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An easy and general protocol for multicomponent coupling reactions of aldehydes, amides, and dienophiles

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Abstract—An improved procedure for the three-component coupling reaction of *a*ldehydes, *a*mides, and *d*ienophiles (AAD-reaction) has been developed. The use of microwave technology enables the *endo*-selective synthesis of *N*-acyl cyclohexenylamines via condensation of readily available aldehydes and amides, and subsequent Diels–Alder reaction with electron-deficient dienophiles in significantly improved yields. Advantageously, there is no need of employing additional solvents and reaction times are drastically reduced compared to similar thermal reactions.

1. Introduction

Multicomponent[1] and domino reactions[2] offer significant advantages compared to the classical step by step formation of individual bonds due to their higher synthetic efficiency. The resulting reduced number of synthetic and purification steps for a given target molecule increases the attractiveness and practicability of the process. As a special benefit, often MCRs also enable the enhancement of structural diversity in an unprecedented way. Due to the wide variation of the starting materials, various opportunities arise for the synthesis of compound libraries. Therefore, in the last decade research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products.[3]

Based on our general interest in homogeneous catalysis, we studied transition metal-catalyzed three- and four-component coupling reactions such as the hydroaminomethylation of olefins,[4] and the amidocarbonylation of aldehydes.[5] With respect to the latter work,[6] we discovered multicomponent 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 involves an Oppolzer–Overman-type 1-(*N*-acylamino)-1,3-butadiene, which easily undergoes Diels–Alder addition to an electron-deficient dienophile.[8] The synthesized three-component adducts exhibit a high degree of diversity, which is based upon structural variations of the simple, ubiquitous components carboxamide, aldehyde, and olefin. More recently, such coupling reactions of aldehydes and dienophiles could be extended from amides to anhydrides (ANAD-reaction), orthoesters (ALAD-reaction), and even to isocyanates (IAD-reaction) (Scheme 1). Covering this broad range of substrates, the generality of the methods has been demonstrated in the synthesis of more than 200 carbo- and heterocyclic compounds.

The versatility of isolated functionalized 1,3-butadienes for Diels–Alder chemistry[8] has also been demonstrated in the preparation of pumiliotoxin,[9] gephyrotoxin,[10] dendrobine,[11] and tabersonine.[12] Furthermore, we have recently demonstrated the synthetic applicability of our MCRs in the preparation of highly substituted aniline,[13] bicyclo[2.2.2]-oct-2-ene,[14] enantiomerically pure cyclohexenol,[15] and cyclohexenylamine,[7e] phthalic acid,[7d] luminol,[16] phenanthridone[17] as well as lactam[18] derivatives.

Here, we wish to report an improved protocol for the coupling of aldehydes, amides, and dienophiles. Taking advantage of microwave radiation functionalized 1-amido-2-cyclohexene derivatives are synthesized in good to excellent yields. To the best of our knowledge, such strategy has not been used for multicomponent couplings of aldehydes and dienophiles till date.

2. Results and discussion

Typically, three-component coupling reactions of aldehydes, amides, and dienophiles have been carried out at 80–120 °C

