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Synthesis of Pyroglutamic Acid Derivatives via Double Michael Reactions of Alkynones

Myriam Scansetti,[†] Xiangping Hu,[†] Benjamin P. McDermott,[‡] and Hon Wai Lam*[,†]

School of Chemistry, University of Edinburgh, Joseph Black Building, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, United Kingdom, and AstraZeneca R&D Alderley Park, Macclesfield, Cheshire SK10 4TF, United Kingdom

h.lam@ed.ac.uk

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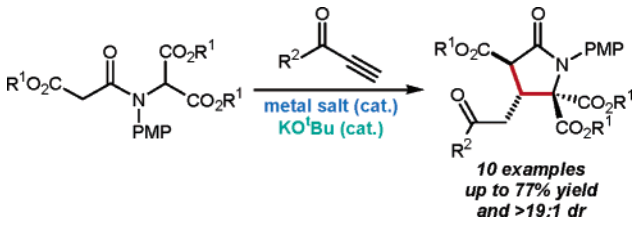
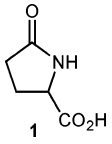
ABSTRACT



In the presence of substoichiometric quantities of potassium *tert*-butoxide and an additional metal salt, amide-tethered diacids undergo double Michael reactions with alkynones to provide highly functionalized pyroglutamic acid derivatives. The metal salt was found to play an important role in improving the diastereoselectivities of the reactions.

Pyroglutamic acid (**1**) and its derivatives are structural units of widespread chemical significance, having been heavily utilized as building blocks for the synthesis of numerous biologically active compounds.[1]



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Considering the multitude of synthetic applications for pyroglutamic acids, much research effort has been devoted to the development of new methods for the synthesis of functionalized derivatives.[1,2] In this Letter, we present a novel route to highly functionalized pyroglutamic acids using double Michael reactions[3] of amide-tethered diacids with alkynones.

Over the past few years, Grossman and co-workers have described a range of reactions where compounds containing two acidic carbon atoms undergo double Michael reactions with electron-deficient alkynes (mostly 3-butyn-2-one) to provide highly functionalized cyclic products.[4,5] Generating two new carbon−carbon bonds and up to three new stereogenic centers with often high levels of diastereoselectivity, this reaction has been effectively utilized in the preparation of a range of five- and six-membered carbocycles.[4] In

[†] University of Edinburgh.
[‡] AstraZeneca.

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(1) For a recent review, see: Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245−2303.

(2) For recent, representative examples, see: (a) Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296−15303. (b) Chang, M.-Y.; Sun, P.-P.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett.* **2003**, *44*, 5271−5273. (c) Alvarez-Ibarra, C.; Csáky, A. G.; Gómez de la Olivia, C. *Eur. J. Org. Chem.* **2002**, 4190−4194. (d) Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 167−172.

(3) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315−512.

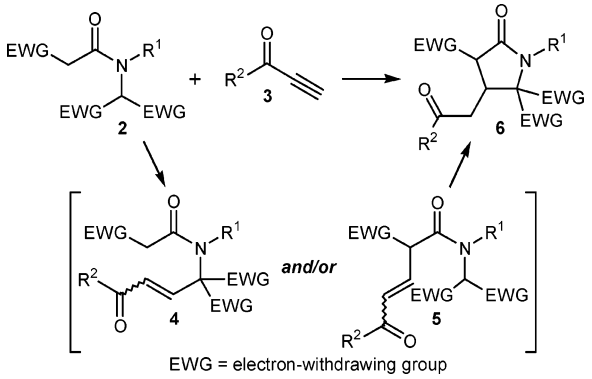
(4) (a) Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340−341. (b) Grossman, R. B.; Rasne, R. M.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7173−7177. (c) Grossman, R. B.; Pendharker, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178−7183. (d) Grossman, R. B.; Skaggs, A. J.; Kray, A. E.; Patrick, B. O. *Org. Lett.* **1999**, *1*, 1583−1586. (e) Grossman, R. B.; Pendharker, D. S.; Rasne, R. M.; Varner, M. A. *J. Org. Chem.* **2000**, *65*, 3255−3258. (f) Grossman, R. B.; Rasne, R. M. *Org. Lett.* **2001**, *3*, 4027−4030. (g) Holeman, D. S.; Rasne, R. M.; Grossman, R. B. *J. Org. Chem.* **2002**, *67*, 3149−3151. (h) Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409−1417. For a review, see: (i) Grossman, R. B. *Synlett* **2001**, 13−21.

