the utility of the *N*-protected isoindolinone synthon (51-93%). While the ensuing benzylic oxidation is employed successfully for converting the *N*-isoindolinone group to the *N*-phthaloyl group in simple substrates, substrates bearing unsaturated or electron-rich side chains respond poorly to the oxidation.

1. Introduction

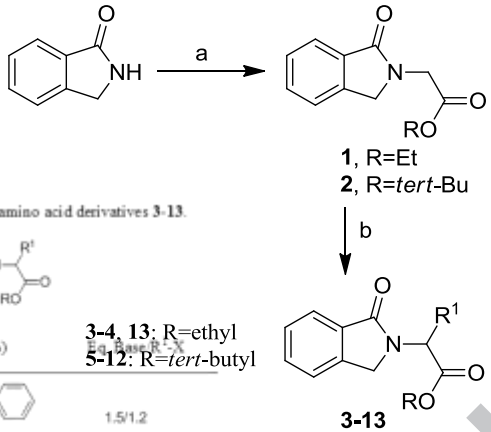
In multistep synthesis, it is possible for protecting groups to perform multiple roles by providing both orthogonal protection as well as activation of neighboring atoms for further bond formation.[1] A notable case in point is the development of the versatile benzophenone imine ($RN=CPh_2$, R=carboxymethylene) derivatives of glycine by O'Donnell and co-workers for the preparation of diverse α-amino acids.[2] Thus, the two-carbon fragments having both the masked nitrogen and the ester functions falls into the category of synthons termed "glycine equivalents."[3] The design and utilization of glycine equivalents allows for the de novo preparation of a plethora of natural and unnatural amino acids.[4] While the need for the de novo synthesis of natural α-amino acids most frequently includes isotopic analogues, the requirement for unnatural or otherwise non-proteinogenic amino acids may stem from the areas of protein engineering, drug design or enzyme modification.[5] Nevertheless, many de novo syntheses require that the α-methylenes or methines of glycine equivalents may be activated to give either anions or cations which then facilitate the attachment of the requisite 'natural or unnatural' side chains.[6] While glycine equivalents typically bear both a protected nitrogen and carboxyl group with the α-methylene group available for C-C bond formation, one must note that protection of the nitrogen is not an absolute necessity-as demonstrated by the chiral amino alcohol-derived glycinamide synthons developed by Myers and coworkers.[7] When N or O protection is warranted, the removal of these types of protecting groups is a distinct consideration and can be one or two-step processes. If the requirements are multistep, the overall process typically renders the deprotection protocol easier when addressing the removal of a particularly robust protecting group-i.e., those typically used for withstanding the more vigorous chemical reactions. While the *N*-isoindolinone group is not a protecting group per se, the capability of converting it into the well-known *N*-phthaloyl group would place it in that class of derivatives. We report herein that an adjoining *N*-isoindolinone group allows the α-methylene of an ethyl- or a *tert*-butyl ester to be deprotonated under basic conditions and facilitates the installation of side chains through the addition of reactive electrophiles such as alkyl halides. After the installation of the new side chain, the *N*-isoindolinone group is then selectively oxidized to the easily-removable *N*-phthaloyl group which is an established protecting group in peptide chemistry. We have reported that the overall process involving the alkylation/*N*-isoindolinone-*N*-phthaloyl interconversion is effective for preparing ethynylalanine derivatives en route to triazolylalanine analogues via click chemistry.[8] More detailed studies are included in this Letter where we report

∗ Corresponding author. Tel.: +0-502-852-7323; fax: +0-502-852-8149; e-mail: faluzz01@louisville.edu

the scope of the alkylation reaction as well as details involving the response of selected substrates to the benzylic oxidation of the *N*-isoindolinone moiety.