Keywords: Aldehydes; Dienophiles; Diels–Alder reaction; Multicomponent reaction; Microwaves.
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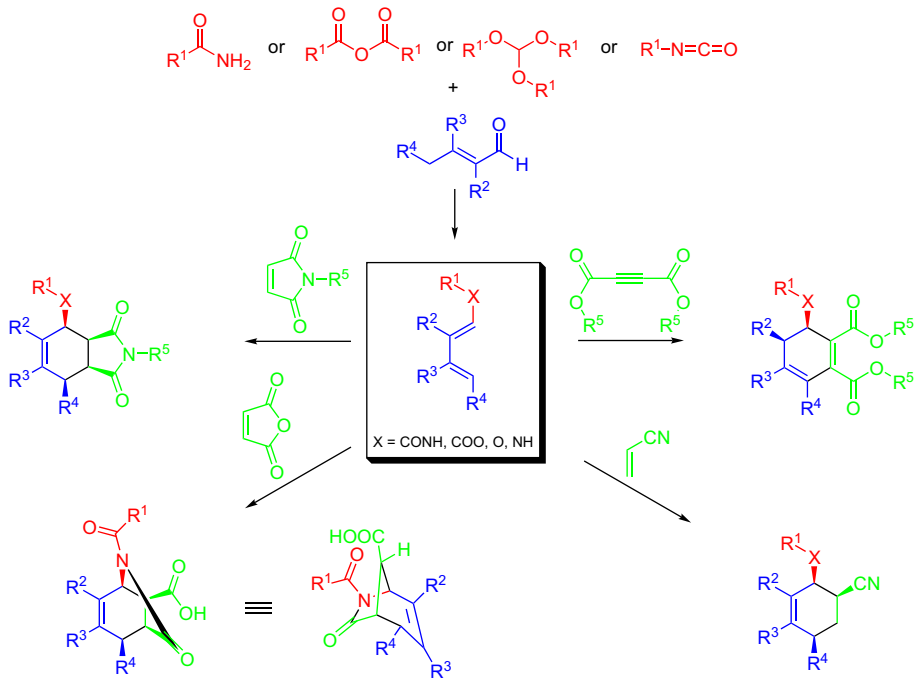


Scheme 1. Schematic representation of the AAD-, ANAD-, ALAD-, IAD-reaction protocols.

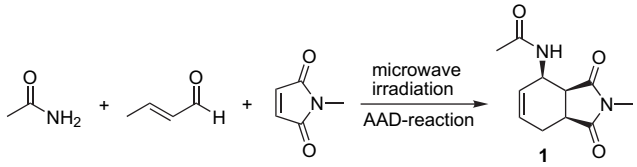
in dipolar, aprotic solvents like NMP (so-called first generation protocol). Despite the generality of these conditions, sometimes aldol-type side-products arise and the purification of the desired product is troublesome. By studying the condensation of amides with more sensitive arylacetylaldehydes in detail, we observed that the presence of aromatic solvents such as toluene or xylene improves the yield of the corresponding MCR-product (so-called second generation protocol). Nevertheless, a drawback of both procedures is the comparatively long reaction time (16–120 h), which is required for full conversion. In order to synthesize compound libraries in a faster manner, we were particularly interested in the development of a short term procedure. For this purpose the application of microwave technology has become the method of choice.[19] For instance, several groups reported on the beneficial use of microwaves for the considerable acceleration of reactions.[20]

As a model reaction we started screening the conversion of crotonaldehyde in the presence of acetamide and *N*-methylmaleimide (Table 1), applying the professional CEM monomode microwave Discover®.[21] It is important to note that all reactions were carried out at maximum microwave power of 50 W. In the first set of experiments, we examined the influence of various reaction media (toluene, 1,4-dioxane, no solvent) and the temperature. Fixing the time and temperature to 20 min and 180 °C, respectively, we observed full conversion and the formation of 4-*N*-acetylamino-2-methyl-*cis*-3a,4,7,7a-tetrahydroisoindole-1,3-dione **1** in 38% yield using the aromatic solvent toluene (Table 1, entry 1). Applying the polar, aprotic solvent 1,4-dioxane, a slightly increased yield of 49% is observed (Table 1, entry 2).

A similar result is obtained for the neat reaction (51%, Table 1, entry 3). Decreasing the reaction temperature to 150 °C did not change the product yield for both solvents (Table 1, entries 4 and 5). Surprisingly, the reaction yield was remarkably increased for the solvent-free reaction (73%, Table 1, entry 6). Additional experiments at a lower temperature of 110 °C resulted in drastically reduced product yields (Table 1, entries 7–9).

