

# Facile Three-Component Coupling Procedure for the Synthesis of Substituted Tetrahydroisindole-1,3-diones from $\alpha,\beta$ -Unsaturated Aldehydes

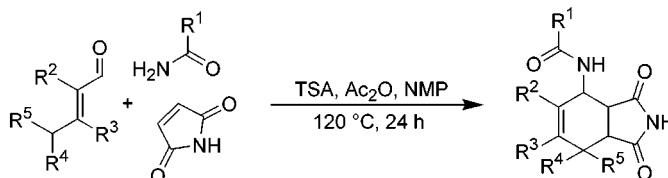
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## ABSTRACT



A new one-pot procedure for the efficient synthesis of a small library of amino-functionalized tetrahydroisindole-1,3-dione derivatives was developed. This three-component coupling reaction comprises subsequent condensation and Diels–Alder reactions of ubiquitous available starting materials ( $\alpha,\beta$ -unsaturated aldehydes, amide, and maleimide). The synthesized compounds share a substituted tetrahydroisindole 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.<sup>1</sup> In this respect, reactions that provide maximum diversity, that is, reactions with high exploratory power, are especially desirable. Here, expeditious multicomponent reactions (MCR)<sup>2</sup> as well as domino reaction sequences offer significant advantages over stepwise procedures.<sup>3</sup> 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.<sup>4</sup>

Recently, we reported a new one-pot protocol for the facile synthesis of diversely substituted amino-functionalized cyclohexene derivatives.<sup>5</sup> 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.<sup>6</sup> 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.; Odon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

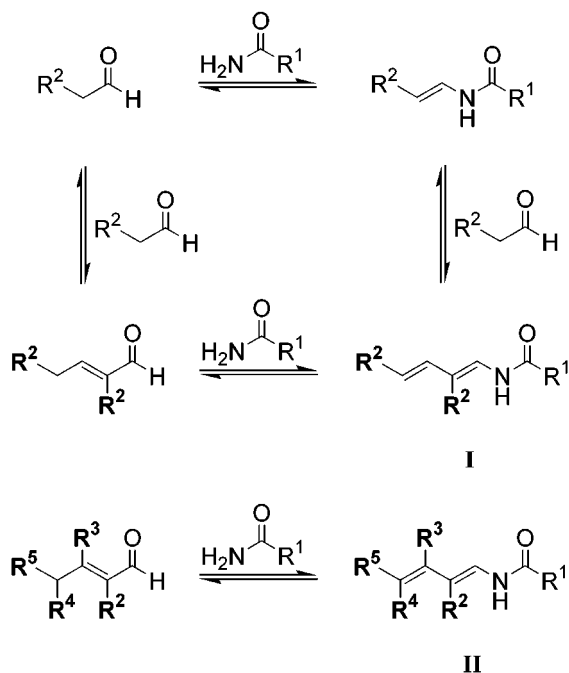
(3) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (c) Tietze, L. F.; Hünert, F. In *Stimulating Concepts In Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCH: Weinheim, 2000; p 39.

(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.

sequential condensations of two  $\alpha$ -CH<sub>2</sub>-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  $\alpha,\beta$ -Unsaturated Aldehydes (bottom, **II**)<sup>7</sup>



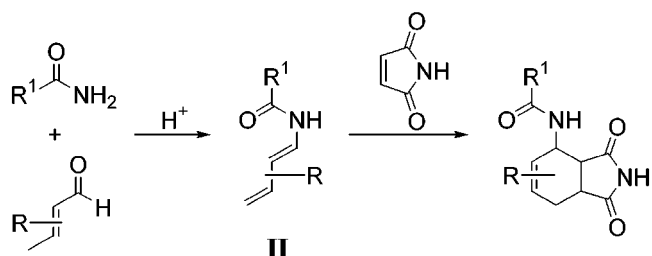
Owing to the incorporation of two identical aldehyde molecules, substitution of the diene backbone in **I** is limited to the 2 and 4 positions only. Obviously, the use of  $\alpha,\beta$ -unsaturated aldehydes, which might constitute an intermediate in the formation of **I**, would afford 1-acylamino-1,3-butadiene 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  $\alpha,\beta$ -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-tetrahydroisindole-1,3-dione derivatives<sup>8</sup> by employing maleimide as a truly powerful dienophile. Initial attempts were undertaken to

(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-Kauhalauma, 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, amins, and 1,3-bis(acylamino)-but-1-ene derivatives, as well as  $\sigma$  and  $\pi$  bond rotamers. See ref 5.

**Scheme 2.** 1-Acylamino-2-cyclohexene Synthesis via a Condensation–Cycloaddition Domino Reaction Sequence Starting from  $\alpha,\beta$ -Unsaturated Aldehydes



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).