(5) Hughes, F., Jr.; Grossman, R. B. *Org. Lett.* **2001**, *3*, 2911−2914.

comparison, application of this methodology to heterocycle construction has been limited, with just one report of a [5 + 1] annulation route to piperidines having been described.[5]

In view of the convergent and modular nature of these transformations, we were drawn to the prospect of utilizing double Michael reactions of alkynones in a concise synthesis of highly functionalized pyroglutamic derivatives, according to the strategy outlined in Scheme 1. It was hoped that under

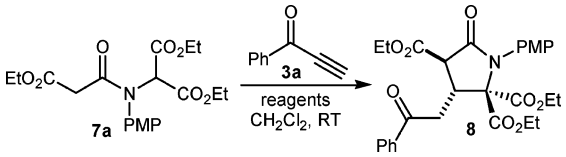
Scheme 1. Proposed Double Michael Addition Route to Pyroglutamic Acid Derivatives



suitable conditions, an amide-tethered diacid **2** would react with an alkynone **3** to first give mono-Michael adduct **4** and/or **5**, which would then cyclize to the pyroglutamic acid derivative **6**.

Our preliminary investigations began with the double Michael reaction of amide-tethered diacid **7a** with aromatic alkynone **3a** (Table 1). In all previous examples of double Michael reactions reported by Grossman and co-workers,[4,5] a mandatory requirement for success is the presence of at least one nitrile substituent in the tethered diacid, which ends up in a pseudoaxial position in the product.[4i] It is proposed

Table 1. Reaction Condition Optimization



entry	reagents	dr[a]	yield (%)[b]
1[c]	PPh_3 (20 mol %)	n/a	0
2	KO^{t}Bu (20 mol %)	1:1	68
3	KO^{t}Bu (20 mol %), $Fe(acac)_3$ (20 mol %)	1:1	31
4	KO^{t}Bu (20 mol %), $Zn(OTf)_2$ (20 mol %)	>19:1	27
5	KO^{t}Bu (20 mol %), $Mg(OTf)_2$ (20 mol %)	11:1	68
6	KO^{t}Bu (20 mol %), $Ni(acac)_2$ (20 mol %)	18:1	76

[a] As determined by ^{1}H NMR analysis of the isolated product. Due to overlapping signals from other compounds, diastereomeric ratios could not be determined from ^{1}H NMR analysis of the unpurified reaction mixtures. [b] Isolated yields of mixtures of diastereoisomers that were inseparable by column chromatography. [c] MeCN used as solvent in place of CH_2Cl_2.

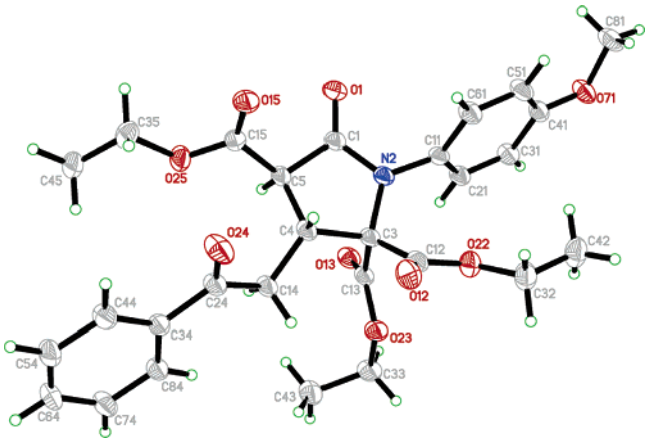


Figure 1. X-ray crystal structure of double Michael product **8**.

that the small size of the nitrile group reduces the magnitude of unfavorable 1,3-diaxial interactions between acidifying groups in the transition state for cyclization, which would otherwise inhibit ring closure.[4i] At the outset of this work, it was therefore uncertain whether diacid **7a**, which does not possess a nitrile substituent, would undergo successful double Michael reaction. Although treatment of a mixture of **7a** and **3a** with PPh_3 in acetonitrile[4c] gave no reaction (entry 1), we found that KO^{t}Bu in CH_2Cl_2[4a] led to the formation of the desired pyroglutamic acid derivative **8**, albeit as a 1:1 mixture of diastereomers (entry 2).