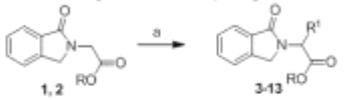
2. Results and Discussion

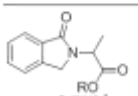
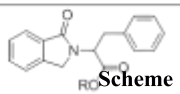
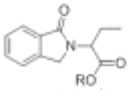
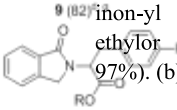
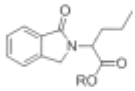
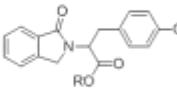
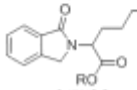
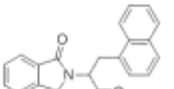
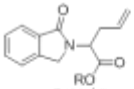
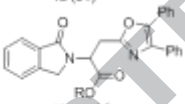
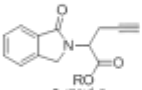
Our synthesis begins with the preparation of *N*-isoindolinone-derived esters **1** and **2** (**Scheme 1**).[9] Generation of the sodium salt of isoindolinone (NaH/THF) followed by slow addition of either ethyl bromoacetate or *tert*-butyl bromoacetate afforded the *N*-isoindolinonoyl esters **1** and **2** as solid materials in yields of 78% and 97% respectively after column chromatography on silica gel. The alkylation reactions involved base mediated anion generation using lithium hexamethyl disilazide (LiHMDS) and entailed a fairly standard protocol entailing addition of LHMDS to a mixture of the electrophile and ester **1** or **2** (**Table 1**). Under similar conditions, bases such as potassium *tert*-butoxide, sodium ethoxide and cesium carbonate did not give promising results. The usage of base was critical as isoindolinones can suffer deprotonation of the benzylic methylene,[10] hence the possibility of multiple alkylated products which result in complex mixtures. While the employment of the ethyl ester **1** with reactive alkyl halides gave the expected products in modest to good yields, less reactive alkyl halides gave poor yields and what appeared to be decomposition of the starting ester **1** during the course of the reaction. For purposes of clarity, we organized the electrophiles and their products (**3-13**, **Table 1**) into three groups. These included the alkyl iodides, affording products **3-6** (70-86%), the allyl/propargyl bromides, giving products **7** and **8** (93, 78%, respectively), and finally the benzylic electrophiles which provided the aromatic-derived products **9-13** (51-82%). For the alkylation reactions, individual procedures for all compounds are presented in the Supplementary Data.



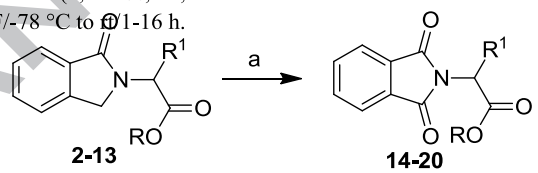
Scheme 1. Preparation of **1, 2** and alkylated *N*-isoindolinon-yl esters **3-13**. Reagents/Conditions: (a) NaH/THF/ethylor *tert*-butyl bromoacetate/20 °C/16 h (**1**, 78%; **2**, 97%). (b) LiHMDS/R^1-X (X=Cl,Br, I)/THF/-78 °C to rt/1-16 h.

Table 1
Alkylation of the *N*-isoindolinone-protected esters **1, 2** to give amino acid derivatives **3-13**.



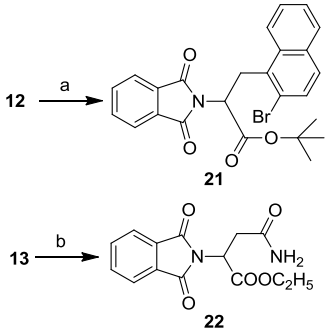
Product (Yield%)[b]	Eq. Base/R^1-X	Product (Yield%)	Eq. Base/R^1-X
 3 (73)[c, f]	1.3/3	 9 (82)[c, g]	1.5/1.2
 4 (70)[c, f]	1.05/5	 10 (60)[c, g]	1.2/1.2
 5 (86)[c, g]	1.2/5	 11 (61)[c, g]	1.2/1.2
 6 (78)[c, g]	1.2/5	 12 (51)[c, g]	1.5/1
 7 (93)[d, g]	1.2/1.2	 13 (63)[e, f]	1.25/1.25
 8 (78)[d, g]	1.5/1.2		

[a]Reagents/Conditions: LiHMDS/THF/ then R^1-X (X=Cl, Br, I)/-78 °C to rt/1-16 h.[b]Yields are of isolated, chromatographically pure products. [c]Alkyl iodide was used. [d]Alkyl bromide was used. [e]Alkyl chloride was used. [f]Ethyl ester **1** was used. [g]*tert*-Butyl ester **2** was used.



