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Facile Three-Component Coupling Procedure for the Synthesis of Substituted Tetrahydroisoindole-1,3-diones from α,β-Unsaturated Aldehydes

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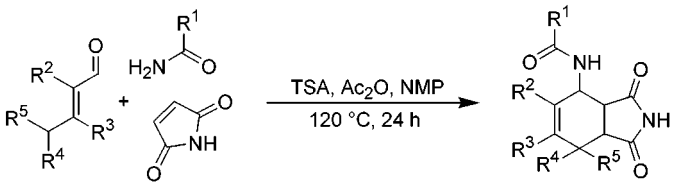
ABSTRACT



A new one-pot procedure for the efficient synthesis of a small library of amino-functionalized tetrahydroisoindole-1,3-dione derivatives was developed. This three-component coupling reaction comprises subsequent condensation and Diels−Alder reactions of ubiquitous available starting materials (α,β-unsaturated aldehydes, amide, and maleimide). The synthesized compounds share a substituted tetrahydroisoindole motif in an *endo* fashion.

In recent years, research in academia and industry has increasingly emphasized the search for atom-efficient transformations of easily available starting materials into complex organic molecules.[1] In this respect, reactions that provide maximum diversity, that is, reactions with high exploratory power, are especially desirable. Here, expeditious multicomponent reactions (MCR)[2] as well as domino reaction sequences offer significant advantages over stepwise procedures.[3] The Diels−Alder reaction provides one of the most powerful tools for the synthesis of complex organic molecules by virtue of its versatility and stereocontrol and therefore typifies a favorable transformation in efficient reaction sequences. Consistently, several reported MCRs feature Diels−Alder chemistry with substituted diene building blocks.[4]

Recently, we reported a new one-pot protocol for the facile synthesis of diversely substituted amino-functionalized cyclohexene derivatives.[5] The developed three-step domino reaction sequence involves the in situ preparation of a 1-acylamino-1,3-butadiene species (**I**) as the key intermediate, which several groups have proven a versatile diene building block for mechanistic investigations and natural product syntheses.[6] Access to **I** was accomplished upon

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Trost, B. M. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 1.

(2) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

(3) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (c) Tietze, L. F.; Haunert, F. In *Stimulating Concepts In Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCH: Weinheim, 2000; p 39.

(4) (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.

(5) Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2001** in press.

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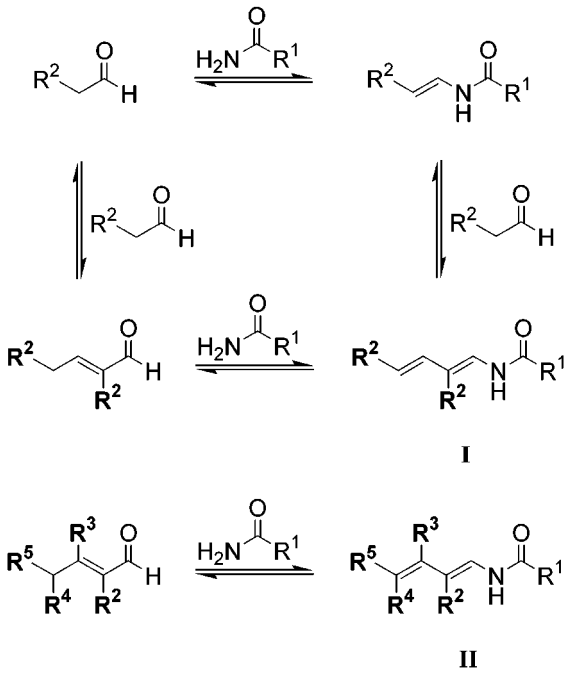
sequential condensations of two α-CH_2-containing aldehydes with an amide according to Scheme 1.

