A New Multicomponent Coupling of Aldehydes, Amides, and Dienophiles: Atom-Efficient One-Pot Synthesis of Highly Substituted Cyclohexenes and Cyclohexadienes

Helfried Neumann, Axel Jacobi von Wangelin, Dirk Gördes, Anke Spannenberg, and Matthias Beller*

Institut für Organische Katalyseforschung an der Universität Rostock e.V., Buchbinderstrasse 5-6 D-18055 Rostock, Germany

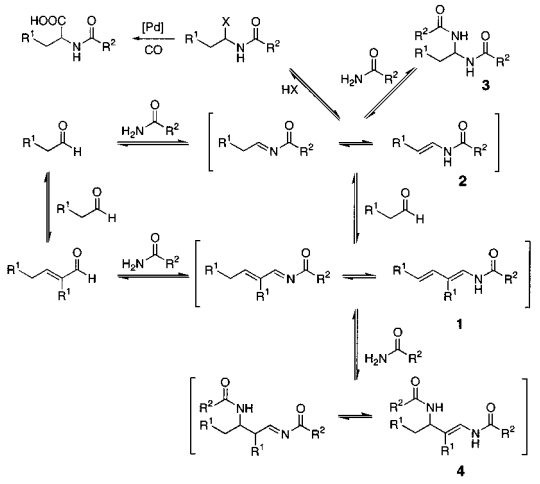
Received February 26, 2001

With regard to green chemistry, atom-efficient transformations of easily available starting materials into complex organic building blocks become increasingly important.[1] Here, multicomponent coupling reactions which directly yield the desired products via domino or tandem reaction sequences offer significant advantages over stepwise procedures.[2] Domino reactions based on Diels−Alder chemistry are important examples for such sustainable methodologies.[3] However, the intricate access to functionalized 1,3-dienes often is the major drawback to a practical use of these reactions.

On the basis of transition metal-catalyzed carbonylations, we were recently able to develop multicomponent coupling reactions for the synthesis of various *N*-acyl α-amino acids[4] and hydantoins.[5] To apply the former on an industrial pilot-plant scale, we investigated the palladium-catalyzed amidocarbonylation[4] of propionaldehyde with acetamide and observed the formation of 1-*N*-acetylamino-2-methyl-1,3-pentadiene (**1**, with $R^1 = R^2 = Me$) as a byproduct (<5%) when significantly decreasing the catalyst concentration ([Pd] < 0.1 mol %). Obviously, **1** does not form via a palladium-catalyzed reaction path but upon simple condensation of two molecules of propionaldehyde with acetamide (Scheme 1).

Several groups have elegantly demonstrated the synthetic versatility of numerous organic systems involving Diels−Alder chemistry with 1-acylamino-1,3-dienes (**1**),[7] and many of them have been exploited for the synthesis of amino functionalized natural products.[8] However, access to **1**[9] often relies upon several reaction steps, crucially lowering its synthetic value. To the best of our knowledge, no precedented use of in situ synthesized 1-acylamino-1,3-butadiene derivatives (**1**) in cycloaddition reactions has been communicated. Here, we report an optimized set of conditions[10] for the direct condensation of simple aldehydes and amides and in situ employment of the resulting 1-acylamino-1,3-butadienes in efficient preparations of highly functionalized cyclohexene and cyclohexadiene derivatives.

Scheme 1. Proposed Mechanism for the Formation of **1**,[6] and Recently Reported Palladium-Catalyzed Amidocarbonylation[4] (X = Br, Cl)



On the basis of our initial observation, preliminary studies focused on the condensation reaction of propionaldehyde and acetamide toward **1**. Interestingly, product formation showed a significant solvent dependence. In toluene, chloroform, and ethanol, the reaction merely afforded the corresponding aminal **3**. Employment of *N*-methylpyrrolidinone (NMP) or DMF proved pivotal for the desired procedure and gave **1** in substantial yield (20−30%). Addition of catalytic amounts of *p*-toluenesulfonic acid as well as stoichiometric amounts of acetic anhydride considerably accelerated the reaction. The optimized set of conditions, with the molar ratio aldehyde/amide surprisingly being 1/1, gave **1** ($R^1 = R^2 = Me$) in 50% yield[11] at 80 °C. Aldehydes and amides with bulkier substituents (e.g., $R^1 = PhCH_2$, *i*-Pr; R^2 = Ph) required higher temperatures and longer reaction times to convert the predominantly formed 1,3-bis(acylamino)but-1-ene derivatives (**4**) into target molecules **1**.

Since formation of **1** proceeds via several equilibrium steps (Scheme 1), we envisaged its use in domino reaction sequences with an irreversible last step, which would be advantageous by shifting the equilibria well to the right. Therefore, subsequent Diels−Alder reactions were studied with electron-deficient alkenes and alkynes. Indeed, in situ trapping of **1** with various dienophiles afforded the corresponding cyclohexene derivatives (Scheme 2[12]) in excellent yields (<92%). The inherent selective telomerization of two aldehydes with one amide molecule in high yields is especially remarkable when considering the numerous side reactions which likely proceed under these conditions (further aldol condensations, oligomerizations).

