ORGANIC LETTERS

2001
Vol. 3, No. 18
2911−2914

A Heterocycle-Forming Double Michael Reaction. [5 + 1] Annulation Route to Highly Substituted and Functionalized Piperidines

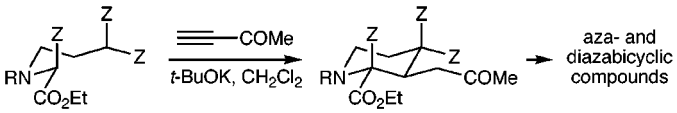
Freddie Hughes, Jr. and Robert B. Grossman*

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506-0055

rbgros1@pop.uky.edu

Received July 5, 2001

ABSTRACT



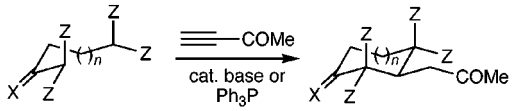
Z = CN (at least one), CO_2Et, NO_2, Me; R = Me, CF_3CO.

Nitrogen-containing tethered diacids, easily prepared by reductive alkylation of diethyl aminomalonate or ethyl cyanoglycinate, undergo double Michael reactions with 3-butyn-2-one to give highly functionalized and substituted piperidines (pipecolic acid derivatives) with surprisingly high stereoselectivity. The heterocyclic double Michael adducts can be induced to undergo further cyclizations to give a variety of azabicyclic and diazabicyclic compounds.

Piperidines are of special interest due to the large number of biologically active compounds containing this moiety.[1] Their importance is reflected in the many routes to these compounds that have appeared in the literature.[2] Herein, we would like to report a novel route to highly substituted and functionalized piperidines via a double Michael reaction[3] of nitrogen-tethered diacids and alkynones. Reactions in which two C−C bonds of a heterocycle are formed by a double Michael reaction are very rare,[4] as are reactions in which heterocycles are formed by the conjugate addition of two nucleophiles to an electrophilic alkyne.[5]

Over the past few years we have shown that compounds consisting of two carbon acids connected by a tether undergo stereoselective double Michael reactions (formal [n + 1] annulations) with 3-butyn-2-one to afford functionalized cyclopentanes and cyclohexanes (Scheme 1).[6] A variety of

Scheme 1



Z = CN (at least one), CO_2Et, NO_2, Me; X = H,H or O; n = 0 or 1

carbo- and azabicyclic compounds can be prepared from the double Michael adducts by a subsequent ring-forming reaction involving the acetonyl group and an acidifying group.

In all of our previous work, the tethered diacids had all-carbon tethers, giving only carbocycles in the double Michael

(1) Angle, S. R.; Breitenbucher, J. G. In *Studies in Natural Products Chemistry, Vol. 16*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers B V: Amsterdam, The Netherlands, 1995; p 453. Ojima, I.; Iula, D. M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier: Amsterdam, The Netherlands, 1999; Vol. 13. Schneider, M. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press Ltd: Oxford, 1996; Vol. 10, p 155.

(2) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633. Wang, C. J. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 583.

(3) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010. Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.

(4) Bhardwaj, C. L.; Ireson, J. C.; Lee, J. B.; Tyler, M. J. *Tetrahedron* **1977**, *33*, 3279. Giardini, A.; Lesma, G.; Passarella, D.; Perez, M.; Silvani, A. *Synlett* **2001**, 132.

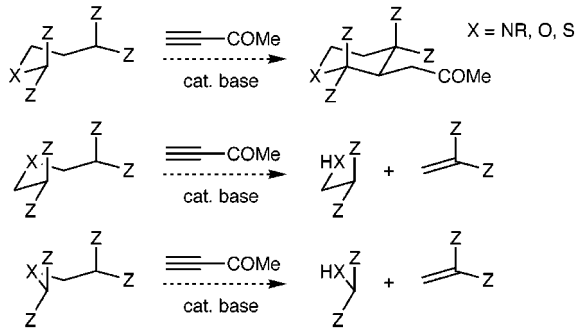
(5) Two recent examples: Ariza, X.; Costa, A. M.; Faja, M.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 2809. Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979.

(6) Grossman, R. B. *Synlett* **2001**, 13.

10.1021/ol016395o CCC: $20.00
Published on Web 08/14/2001

reaction. We wondered whether we could prepare heteroatom-tethered diacids and use them to construct heterocycles by a double Michael reaction (Scheme 2). We chose to focus

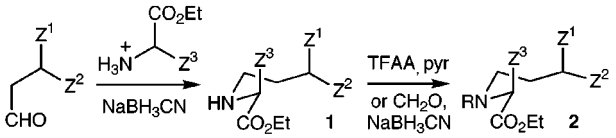
Scheme 2



our efforts on tethered diacids with X−C−C tethers, as we feared that substrates with C−X−C or X−C tethers would undergo β-elimination more readily than the double Michael reaction.[7] As for the nature of the heteroatom X, we thought that nitrogen-tethered diacids would be most accessible synthetically, so we decided to pursue these compounds.