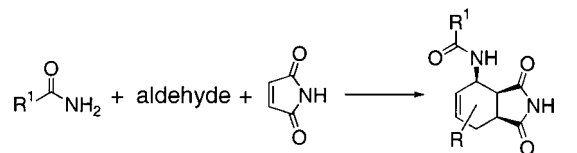
Ubiquitous available amides, such as acetamide ( $R^1 = \text{Me}$ ) and benzamide ( $R^1 = \text{Ph}$ ), cleanly reacted with crotonaldehyde to give the desired bicyclic systems in 85% and 91% yield, respectively. Other commercially available  $\alpha,\beta$ -unsaturated aldehydes afforded the corresponding 3a,4,7,7a-tetrahydroisindole-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 <sup>1</sup>H and <sup>13</sup>C NMR and MS. The latter exhibited the parent ions and the expected fragmentation patterns involving cleavage of the amide moiety. Two-dimensional <sup>1</sup>H–<sup>1</sup>H and <sup>1</sup>H–<sup>13</sup>C NMR experiments unambiguously established the stereochemical structure of the synthesized products. As with our recently reported multicomponent coupling involving simple aldehydes,<sup>5</sup> 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 <sup>1</sup>H–<sup>1</sup>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.<sup>9</sup> Subjection of *N,N*-dimethyl urea as amide equivalent to the described one-pot reaction conditions afforded the

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

**Table 1.** Acetamide ( $R^1 = \text{Me}$ ) and Benzamide ( $R^1 = \text{Ph}$ ) Functionalized Tetrahydroisindole-1,3-dione Derivatives<sup>a</sup>



$R^1 = \text{Me} : \mathbf{1a} - \mathbf{6a}$

$R^1 = \text{Ph} : \mathbf{1b} - \mathbf{6b}$

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

<sup>a</sup> Conditions: 10 mmol amide, 5 mmol aldehyde, 10 mmol maleimide, 5 mmol  $\text{Ac}_2\text{O}$ , 1 mol % *p*-TSA, 10 mL of NMP; 120 °C, 24 h. <sup>b</sup> Isolated, nonoptimized yields.

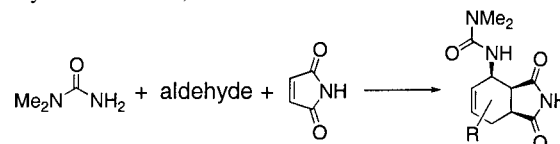
corresponding *N*-4-ureyl-3a,4,7,7a-tetrahydroisindole-1,3-dione derivatives. Yields are slightly lower compared to acetamide, mostly as a result of elimination of urea from the target molecule.<sup>10</sup> Again, all Diels–Alder adducts contain an *endo* bicyclic system with all substituents on one 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.; Gordes, D.; Beller, M. Unpublished results.

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

**Table 2.** *N,N*-Dimethyl Urea Functionalized Tetrahydroisindole-1,3-dione Derivatives<sup>a</sup>

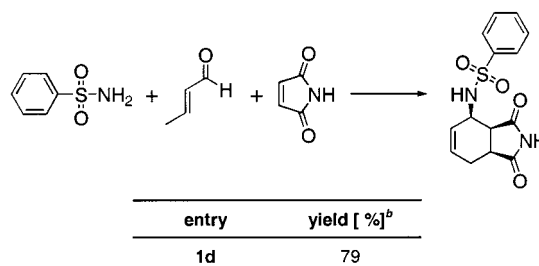


entry	aldehyde	product	yield [%] <sup>b</sup>
2c			48
3c			56
4c			62

<sup>a</sup> Conditions: 10 mmol amide, 5 mmol aldehyde, 10 mmol maleimide, 5 mmol  $\text{Ac}_2\text{O}$ , 1 mol % *p*-TSA, 10 mL of NMP; 100 °C, 24 h. <sup>b</sup> Isolated, nonoptimized yields.

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

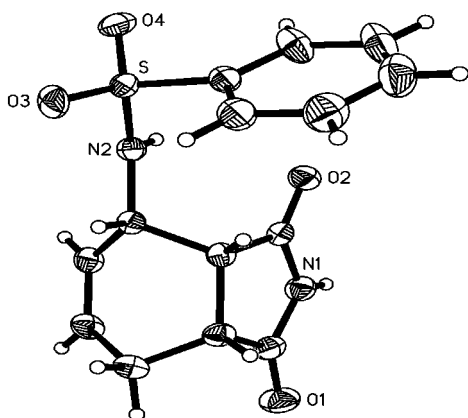
**Scheme 3.** Benzenesulfonamide Functionalized Tetrahydroisindole-1,3-dione Derivative<sup>a</sup>



<sup>a</sup> Conditions: 10 mmol amide, 5 mmol aldehyde, 10 mmol maleimide, 5 mmol  $\text{Ac}_2\text{O}$ , 1 mol % *p*-TSA, 10 mL of NMP; 120 °C, 48 h. <sup>b</sup> Isolated, nonoptimized yields.

of **1d**<sup>11</sup> 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 K $\alpha$  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  $0.5 \times 0.5 \times 0.4$ , colorless prisms, space group  $P2_1/n$ , monoclinic,  $a = 10.707(2)$ ,  $b = 6.907(1)$ ,  $c = 19.518(4)$  Å,  $\beta = 98.39(3)^\circ$ ,  $V = 1428.0(4)$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho_{\text{calcd}} = 1.425$  g cm<sup>-3</sup>, 4084 reflections measured, 2161 were independent of symmetry, and 1762 were observed ( $I > 2\sigma(I)$ ),  $R1 = 0.040$ ,  $wR2$  (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  $\alpha,\beta$ -unsaturated aldehydes, various amides, and maleimide readily react in a one-

pot procedure to give *N*-4-acylamino-3a,4,7,7a-tetrahydroisindole-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  $\alpha,\beta$ -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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