Ubiquitous available acetamide, 1,1-dimethyl urea, and benzamide were employed as acylamine equivalents and reacted in a one-pot procedure with several linear and branched aliphatic aldehydes and the dienophiles. In no case were hetero Diels−Alder adducts isolated. Table 1[12] summarizes the synthesis of a series of penta-substituted cyclohexenes, prepared in a one-pot procedure by cycloadding maleimide to in situ prepared amidodienes **1**.

Reactions with maleimide selectively led to the *endo* adducts, verifying that only the *s-cis*-1*E*,3*E*-dienamide isomer cyclized in Diels−Alder fashion. However, we cannot exclude the existence

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 1.

(2) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

(3) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.

(4) (a) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1010. (b) Beller, M.; Moradi, W.; Eckert, M.; Neumann, H. *Tetrahedron Lett.* **1999**, *40*, 4523. (c) Beller, M.; Eckert, M.; Moradi, W. *Synlett* **1999**, 108. (d) Beller, M.; Eckert, M.; Geissler, H.; Napierski, B.; Rebenstock, H.-P.; Holla, E. W. *Chem. Eur. J.* **1998**, *4*, 935. (e) Beller, M.; Eckert, M.; Holla, E. W. *J. Org. Chem.* **1998**, *63*, 5658.

(5) Beller, M.; Eckert, M.; Moradi, W. A.; Neumann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1454.

(6) Not all possible isomers and double bond isomers are depicted.

(7) (a) Bochu, C.; Couture, A.; Grandclaudon, P. *J. Org. Chem.* **1988**, *53*, 4852. (b) Braisted, A. C.; Schultz, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 7430. (c) Yli-Kauhaluoma, J. T.; Ashley, J. A.; Lo, C.-H.; Tucker, L.; Wolfe, M. M.; Janda, K. D. *J. Am. Chem. Soc.* **1995**, *117*, 7041.

(8) (a) Overman, L. E.; Jessup, P. J. *Tetrahedron Lett.* **1977**, *18*, 1253. (b) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373. (c) Martin, S. F.; Li, W. *J. Org. Chem.* **1991**, *56*, 642.

(9) (a) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 587. (b) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352, 8295. (c) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.

(10) Aldehyde, amide, dienophile, Ac_2O (each 15 mmol), *p*-TSA·H_2O (1.5 mol %), NMP (10 mL); >20 h, >80 °C.

(11) (a) Exclusive formation of all-*trans*-**1** ($R^1 = R^2 = Me$). (b) GC yield.

(12) (a) Products are racemic mixtures of one diastereomer. Only one enantiomer is depicted. (b) Given yields are not optimized.

10.1021/ja010503k CCC: $20.00
Published on Web 08/02/2001

Scheme 2. Diels-Alder Trapping of Intermediate 1-Acylamino-1,3-butadienes (1)[12]

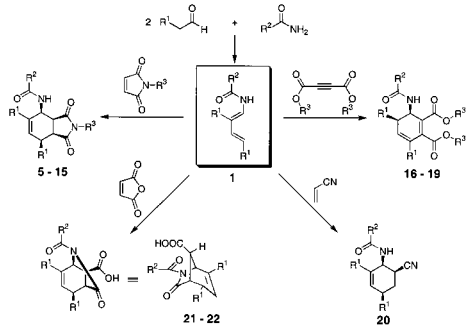
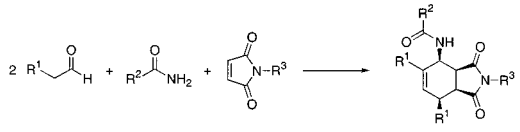


Table 1. Amino Functionalized Tetrahydro*iso*indole-1,3-diones[12]



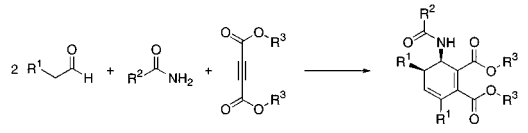
	R^1	R^2	R^3	t [h]	T [°C]	Yield [%]
5	H	Me	H	48	120	53
6	Me	Me	H	24	120	80
7	Et	Me	H	24	120	92
8	Hex	Me	H	24	120	86
9	*i*-Pr	Me	H	90	120	74
10	Bn	Me	H	68	120	82
11	Me	Ph	H	20	120	83
12	Et	Ph	H	20	120	90
13	Me	Me_2N	H	20	80	81
14	Et	Me_2N	H	20	80	74
15	Me	Me	Me	24	100	71

of equilibrating isomeric dienamides under the reaction conditions (Scheme 1).[12] DFT calculations[14] on the model reaction of **1** (R^1= R^2= Me) with maleimide align with the experimental observations. The boatlike *endo* transition state is about 8 kcal/mol more stable than the corresponding *exo* transition state, kinetically favoring the *endo* pathway by 10^6. Furthermore, the *endo* adduct is thermodynamically stabilized with respect to the *exo* isomer.