We next investigated the effect of Lewis acidic additives on the reaction.[6] Substoichiometric quantities of $Fe(acac)_3$[7] and $Zn(OTf)_2$[8] were found to inhibit the reaction (entries 3 and 4), though $Zn(OTf)_2$ had a beneficial effect on diastereoselectivity (entry 4). Finally, we identified $Mg(OTf)_2$[9] (entry 5) and $Ni(acac)_2$[10] (entry 6) as promising additives, allowing double Michael product **8** to be isolated in 68−76% yield and with up to 18:1 diastereomeric ratio.

Recrystallization of **8** from a mixture of diethyl ether and hexane afforded crystals that were suitable for X-ray crystallography, which allowed us to confirm that the major diastereomer obtained in these reactions possesses *trans* stereochemistry (Figure 1).

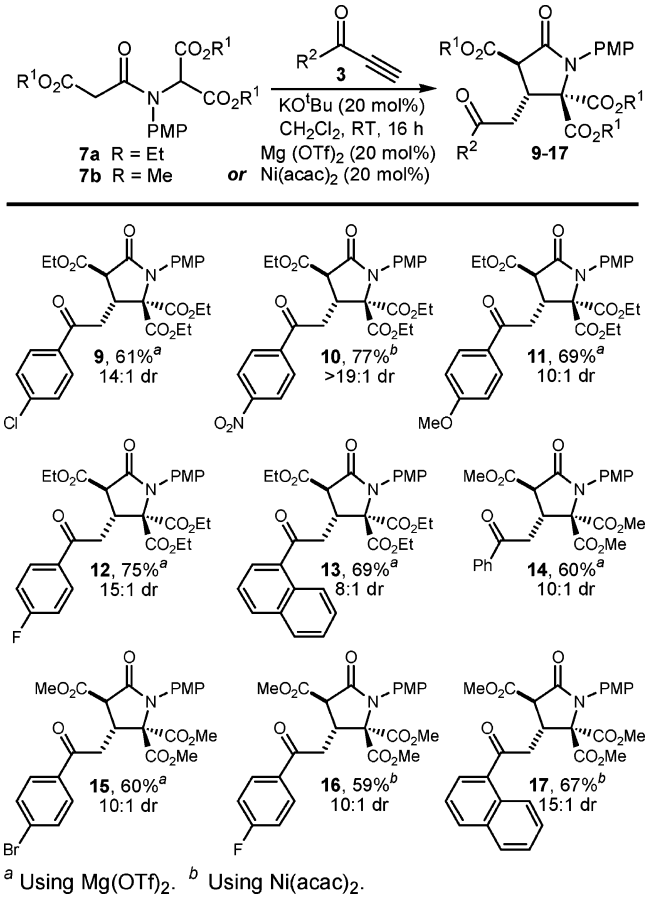
With optimized conditions in hand, the scope of the reaction was explored (Figure 2). Using **7a** as the tethered

(6) For a review of transition-metal-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259−1266.

(7) For examples of iron-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: (a) Fei, C. P.; Chan, T. H. *Synthesis* **1982**, 467−468. (b) Kočovksý, P.; Dvořák, D. *Tetrahedron. Lett.* **1986**, *27*, 5015−5108. (c) Christoffers, J. *Chem. Commun.* **1997**, 943−944. (d) Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141−3149. (e) Christoffers, J. *Synlett* **2001**, 723−732.

(8) For examples of zinc-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: Brunner, H.; Krumey, C. *J. Mol. Catal. A* **1999**, *142*, 7−15.

(9) For examples of magnesium-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215−10216. (b) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097−13105. (c) MacCulloch, A. C.; Yolka, S.; Jackson, R. F. W. *Synlett* **2002**, 1700−1702.



[a] Using Mg(OTf)$_2$. [b] Using Ni(acac)$_2$.

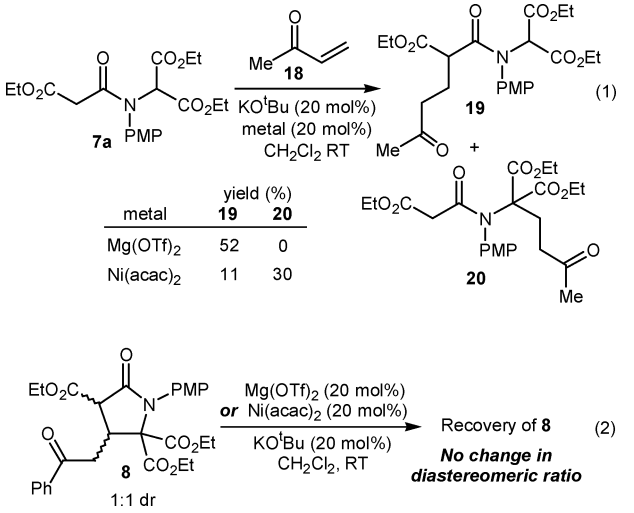
Figure 2. Double Michael reactions of amide-tethered diacids **7a** and **7b** with assorted aromatic alkynones. Cited yields are of isolated inseparable mixtures of diastereoisomers. Diastereomeric ratios were determined by ^{1}H NMR analysis of the isolated products. Due to overlapping signals from other compounds, diastereomeric ratios could not be determined by ^{1}H NMR analysis of unpurified reaction mixtures.