Next, we studied the variation of reaction times at 150 °C. However, improved yields were obtained neither for shorter

Table 1. Microwave-assisted synthesis of 4-*N*-acetylamino-2-methyl-*cis*-3a,4,7,7a-tetrahydroisoindole-1,3-dione (**1**)



Entry	Solvent	*T* [°C]	*t* [min]	Additives	Yield [%]
1	Toluene	180	20	—	38
2	Dioxane	180	20	—	49
3	—	180	20	—	51
4	Toluene	150	20	—	38
5	Dioxane	150	20	—	49
6	—	150	20	—	73
7	Toluene	110	20	—	19
8	Dioxane	110	20	—	31
9	—	110	20	—	54
10		150	10	—	47
11	—	150	30	—	63
12	—	150	60	—	58
13	—	150	20	1 mmol crotonaldehyde	85
14	—	150	20	1 mmol crotonaldehyde, 1 mmol Ac_2O	90
15	Toluene	110	960	—	61[a]

Conditions: 1 mmol acetamide, 1 mmol crotonaldehyde, 1.5 mmol *N*-methylmaleimide, 2 mol % *p*-TSA, 2 mL solvent, max 50 W microwave irradiation.
[a] Second generation procedure: 5 mmol acetamide, 5 mmol crotonaldehyde, 7.5 mmol *N*-methylmaleimide, 5 mmol Ac_2O, 2 mol % *p*-TSA, 20 mL toluene.

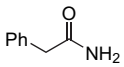
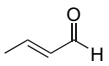
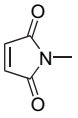
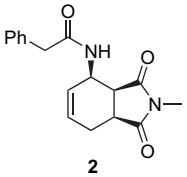
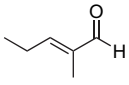
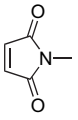
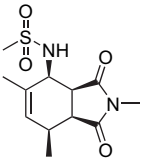
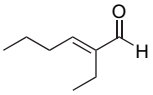
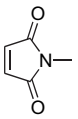
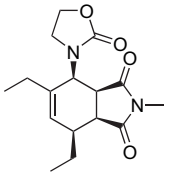
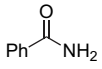
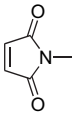
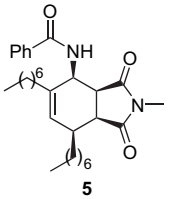
nor for longer reaction times (Table 1, entries 10–12). Increasing the amount of crotonaldehyde to 2 equiv (with respect to acetamide) resulted in 85% yield of the desired tetrahydroisoindole-1,3-dione derivative (Table 1, entry 13). In accordance with experiments under thermal conditions, the addition of acetic acid anhydride as water removing reagent to the reaction mixture led to an additional beneficial effect. Hence, the model product **1** is obtained in an excellent yield of 90% (Table 1, entry 14).[22] It is worth mentioning that the classical first and second generation AAD-procedures resulted, at their standard conditions, in <61% product yield, requiring a nearly fifty times longer reaction time of 16 h (Table 1, entry 15).

In order to prove the generality of the optimized set of conditions, we applied the microwave-assisted protocol to other starting materials. Here, differently functionalized amide derivatives were reacted with aliphatic as well as α,β-unsaturated aldehydes in the presence of suitable dienophiles providing a series of 1-acylamino-2-cyclohexene derivatives. For a number of reactions the use of NMP (first generation protocol), toluene (second generation protocol), and the solvent-free, microwave-assisted procedure were compared under optimized conditions. As shown in Table 2, in most cases studied, the new protocol gave higher yields compared to our previous procedures. For example, aliphatic and aromatic amides, as well as sulfonamides react nearly quantitatively with α,β-unsaturated aldehydes and *N*-methylmaleimide (79–96% yield; Table 2, entries 1, 2, 5).

Only in the case of the cyclic oxazolidin-2-one, a lower yield of 52% is obtained (Table 2, entry 3). In addition, aliphatic aldehydes furnish the corresponding products in excellent yields (81–95% yield; Table 2, entries 4, 6). In order to study the influence of other dienophiles also, we employed maleic acid anhydride, diethyl but-2-ynedioate, and acrylonitrile as substrates, which gave the corresponding products in 26–31% yield (Table 2, entries 7–9). Interestingly, in the case of diethyl but-2-ynedioate, for the first time a 1,4-cyclohexadiene derivative is obtained as product.

