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A Novel MCR of Isocyanates, Aldehydes, and Dienophiles

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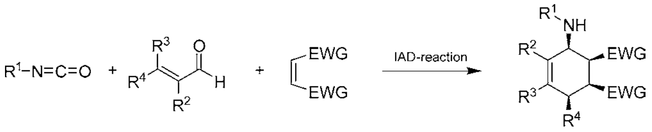
ABSTRACT

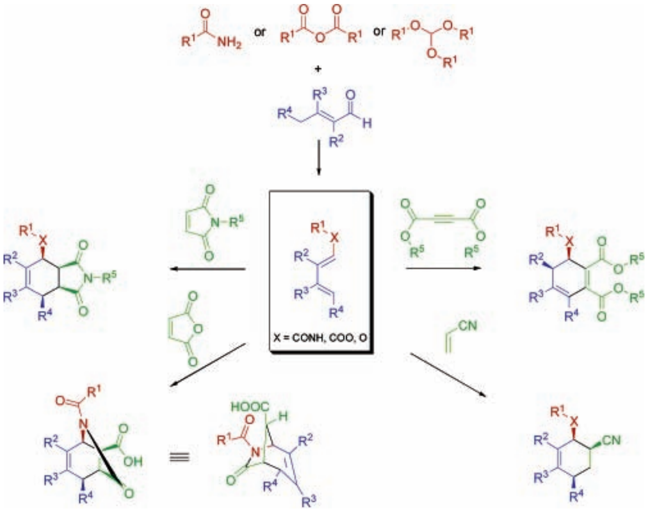


A novel one-pot procedure for the three-component coupling reaction of isocyanates, aldehydes, and dienophiles (IAD reaction) has been developed. Condensation of isocyanates and aldehydes and subsequent Diels–Alder reactions with electron-deficient dienophiles furnishes *endo*-selective amino-substituted cyclohexenes in good yield.

The development of multicomponent (MCR)[1] and domino reactions[2] is an important topic in organic chemistry. Compared to the classical step-by-step formation of individual bonds for a given target molecule, MCRs or domino reactions take advantage of the simultaneous formation of several bonds in only one operational step. In the past decade, research in academia and industry has increasingly emphasized the use of MCRs for a broad range of products.[3]

On the basis of our interest in carbonylation reactions, we developed novel catalysts for three- and four-component coupling reactions, such as the hydroaminomethylation of olefins[4] and the amidocarbonylation of aldehydes.[5] On the basis of the latter work,[6] we discovered novel coupling reactions of *a*ldehydes, *a*mides, and *d*ienophiles (AAD reaction) for the straightforward synthesis of a large variety of carbo- and heterocyclic amides.[7] As shown in Scheme 1, the underlying mechanism takes advantage of an initial condensation reaction of amides and aldehydes to give amido-substituted 1,3-butadienes as key intermediates, which are subsequently converted with electron-deficient dienophiles to the corresponding MCR products. Earlier on, several groups have demonstrated the versatility of isolated amido-functionalized 1,3-butadienes for Diels−Alder chemistry.[8] Prominent examples include the preparation of pumiliotoxin,[9] gephyrotoxin,[10] dendrobine,[11] and tabersonine.[12]

Scheme 1. Schematic Representation of the AAD, ANAD, ALAD Reaction Protocols



Furthermore, we have demonstrated the synthetic usefulness of *in situ* produced 1-amido-1,3-butadienes in the preparation of highly substituted anilines,[13] bicyclo[2.2.2]-oct-2-enes,[14] enantiomerically pure cyclohexenols,[15] and cyclohexenylamines,[16] phthalic acids,[17] luminoles,[18] phenan-

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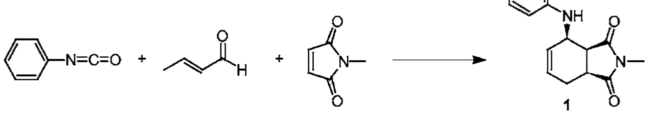
thridones,[19] as well as lactam derivatives. More recently, this type of three-component coupling reaction of aldehydes and dienophiles could be extended from amides to anhydrides (ANAD reaction), and ortho esters (ALAD reaction).[15] Covering this broad range of substrates, the generality of the method has already been demonstrated in the synthesis of more than 200 carbo- and heterocyclic compounds. Here, we wish to report the extension of our previous protocols to multicomponent coupling reactions of isocyanates, α,*β*-unsaturated aldehydes, and dienophiles for the straightforward synthesis of 1-amino-2-cyclohexene derivatives. Although isocyanides have been extensively used in various MCRs, especially the Ugi reaction,[20] to the best of our knowledge, there are only a few reported examples of multicomponent or domino reactions applying isocyanates.[21]