Nitrogen-containing tethered diacids **1** are easily prepared by reductive alkylation of diethyl aminomalonate or ethyl cyanoglycinate[8] with the appropriate aldehydes (Scheme 3).[9]

Scheme 3

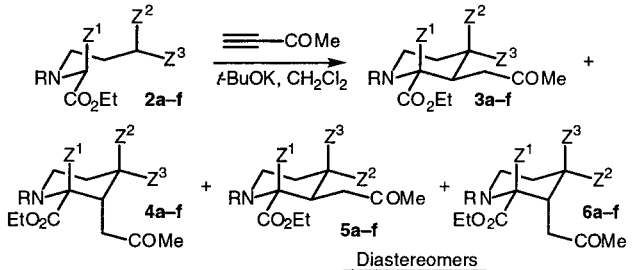


1	Z^1	Z^2	Z^3	Yield	2	R	Yield
a	CO_2Et	CO_2Et	CN	34%	**a**	Me	53%
b	CN	CO_2Et	CN	41%	**b**	Me	55%
c	Me	NO_2	CN	24%	**c**	Me	52%
d	CN	CO_2Et	CO_2Et	60%	**d**	Me	49%
					e	$COCF_3$	83%
f	CN	CN	CO_2Et	17%	**f**	$COCF_3$	99%

Most of the aldehydes are prepared by ozonolysis of alkenes,[10] although the precursor to **1c** is made by conjugate addition of $NaNO_2$ to crotonaldehyde.[11] Considering the propensity of γ-amino esters such as **1a**−**d** to cyclize when they are prepared by reductive amination,[12] it is somewhat surprising that the yields are as good as they are. We attribute the somewhat diminished tendency of **1** to lactamize to steric and electronic deactivation of the nucleophilic N atom by the two neighboring electron-withdrawing groups. Reductive *N*-methylation of **1a**−**d** affords **2a**−**d** in moderate yield. Aminomalonate derivatives **1d** and **1f** are easily trifluoroacetylated to give **2e** and **2f** in excellent yield, but this reaction fails with **1a**−**c**.

Tethered diacids **2a**−**f** undergo double Michael additions to 3-butyn-2-one in CH_2Cl_2 under catalysis by *t*-BuOK to give the corresponding double Michael adducts in generally good yields (with the exception of **3f**) (Scheme 4). The

Scheme 4



2	R	Z^1	Z^2	Z^3	Diastereomers Total #	Diastereomers Obs'd	Isol'd Yield
a	Me	CN	CO_2Et	CO_2Et	2	**3a**	99%
b	Me	CN	CO_2Et	CN	4	**3b**, **4b**	69%, 7%
c	Me	CN	Me	NO_2	4	**3c**, **5c**	50%, 10%
d	Me	CO_2Et	CN	CO_2Et	2	**3d**	72%
e	$COCF_3$	CO_2Et	CN	CO_2Et	2	**3e**, **4e**	61% (16:1 dr)
f	$COCF_3$	CO_2Et	CN	CN	1	**3f**	13%

structures of **3b**, **3c**, and **3e** were determined by X-ray crystallographic analysis, whereas those of **3a**, **4b**, and **5c** were determined by NOESY experiments. Compound **3e** is disordered in the solid state: 85% of **3e** is in the chair conformation and 15% is in the twist-boat conformation. Allylic 1,3-strain between the amide oxygen and the equatorial ester in **3e** raises the energy of the chair conformer to within 0.6 kcal/mol of the twist-boat conformer.[13]

Tethered diacid **2c** has unusual reactivity. When it is combined with 3-butyn-2-one and *t*-BuOK at room temperature, only an acyclic, "mono-Michael" adduct is obtained, and closure to **3c** requires refluxing with NaH in THF for 1 d. We have never observed such slow intramolecular Michael reactions up to now. The shorter N−C bonds in the rings of **3**−**6** may increase the steric interactions in these compounds over those in all-carbon rings, slowing the ring-closing, intramolecular Michael reaction in the case of **3c**.

The stereoselectivities of the present double Michael reactions deserve some comment. Clearly, the double

(7) β-Aminomalonates and β-amino-α-cyanocarboxylates are final intermediates in Knoevenagel condensations, wherein they undergo β-elimination of amine under very mild conditions.

(8) Brown, T.; Shaw, G.; Durant, G. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2310.