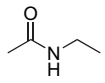
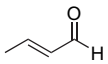
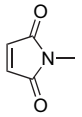
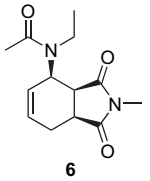
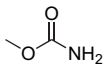
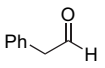
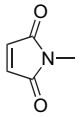
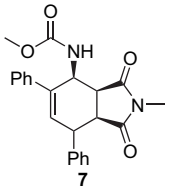
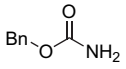
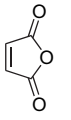
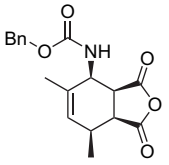
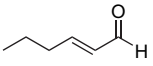
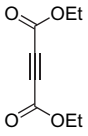
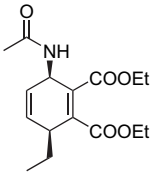
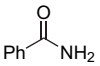
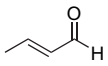
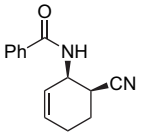
For all products one- and two-dimensional NMR experiments unambiguously established the stereochemical structure. Although up to four stereogenic centers are created, only one diastereomer is formed selectively. In agreement with our previously reported multicomponent coupling reactions, we observe the selective *endo* addition of the dienophile during the Diels–Alder step. Thus, analyses of the ^{1}H–^{1}H coupling constants of the amido-, as well as the other alkyl-substituents on the cyclohexene ring reveal the exclusive formation of the all-*syn* product. This results in bowl- or crown-shaped cyclohexene derivatives with all substituents on one side of the ring.

Table 2. Microwave-assisted synthesis of various AAD-products

Entry	Amide	Aldehyde	Dienophile	AAD-product	First generation yield [%]	Second generation yield [%]	Third generation yield [%]
1				 **2**	58	72	96
2				 **3**	nd	88	85
3				 **4**	nd	73	52
4				 **5**	nd	70	95

(*continued*)

Table 2. (*continued*)

Entry	Amide	Aldehyde	Dienophile	AAD-product	First generation yield [%]	Second generation yield [%]	Third generation yield [%]
5				 **6**	0	69	79
6				 **7**	5	70	81
7				 **8**	nd	72	31
8				 **9**	nd	0	26
9				 **10**	76	8	31[a]

Reaction conditions: 1 mmol amide, 2 mmol α,β-unsaturated aldehyde or 4 mmol aldehyde, 1.5 mmol dienophile, 1 mmol Ac_2O, 2 mol % *p*-TSA, 150 °C, 20 min, max 50 W microwave irradiation.

[a] Acrylonitrile: 5 mmol; 120 min.

3. Conclusion

In summary, we have developed an improved multicomponent reaction of aldehydes, amides, and dienophiles, which features the domino formation of three carbon–carbon and one carbon–nitrogen bonds. The described methodology constitutes probably the most simple and direct approach to 1-amido-2-cyclohexenes. Taking advantage of microwave irradiation, reaction times could be significantly reduced, and often product yields are improved compared to our previous AAD-protocols. With regard to green chemistry, there is no need of adding solvents and it is interesting to emphasize that the ubiquitous, off-shelf starting materials readily react even without special exclusion of air and water.