Table 1. *I*socyanate *A*ldehyde *D*ienophile (*IAD*) Model Reaction[a]



entry	solvent	aldehyde (equiv)	*T* (°C)	*t* (h)	yield (%)
1	toluene	1.5	110	16	11
2	NMP	1.5	110	16	48
3	MeCN	1.5	110	16	55
4	1,4-dioxane	1.5	110	16	67
5	1,4-dioxane	1.5	80	16	39
6	1,4-dioxane	3	110	16	68
7	1,4-dioxane	1.5	110	8	54
8	1,4-dioxane	1.5	110	24	71
9	1,4-dioxane	1.5	110	40	65

[a] Reaction conditions: phenyl isocyanate (2 mmol), crotonaldehyde (3−6 mmol), *N*-methylmaleimide (3 mmol), *p*-TSA (2 mol %), solvent (8 mL).

On the basis of our standard reaction protocol (2 mol % *p*-toluenesulfonic acid monohydrate, toluene, 16 h, 110 °C) for the ANAD reaction, we initially examined the conversion of phenyl isocyanate, crotonaldehyde, and *N*-methylmaleimide as a model reaction. To our surprise, we did not observe any expected carbamate after work up; instead, the thermodynamically more stable compound 3a,4,7,7a-tetrahydro-2-methyl-4-(phenylamino)-2*H*-isoindole-1,3-dione **1** was obtained in 11% yield (Table 1, entry 1). As shown in Scheme 2, the formation of **1** can be explained either by decarboxylation of the carbamoyl-derived cycloaddition adduct **B** or by the decomposition of intermediate **A**. In the

Scheme 2. Formation of 3a,4,7,7a-Tetrahydro-2-methyl-4-(phenylamino)-2*H*-isoindole-1,3-dione **1**

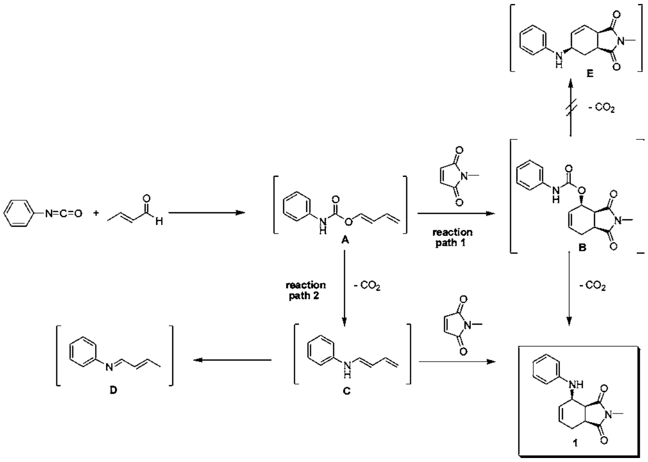


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Table 2. Synthesis of Various IAD Products[a]

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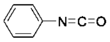
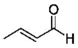
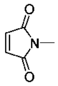
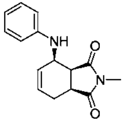
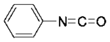
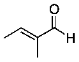
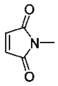
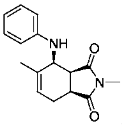
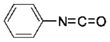
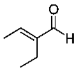
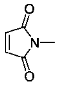
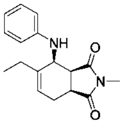
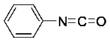
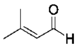
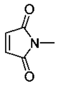
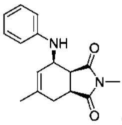
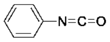
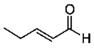
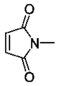
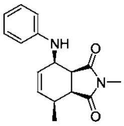
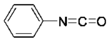
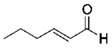
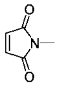
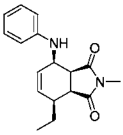
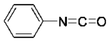
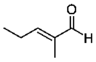
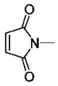
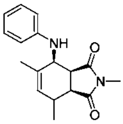
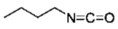
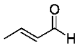
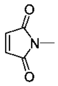
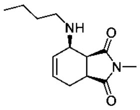
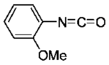
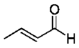
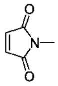
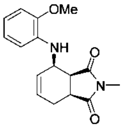
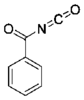
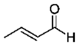
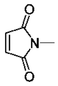
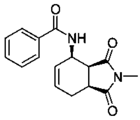
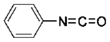
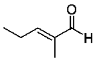
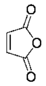
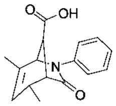
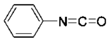
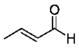
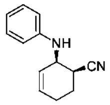
1				 **1**	71
2				 **2**	73
3				 **3**	68
4				 **4**	64
5				 **5**	67
6				 **6**	71
7				 **7**	75
8					0
9				 **8**	72[b]
10				 **9**	12
11				 **10**	76[c]
12				 **11**	51[d]