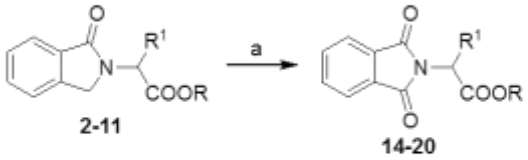
Scheme 2. Selective oxidation of *N*-isoindolinon-yl esters **2-13** to phthalimides **14-20**. Reagents/Conditions: Oxone®/KBr/MeCN-H_2O/40-45 °C/16 h (70-98%, See **Table 2**).

A number of reagents/conditions were evaluated for the benzylic oxidation of the lactam moiety of alkylation products **3-13** to the corresponding *N*-phthaloyl derivatives **14-20** (**Scheme 2**).[11] With attention to expense and ease of protocol, systems such as MCPBA (*m*-chloroperbenzoic acid) and combinations of oxygen, or 2,2'-bipyridinium chlorochromate (BPCC)/MCPBA, SeO_2, Oxone®/KI were unreactive or gave complex mixtures. Finally, an optimal system composed of Oxone®/KBr in acetonitrile-water gave the best results in benzylic oxidation thereby delivering the *N*-phthaloyl products **14-20** (**Table 2**).[12] While substrate **2** (**Table 2**) is the starting material for alkylation and is not an alkylation product per se, it does represent a 'glycine equivalent' and for purposes of completeness it was included in the oxidations and gave the *N*-phthaloyl ester **14**. It should be noted that the Oxone®/KBr system is the first application of this type of oxidant to an isoindolinone to give the corresponding imide.[8,11] While the benzylic oxidations to the phthalimides appear to be a straightforward process, some examples were not without anomalous or unexpected results.



Scheme 3. Benzylic oxidation of selected substrates **12** and **13**. Reagents/Conditions: (a) Oxone®/IBX/KBr MeCN-H_2O/40-45 °C/16 h. (b) Oxone®/KBr/MeCN-H_2O/40-45 °C/3 h..

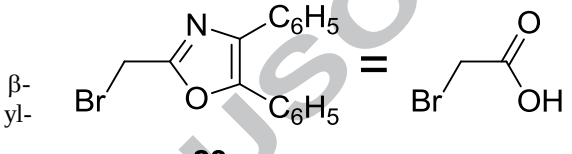
Table 2
Oxidation of the *N*-isoindolinone group of esters **2-13** to give the *N*-phthaloyl group of amino acid derivatives **14-20**.



Substrate[b]	Product (Yield%)[c]
2, R^1=H	PhthN(H)COOR **14** (85)
3, R^1=CH_3	PhthN(CH_3)COOR **15** (70)
4, R^1=C_2H_5	PhthN(C_2H_5)COOR **16** (76)
5, R^1=C_3H_7	NPhth(C_3H_7-*n*)COOR **17** (98)
6, R^1=C_4H_9	NPhth(C_4H_9-*n*)COOR **18** (80)
7, R^1=allyl	NR
8, R^1=propargyl	NR
9, R^1=benzyl	PhthN($CH_2C_6H_5$)COOR **19** (88)
10, R^1=4-fluorobenzyl	PhthN($CH_2C_6H_4$-4-F)COOR **20** (72)
11, R^1=4-methoxybenzyl	NR

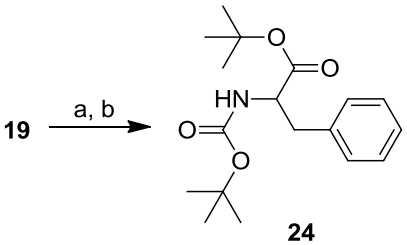
[a]Reagents/Conditions: Oxone®/KBr/MeCN/H_2O/40-45 °C/16 h. [b]R=*tert*-butyl; **3** and **4**, R=ethyl. [c]Yields are of isolated chromatographically-pure products.