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22. (a) Procedure for the synthesis of *N*-(2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-7-yl)-acetamide (**1**): acetamide (1 mmol), *N*-methylmaleimide (1.5 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol %) were combined in a CEM-Discover microwave pressure tube and crotonaldehyde (2 mmol) and Ac_2O (1 mmol) were added. Then, the reaction was stirred at 150 °C for 20 min at max 50 W microwave irradiation. After cooling, the crude mixture was dissolved in NMP and hexadecane (1 mmol) was added as an internal standard for the determination of product yield by GC. R_f (SiO_2, *n*-heptane/EtOAc=1/1): 0.21. Yield: 90 %. ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.10 (d, *J*=7.6 Hz, CON*H*), 5.87 and 5.73 (m, 1H and dt, *J*=9.3 Hz and *J*=3.0 Hz, 1H, C*H*=C*H*), 4.43 (m, 1H, C*H*NH), 3.38 (m, 1H, CHC*H*CO), 3.19 (m, 1H, CH_2CHCO), 2.76 (s, 3H, CONCH_3), 2.50 and 2.17 (both m, both 1H, CH_2), 1.88 (s, 3H, CH_3CO). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=179.6 and 177.2 (2 CH*C*ON), 169.0 (*C*ONH), 130.9 and 127.8 (*C*H=*C*H), 45.2 (*C*HNH), 44.9 and 38.6 (2 C*H*CON), 24.4 (CON*C*H$_3$), 23.4 (*C*H$_2$), 22.6 (*C*H$_3$CO). MS (EI, 70 eV): *m*/*z* (%)=222 (2) [M]$^+$, 179 (100) [M−Ac]$^+$, 94 (35), 69 (43), 43 (23) [Ac]$^+$, no other peaks >10%. IR (KBr): 1/λ=3255 (s), 3086 (m), 2956 (w), 2874 (w), 1775 (m), 1692 (vs), 1644 (m), 1571 (s), 1441 (s), 1288 (s), 1119 (s), 1010 (m), 793 (m), 722 (m), 605 (m), 579 (m) cm^{-1}. HRMS (EI): calcd for $C_{14}H_{14}N_2O$: 222.10120; found: 222.10045 [M]$^+$.(b) Procedure for the synthesis of diethyl 3-acetamido-6-ethyl-cyclohexa-1,4-diene-1,2-dicarboxylate (**9**): acetamide (1 mmol), diethyl but-2-ynedioate (1.5 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol %) were combined in a CEM-Discover microwave pressure tube and hex-2-enal (2 mmol) and Ac_2O (1 mmol) were added. Then, the reaction was stirred

at 150 °C for 20 min at max 50 W microwave irradiation. After cooling, all volatile compounds were removed under reduced pressure. Silicagel column chromatography afforded the corresponding product as a colorless oil. R_f (SiO_2, *n*-heptane/EtOAc=1/1): 0.41. Yield: 26%. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.95 (d, J=8.52 Hz, 1H, CON*H*), 5.81 and 5.61 (both m, both 1H, C*H*=C*H*), 5.17 (m, 1H, C*H*NH), 4.15–4.01 (m, 4H, 2 OCH_2), 2.98 (m, 1H, CH_2C*H*), 1.77 (s, 3H, CH_3CO), 1.72–1.59 (m, 2H, CH_3CH_2CH), 1.18 and 1.13 (both t, J=7.23 Hz and J=7.63 Hz, both 3H, 2 CH_3CH$_2$O), 0.84 (t, J=7.53 Hz, CH_3CH$_2$CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=168.5 and 166.9 (2 *C*OO), 166.0 (*C*ONH), 139.0 and 132.7 (*C*=*C*), 128.8 and 124.7 (*C*H=*C*H), 60.8 and 60.6 (2 OCH_2), 43.0 (*C*HNH), 37.6 (CH_2*C*H), 26.2 (CH_3*C*H_2CH), 22.3 (*C*H_3CO), 13.7 (2 *C*H_3CH$_2$O), 10.4 (*C*H_3CH$_2$CH). MS (EI, 70 eV): m/z (%)=309 (1) [M]$^+$, 234 (81), 190 (22), 164 (100), 148 (17), 43 (68) [Ac]$^+$, no other peaks >10%. IR (KBr): 1/λ=3465 (s), 3051 (w), 2951 (w), 1678 (m), 1604 (s), 1436 (m), 1384 (m), 1346 (m), 1281 (m), 1250 (m), 1170 (m), 1119 (m), 1034 (m), 978 (m), 930 (w), 840 (w), 793 (w), 671 (w), 580 (w) cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{23}NO_5$: 309.15762; found: 310.16517 [M]$^+$.