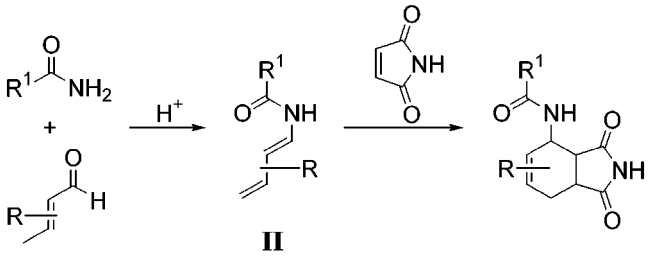
Scheme 1. Condensation Sequences toward Substituted 1-Acylamino Butadiene Building Blocks Starting from Simple Aldehydes (top, **I**) or α,β-Unsaturated Aldehydes (bottom, **II**)[7]



Owing to the incorporation of two identical aldehyde molecules, substitution of the diene backbone in **I** is limited to the 2 and 4 positions only. Obviously, the use of α,β-unsaturated aldehydes, which might constitute an intermediate in the formation of **I**, would afford 1-acylamino-1,3-butadiene building blocks with four potential substitution centers along the 1,3-butadiene backbone (**II**) and hence significantly increase the substrate diversity.

Here, we report the first multicomponent coupling reaction of α,β-unsaturated aldehydes with various amides (via type **II** dienes) and a dienophile, providing a series of 1-acylamino-2-cyclohexene derivatives. We focused on the synthesis of 4-*N*-acylamino-3a,4,7,7a-tetrahydroisoindole-1,3-dione derivatives[8] by employing maleimide as a truly powerful dienophile. Initial attempts were undertaken to perform the desired reaction sequence in a stepwise manner. However, isolation of 1-acylamino-1,3-butadienes proved quite troublesome, and as a result of the presence of several equilibrating species, yields are generally poor. Fortunately, in situ trapping of the intermediate amidodienes with maleimide selectively gave the corresponding 1-acylamino-2-cyclohexene Diels−Alder adducts in good yields (Scheme 2, Table 1).

Scheme 2. 1-Acylamino-2-cyclohexene Synthesis via a Condensation−Cycloaddition Domino Reaction Sequence Starting from α,β-Unsaturated Aldehydes



Ubiquitous available amides, such as acetamide (R^1 = Me) and benzamide (R^1 = Ph), cleanly reacted with crotonaldehyde to give the desired bicyclic systems in 85% and 91% yield, respectively. Other commercially available α,β-unsaturated aldehydes afforded the corresponding 3a,4,7,7a-tetrahydroisoindole-1,3-dione systems in somewhat lower yields (56−82%). In general, the product yields decrease as the substituents become bulkier. Both acetamide and benzamide exhibited equivalent reactivities with similar yields, with conversions being best accomplished after 24 h at 120 °C. A notable aspect that adds to the facile practicality of the reaction is the workup procedure. Isolation and purification of the acetamide- and benzamide-bearing compounds was achieved by removal of the solvent and subsequent washing with ethyl acetate and ethanol, respectively.

Spectroscopic characterization of the Diels−Alder adducts was achieved by ^{1}H and ^{13}C NMR and MS. The latter exhibited the parent ions and the expected fragmentation patterns involving cleavage of the amide moiety. Two-dimensional ^{1}H−^{1}H and ^{1}H−^{13}C NMR experiments unambiguously established the stereochemical structure of the synthesized products. As with our recently reported multicomponent coupling involving simple aldehydes,[5] all Diels−Alder adducts were found to adopt an *endo* configuration. In no case were hetero Diels−Alder adducts observed.