(9) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T. *Tetrahedron* **1983**, *39*, 2399. Heitsch, H.; Wagner, A.; Yadav-Bhatnagar, N.; Griffoul-Marteau, C. *Synthesis* **1996**, 1325.

(10) Diethyl prenylmalonate: Staudinger, H.; Kreis, W.; Schilt, W. *Helv. Chim. Acta* **1922**, *5*, 743. Ethyl cinnamylcyanoacetate: Gagnon, P. E.; Boivin, J. L.; Boivin, P. A.; Jones, R. N. *Can. J. Chem.* **1951**, *29*, 182. Prenylmalononitrile: Kolsaker, P.; Storesund, H. J.; Gulbrandsen, T.; Woien, G. *Acta Chem. Scand. Ser.* **1983**, *B37*, 187. A procedure developed for propargylmalononitrile was used to prepare prenylmalononitrile: Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2157.

(11) Oehrlein, R.; Jaeger, V. *Tetrahedron Lett.* **1988**, *29*, 6083.

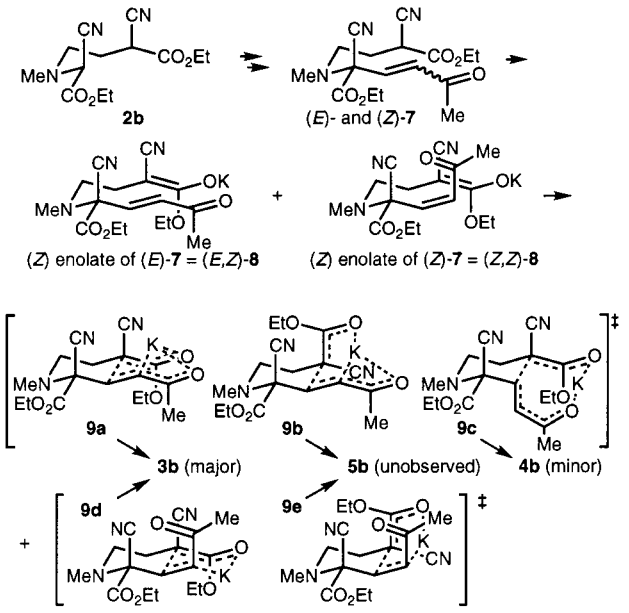
(12) Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81.

(13) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

Michael reactions are kinetically controlled. Compounds **3** and **5** have one fewer 1,3-diaxial interaction (because the lone pair of the ring N occupies an axial position) but two more gauche interactions than **4** and **6**, so all four compounds are quite close in energy. In fact, the relative energies of **3a** and **4a** are calculated approximately to be 0.0 and 0.1 kcal/mol, respectively, those of **(3−6)b** to be 0.0, 0.6, 1.1, and 1.1 kcal/mol, respectively, and those of **(3−6)c** to be 0.6, 0.5, 0.0, and 0.2 kcal/mol, respectively.[14] If the reactions were thermodynamically controlled, the dr values of **3a−e** would be much lower than observed and **3c** would not even be a major product.

The relative stereochemistry of each double Michael adduct is determined in the second, intramolecular Michael reaction. We have not investigated experimentally why the stereoselectivities are so high, but if we assume a preference for a cyclic TS with chelation of K^+, a reasonable assumption when CH_2Cl_2 is the solvent, an explanation can be formulated for most cases. For example, consider the double Michael reaction of **2b** and 3-butyn-2-one (Scheme 5). The first