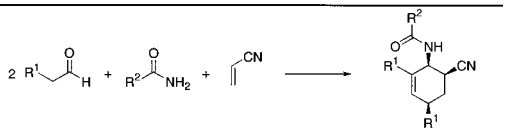
Conversions were usually accomplished after 20 h. Sterically more demanding 3-methylbutyraldehyde and, surprisingly, acetaldehyde required longer reaction times for complete conversion (**9**, **5**). On the other hand, reactive *N*,*N*-dimethyl urea allowed for an efficient coupling at lower reaction temperatures (**13**, **14**). Next, we extended the procedure to other dienophiles (Table 2[12]). Dialkyl acetylenedicarboxylates afforded the corresponding 1-acylamino cyclohexa-2,4-diene derivatives in good yields (**16**−**19**). Formation of these dienes proceeds via concomitant double bond shift to give a conjugated diene moiety. Reaction with acrylonitrile, as an "asymmetric" dienophile, selectively gave the "ortho" cyano-substituted product **20**. Analogous employment of maleic anhydride as dienophile afforded rearranged products **21** and **22**. These bicyclic structures are generated by subsequent intramolecular amidation[15] of one carboxylic moiety. This procedure allows for a facile and direct synthesis of this class of bicyclic compounds for the first time.

The presented new multicomponent reaction features the formation of three carbon−carbon bonds and one carbon−nitrogen bond. Although up to four stereogenic centers are created, only one diastereomer was isolated. $^1H-^1H$ and $^1H-^{13}C$ NMR spectra as well as $^1H-^1H$ coupling patterns unambiguously established the constitutions and conformations (*endo*) of all Diels−Alder adducts. In addition, we were able to confirm the structure of **20** by X-ray analysis.[14] Owing to the *endo* addition of the dienophile to the 1E,3E-amidodiene, all substituents on the cyclohexene ring of **20** are *syn* which results in a crown-like structure.

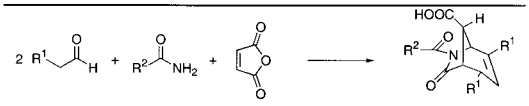
Table 2. Multicomponent Coupling with Other Dienophiles[12]



	R^1	R^2	R^3	t [h]	T [°C]	Yield [%]
16	Me	Me	Me	24	120	62
17	Et	Me	Me	24	120	77
18	Me	Me	Et	24	120	67
19	Et	Me	Et	24	120	84



	R^1	R^2	t [h]	T [°C]	Yield [%]
20	Me	Me	48	120	65



	R^1	R^2	t [h]	T [°C]	Yield [%]
21	Me	Me	24	100	69
22	Et	Me	24	100	63

Initial efforts have been undertaken with regard to diastereoselective multicomponent coupling reactions. Employment of chiral α,β-unsaturated *N*-acyl oxazolidinones[16] as dienophiles yielded the corresponding cyclohexene derivative with stereoselectivities (de) of >90%.[17]

The described methodology constitutes the most simple and direct high-yield approach to a variety of amino functionalized cyclohexene and cyclohexadiene derivatives. To the best of our knowledge, this reaction sequence is the first example of a multicomponent coupling of aldehydes, amides, and olefins (or alkynes). The ubiquitous, off-shelf starting materials readily react even in the presence of air or water.

Acknowledgment. We thank Dr. Haijun Jiao (Universität Erlangen) for providing computations and the state of Mecklenburg-Vorpommern and the Degussa-Hüls AG for financial support.

Note Added after ASAP. There were errors in the references cited in the version posted ASAP August 2, 2001. Reference 12 is cited after Scheme 1 and not ref 15. Reference 14 is cited after DFT in footnote 13 and not ref 15. The corrected version was posted August 7, 2001.

Supporting Information Available: Details on experimentations analyses, computations, crystal data (PDF). Crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JA010503K

(13) (a) DFT[14] calculations on all possible isomers of **1** ($R^1 = R^2 = Me$) point to an almost exclusive (>95%, referenced to thermodynamic equilibration) presence of the all-*trans* isomer. (b) For bulkier substituents ($R \neq Me$), the all-*trans* isomer might likely be less favored. Consistently, syntheses of **1** with R^1 = Et, *i*Pr gave two double bond isomers.

(14) For more details see Supporting Information.

(15) Kvita, V.; Sauter, H.; Rihs, G. *Helv. Chim. Acta* **1983**, *66*, 2769.

(16) According to: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(17) Reaction of (*4S*)-5-(2-propenoyl)-4-(phenylmethyl)-2-oxazolidinone with benzamide and octanal, and subsequent silica gel chromatography gave only one diastereomer in 28% yield (de > 90%, by ^1H NMR).