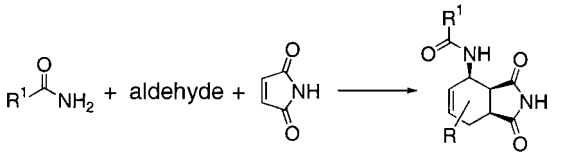
Regarding the stereochemistry of the amide moiety and of the methyl substituents in **4a**,**b** and **5a**,**b**, analyses of the ^{1}H−^{1}H coupling constants revealed the exclusive formation of the all-*syn* products. This results in bowl-shaped cyclohexenes with all substituents on one side of the ring (*syn*). Equivalent structures have been crystallographically confirmed.[9] Subjection of *N*,*N*-dimethyl urea as amide equivalent to the described one-pot reaction conditions afforded the

(6) Syntheses involving 1-acylamino-1,3-butadienes: (a) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 587. (b) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590. (c) Oppolzer, W.; Fröstl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593. (d) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204. (e) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352, 8295. (f) Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, *36*, 3089. (g) Overman, L. E.; Jessup, P. J. *Tetrahedron Lett.* **1977**, *18*, 1253. (h) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164. (i) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373. (j) Martin, S. F.; Li, W. *J. Org. Chem.* **1991**, *56*, 642. (k) Alonso, D. A.; Alonso, E.; Najera, C.; Yus, M. *Synlett* **1997**, 491. Antibody-catalyzed reactions: (l) 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.

(7) A complete reaction scheme would also involve several other equilibrating species, such as imines, aminals, and 1,3-bis(acylamino)-but-1-ene derivatives, as well as σ and π bond rotamers. See ref 5.

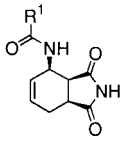
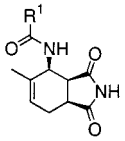
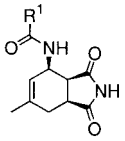
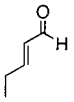
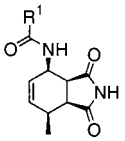
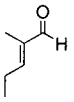
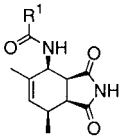
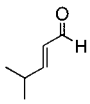
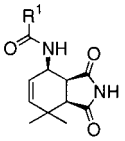
(8) A solid-phase approach toward hydroxy-substituted tetrahydroisoindole-1,3-diones involving silyldienol ether substrates has recently been reported: Smith, E. M. *Tetrahedron Lett.* **1999**, *40*, 3285.

Table 1. Acetamide (R^1 = Me) and Benzamide (R^1 = Ph) Functionalized Tetrahydroisoindole-1,3-dione Derivatives[a]



R^1= Me : **1a - 6a**

R^1= Ph : **1b - 6b**

entry	aldehyde	product	yield [%][b]
1a			85
1b			91
2a			82
2b			72
3a			67
3b			69
4a			77
4b			77
5a			63
5b			56
6a			66
6b			58

[a] Conditions: 10 mmol amide, 5 mmol aldehyde, 10 mmol maleimide, 5 mmol Ac_2O, 1 mol % *p*-TSA, 10 mL of NMP; 120 °C, 24 h. [b] Isolated, nonoptimized yields.

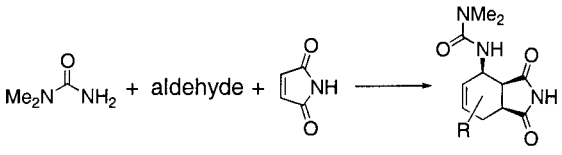
corresponding *N*-4-ureyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione derivatives. Yields are slightly lower compared to acetamide, mostly as a result of elimination of urea from the target molecule.[10] Again, all Diels−Alder adducts contain an *endo* bicyclic system with all substituents on one side of the cyclohexene ring (*syn*).

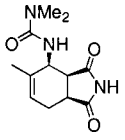
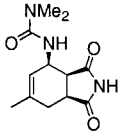
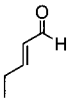
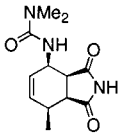
Sulfonamides are another family of amide equivalents this one-pot protocol has been successfully applied to. When employing crotonaldehyde, *N*-4-benzenesulfonylamino-

(9) Spannenberg, A.; Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Beller, M. Unpublished results.

(10) Traces of elimination product (dihydroisoindole-1,3-dione) were detected.