[a] Reaction conditions: isocyanate (5 mmol), α,β-unsaturated aldehyde (7.5 mmol), dienophile (7.5 mmol), *p*-TSA (2 mol %), 1,4-dioxane (20 mL), 110 °C, 24 h. [b] Reaction mixture was stirred for 48 h. [c] Maleic acid anhydride (5 mmol). [d] Acrylonitrile (40 mmol).

latter case, an acid-catalyzed nucleophilic attack of the carbamate nitrogen to the O-carbamoyl-substituted carbon atom would directly cause the formation of **C** via an intramolecular decarboxylation. Experiments to prove the existence of **D** by trapping it with electron-rich dienophiles in inverse Diels–Alder reactions remained unsuccessful. Interestingly, there is no 6-phenylamino-substituted isoindole-1,3-dione **E** observed. Hence, the decarboxylation does not take place in the form of a pericyclic rearrangement. Changing the solvent to *N*-methyl-2-pyrrolidinone, acetonitrile, and 1,4-dioxane led to significantly improved yields of **1** (48, 55, and 67%, respectively) (Table 1, entries 2−4). This beneficial effect might be explained by the capability of polar, aprotic solvents to enable aldehyde condensation with phenyl isocyanate at a higher reaction rate. Due to the superior properties of dioxane, we studied variations of the reaction conditions in this solvent. Selected results are shown in Table 1. Decreasing of the temperature to 80 °C gave a lowered yield (39%, Table 1, entry 5). Increasing the concentration of crotonaldehyde led to a slightly higher yield of **1** (68%, Table 1, entry 6). Similarly, at longer reaction times (24 h), an improved yield (71%) was obtained. Noteworthy, the direct use of aniline as a more atom economic substrate resulted only in traces of the model substrate **1** ($<$3% yield).

Next, we were interested in applying the novel protocol for other starting materials. Therefore, a variety of α,β-unsaturated aldehydes were reacted with phenyl isocyanate and *N*-methylmaleimide. As a result, differently substituted phenylaminocyclohexenes were obtained in good yields ranging from 64 to 75% (Table 2, entries 2−7). The use of 2-methoxyphenylisocyanate resulted in 72% yield for 4-(2-methoxyphenylamino)-3a,4,7,7a-tetrahydro-2-methyl-2*H*-isoindole-1,3-dione **8** (Table 2, entry 9). Unfortunately, *n*-butyl isocyanate did not react in the desired manner (Table 2, entry 8).[22] Application of benzoyl isocyanate as starting material afforded the corresponding amido-substituted cyclohexene in low yield of 12% (Table 2, entry 10). However, this latter compound is readily accessible by our previously reported AAD reaction protocol using benzamide.[7] Noteworthy, the synthesized isoindole-1,3-diones (**1**−**9**) are useful precursors for heteroanalogous derivatives of marine antibacterial metabolites, such as corollosporine.[23] To study the influence of other dienophiles, we employed acrylonitrile and maleic acid anhydride as substrates. The corresponding products **10** and **11** were isolated in 76 and 51% yield, respectively (Table 2, entries 11 and 12). In the case of **10**, we observed the exclusive formation of the bicyclic adduct, caused by a subsequent intramolecular amidation.

For all products, one- and two-dimensional NMR experiments established the stereochemical structure. In all cases, we observe the selective *endo* addition of the dienophile during the Diels−Alder step.

In summary, we have synthesized new 1-amino-2-cyclohexene derivatives in good yield, taking advantage of the multicomponent coupling reaction of isocyanates, aldehydes, and dienophiles (IAD reaction). Although up to four stereogenic centers are created, only one diastereomer is formed selectively. The described methodology constitutes the most simple and direct high-yield approach to this class of compounds.

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

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