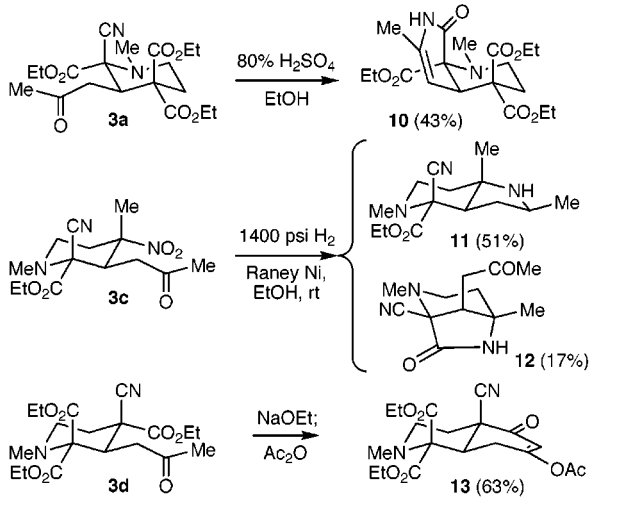
Scheme 5



addition occurs at the carbon adjacent to the nitrogen, the most acidic site, to give "mono-Michael" adduct **7** as an *E*/*Z* mixture.[15] Deprotonation of the α-cyano ester group of **7** then affords an enone−enolate, **8**, with a total of four possible diastereomers; the two (*Z*)-enolate isomers are expected to predominate so that K^+ may reside as close as possible to the centers of negative charge. Enone−enolate (*E*,*Z*)-**8** can undergo the intramolecular Michael reaction through cyclic TSs **9a−c**, and enone−enolate (*Z*,*Z*)-**8** can undergo the intramolecular Michael reaction through cyclic TSs **9d**,**e**. In one TS (**9a**) leading to major product **3b**, the K^+ ion can coordinate to both the enone O and the enone C in a boatlike six-membered ring, and in the other TS (**9d**) leading to **3b**, the K^+ ion can coordinate to the enone C in a chairlike six-membered ring. By contrast, in the TS (**9c**) leading to minor product **4b**, an eight-membered ring is required, and in both TSs (**9b** and **9e**) leading to unobserved product **5b**, there are severe interactions between an axial H atom and the EtO group of the enolate.[16] Similar arguments can explain the stereoselectivities of the double Michael reactions of **2a**, **2d**, and **2e**. One piece of evidence in support of the argument that the stereochemistry is determined by the requirements of a closed TS is that in the case of **2e**, the dr drops from 16:1 to 3:1 when the double Michael reaction is catalyzed by TBAF in THF instead of *t*-BuOK in CH_2Cl_2. However, the argument outlined here fails for the NO_2-containing tethered diacid **2c**, as low-energy six-membered chelated TSs that lead to unobserved, low-energy products **4c** and **6c** can easily be envisioned.[17]

The double Michael adducts **3a−f** are potentially useful starting materials for the preparation of a variety of aza- and diazabicyclic compounds (Scheme 6). Hydration of **3a** in

Scheme 6



80% H_2SO_4 in EtOH gives *cis*-hexahydro[1,7]naphthyridin-8-one **10** in 43% yield.[18] When nitro-containing double Michael adduct **3c** is hydrogenated over Raney nickel,[17,19]

(14) Carroll, F. A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole Publishing Co.: Pacific Grove, CA, 1998. These steric energies are calculated from generally accepted values for 1,3-diaxial and gauche interactions in substituted cyclohexanes. Two simplifying assumptions are made: the effect of the shorter N−C bond distances in the ring is neglected and 1,3-diaxial interactions between CN groups and larger groups (CO_2Et, Me) are assumed to have the same energetic price as interactions between H and those groups.

(15) The mono-Michael adduct derived from **2c** is obtained as a 3:1 *E*/*Z* mixture. Other mono-Michael adducts have also been obtained as *E*/*Z* mixtures: Grossman, R. B.; Pendharkar, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178.

(16) The latter interactions may be worse in the TSs than in the products, as rotation to reduce the interactions is much more circumscribed in the TSs.

(17) Grossman, R. B.; Rasne, R. M.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7173.

(18) Grossman, R. B.; Pendharkar, D. S.; Rasne, R. M.; Varner, M. A. *J. Org. Chem.* **2000**, *65*, 3255.

(19) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1998**, *63*, 10052.

the nascent NH_2 group is reductively alkylated with the pendant ketone or (after a ring flip) acylated with the transannular CO_2Et group, providing *trans*-perhydropyrrolo-[3,2-c]pyridine **11** and 2,6-diazabicyclo[3.2.1]octan-7-one **12** in 51% and 17% yields, respectively. Finally, when double Michael adduct **3d** is treated with NaOEt and then Ac_2O, *trans*-octahydroisoquinolin-5-one **13** is obtained in 63% yield.[17,20] These transformations proceed chemoselectively and in reasonably good yield, preserving the dense functionality and abundant chemical information of the double Michael adducts.

We hope that this new [5 + 1] annulation route to highly substituted and functionalized piperidines will find application in the synthesis of biologically active compounds. We also hope to extend this double Michael reaction to the synthesis of other heterocycles. Future work in these areas will be reported in due course.

Acknowledgment. We thank Dr. Sean Parkin and Prof. Carolyn P. Brock for the X-ray crystallographic analyses. We also thank the National Science Foundation (CAREER award to R.B.G., CHE-9733201, and CRIF program for NMR instruments, CHE-997841) and the Research Challenge Trust Fund of the University of Kentucky (Graduate Fellowship to F.H. and matching funds for CRIF program) for their support of this research.

Supporting Information Available: Experimental details for the preparation and characterization of compounds **1**−**3**, **4b**, **5c**, and **10**−**13** and data from X-ray crystallographic analyses of **3b**, **3c**, and **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016395O

(20) Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340.