Table 2. *N*,*N*-Dimethyl Urea Functionalized Tetrahydroisoindole-1,3-dione Derivatives[a]

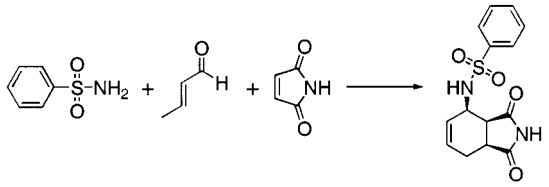


entry	aldehyde	product	yield [%][b]
2c			48
3c			56
4c			62

[a] Conditions: 10 mmol amide, 5 mmol aldehyde, 10 mmol maleimide, 5 mmol Ac_2O, 1 mol % *p*-TSA, 10 mL of NMP; 100 °C, 24 h. [b] Isolated, nonoptimized yields.

3a,4,7,7a-tetrahydroisoindole-1,3-dione (**1d**) was obtained in 79% yield (Scheme 3). The X-ray crystal structure analysis

Scheme 3. Benzenesulfonamide Functionalized Tetrahydroisoindole-1,3-dione Derivative[a]



entry	yield [%][b]
1d	79

[a] Conditions: 10 mmol amide, 5 mmol aldehyde, 10 mmol maleimide, 5 mmol Ac_2O, 1 mol % *p*-TSA, 10 mL of NMP; 120 °C, 48 h. [b] Isolated, nonoptimized yields.

of **1d**[11] confirmed the proposed *endo* configuration of the bicyclic system with *syn*-substitution on the cyclohexene ring.

(11) X-ray data of **1d** were collected on a STOE-IPDS diffractometer using graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXS-86, Sheldrick, G. M. *Acta Crystallogr. A* **1990**, *46*, 467.) and refined by full matrix least-squares techniques against F^2 (SHELXL-93, Sheldrick, G. M., University of Göttingen, Germany, 1993.). XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure representations. Crystal data for **1d**: crystal dimensions 0.5 × 0.5 × 0.4, colorless prisms, space group $P2_1/n$, monoclinic, a = 10.707(2), b = 6.907(1), c = 19.518(4) Å, β = 98.39(3)°, V = 1428.0(4) Å^3, Z = 4, ρ_{calcd} = 1.425 g cm^{-1}, 4084 reflections measured, 2161 were independent of symmetry, and 1762 were observed ($I > 2\sigma(I)$), $R1$ = 0.040, wR^2 (all data) = 0.111, 211 parameters

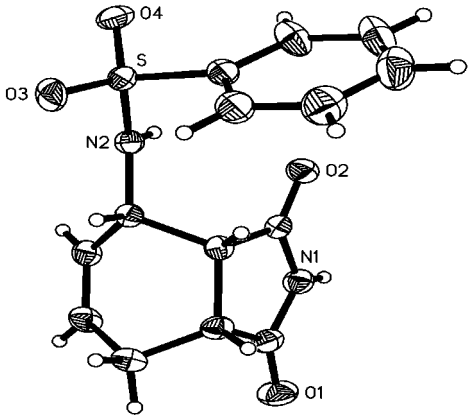


Figure 1. Crystal structure of **1d** (ellipsoids at the 30% level).

The molecular structure is depicted in Figure 1. Bond distances and angles are in the expected ranges.

In conclusion, we have shown that α,*β*-unsaturated aldehydes, various amides, and maleimide readily react in a one-pot procedure to give *N*-4-acylamino-3a,4,7,7a-tetrahydroisoindole-1,3-diones.

The described methodology constitutes the most simple and direct high-yield approach to this class of compounds and, to the best of our knowledge, is the first example of a multicomponent coupling of α,*β*-unsaturated aldehydes, amides, and olefins.

Dienophiles other than maleimide, such as maleic anhydride, acrylonitrile, and dialkyl acetylenedicarboxylates, give somewhat lower yields in Diels−Alder adducts, and these results will soon be communicated.

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Supporting Information Available: Crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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