diacid, a range of different aromatic alkynones **3** possessing substituents of varying electronic character underwent double Michael reactions to provide pyroglutamic acid derivatives **9**−**13** in 61−77% yield. Tethered diacid **7b**, containing methyl esters in place of the ethyl esters in **7a**, also underwent reaction uneventfully, affording double Michael products **14**−**17**.

Additional experiments provided some insight into the reaction pathway and the role played by the metal salts (Scheme 2). Equation 1 highlights differences in the effect of Mg(OTf)$_2$ and Ni(acac)$_2$. Reaction of methyl vinyl ketone (**18**) with diacid **7a** using Mg(OTf)$_2$ as additive led to **19** as

(10) For examples of nickel-catalyzed Michael reactions of 1,3-dicarbonyl compounds, see: (a) Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246−1249. (b) Clariana, J.; Gálvez, N.; Marchi, C.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **1999**, *55*, 7331−7344. (c) Christoffers, J.; Rö*β*ler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, 701−705. (d) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958−9959. (e) Evans, D. A.; Thomson, R. J.; Franco, F. *J. Am. Chem. Soc.* **2005**, *127*, 10816−10817. (f) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979−981. (g) Yanagita, H.; Kodama, K.; Kanemasa, S. *Tetrahedron Lett.* **2006**, *47*, 9353−9357.

Scheme 2. Experiments Probing the Role of Mg(OTf)$_2$ and Ni(acac)$_2$

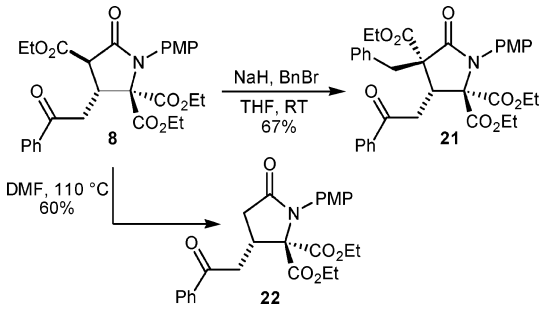


the only observable Michael product in 52% yield, with the remainder of material being unreacted **7a**. This experiment indicates that under these conditions, the methylene carbon adjacent to the amide carbonyl of **7a** is the more reactive of the two acidic positions. However, the analogous experiment using Ni(acac)$_2$ provided a mixture of **19** and the alternative Michael product **20**, among other side-products.

Exposure of a 1:1 diastereomeric mixture of double Michael product **8** obtained using KO^{t}Bu alone (Table 1, entry 2) to standard reaction conditions *including* additional Mg(OTf)$_2$ or Ni(acac)$_2$ led to recovery of **8** in high yield with no discernible change in diastereomeric composition (eq 2). These experiments suggest that under these conditions, post-cyclization epimerization (which could occur via a deprotonation−reprotonation sequence or a retro-Michael−Michael sequence) does not occur, and therefore diastereoselection observed in the presence of additional metal salt is the result of a kinetically controlled process. However, the manner in which the metal salt imparts diastereoselectivity is not clear at this time.

Conversion of double Michael product **8** into other potentially useful compounds is shown in Scheme 3. Treatment of **8** with NaH and BnBr provided alkylated product

Scheme 3. Elaboration of Double Michael Product **9**



21,[11] and monodecarboxylation to **22** was accomplished by heating a DMF solution of **8** to 110 °C.

In summary, we have developed a double Michael addition route to highly functionalized pyroglutamic acid derivatives that utilizes amide-tethered carbon diacids and aromatic alkynones as substrates. The reactions proceed with good levels of *trans*-diastereoselectivity, provided that substoichiometric quantities of $Mg(OTf)_2$ or $Ni(acac)_2$ are employed as additives. Further work will address the development of enantioselective variants of these reactions.

(11) Tentative relative stereochemical assignment. NOESY spectra proved inconclusive in establishing the relative stereochemistry of **21**.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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