The failure of substrates **7**, **8** and **11** to respond to the Oxone®/KBr system may stem from the relatively electron-rich nature of the allyl, propargyl and 4-methoxybenzyl side chains of these substrates. Using optimized conditions, oxidation of the naphthylmethyl isoindolinone derivative **12** did effect the expected conversion of the benzylic methylene to the carbonyl, but with accompanying bromination on the 2-position of the naphthyl ring to afford the monobromo derivative **21** (80%) (**Scheme 3**). Using isoindolinone ethyl ester **1**, LiHMDS and 2-bromomethyl-4,5-diphenyloxazole **23** as a co-reactant,[13] the



23

β-yl-oxazol-2-(methyl)-substituted derivative **13** was isolated (63%, **Table 1**). Considering that the 2-substituted-4,5-diphenyloxazole group is a masked carboxyl equivalent,[14] the alkylation reaction gave essentially the aspartate derivative **13** with both carboxyl groups protected. Oxidation of **13** with Oxone®/KBr in acetonitrile/water transformed the *N*-isoindolinone group into the *N*-phthaloyl group, but also resulted in oxazole cleavage to give the *N*-phthaloylasparagine ester **22** (65%) (**Scheme 3**). A straightforward adaptation of the overall method for peptide chemistry is shown in **Scheme 4**. The *N*-phthaloyl phenylalanine derivative **19** was treated with hydrazine hydrate (MeOH-H_2O) followed by direct treatment with di-*tert*-butyl dicarbonate ($NaHCO_3$/dioxane). Thus, the racemic *N*-BOC phenylalanine *tert*-butyl ester derivative **24** was obtained in 81% yield over two steps whereby the spectral properties of the *N*-BOC amino acid ester **24** matched those as previously reported (See Supplementary Material).



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Scheme 4. Conversion of **19** to a standard phenylalanine derivative **24**. Reagents/Conditions: (a) N_2H_4/MeOH-H_2O/rt/16 h. (b) di-*tert*-butyl dicarbonate/$NaHCO_3$/dioxane/rt/16 h (81%, a and b).

In summary, the expedient of the *N*-isoindolinone group as a nitrogen protecting group for a two carbon 'glycine eqivalent' is demonstrated by submission of the scaffold to a series of selective alkylation reactions. Removal of the *N*-isoindolinone group is facilitated by conversion to the more labile *N*-phthaloyl group through a selective benzylic oxidation using Oxone®. Using a diverse array of alkylating agents, the *N*-isoindolyl-protected 'glycine equivalent' served as a starting point for α-amino acid construction and proved to be robust through further manipulation. An added bonus may be the increased stability of the isoindolinone group to mildly acidic conditions as compared to the O'Donnell derivatives. While the majority of isoindolinone substrates did afford the corresponding *N*-phthaloylated products upon oxidation, the vinylalanine-, ethynylalanine- and electron-rich substrates such as methoxyphenylalanine analogues did not respond to oxidation. A noteworthy example was the de novo preparation of the asparagine derivative **22** which resulted from both the benzylic oxidation and an oxazole cleavage. While the isoindolinone core has been common to medicinal compounds,[15] experimental therapeutics[16] and natural products,[17] its employment as a protecting group has received no attention. An asymmetric variant of the isoindolinone oxidation scheme is under investigation and the results will be reported in due course.

Acknowledgments

The measurement of high and low resolution mass spectra by Dr. Michael Walla of the Mass Spectrometry Laboratory, Department of Chemistry and Biochemistry, University of South Carolina is acknowledged. Financial support from the NIH/NIDCR through grant 1RO1DE023206 is gratefully acknowledged.

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A. Supplementary Material

General procedures and supplementary data (FTIR, ^{1}H NMR, ^{13}C NMR) for compounds **1, 2, 3-13** and **14-22** and HRMS data for all new compounds associated with this article can be found, in the online version, at http://dx.doi.org/j.tetlet,

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Highlights
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TETL-D-17-01420-Revised

- **A range of α–amino acid derivatives may be prepared depending on the alkyl halide.**
- **The *N*-isoindolinone protecting group is removed by a mild two-step sequence.**
- **Oxidation of the isoindolinone gives the easily-removable *N*-phthaloyl group.**
- **A de novo synthesis of an *N*-, carboxyl-protected arginine derivative was done.**
- **The oxidation method may be useful for 4,5-diphenyloxazole cleavage.**