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From a spin-off to the advantageous use in Diels–Alder reactions: a combined synthetic, spectroscopic and computational approach to *N*-(dienyl)acylamines

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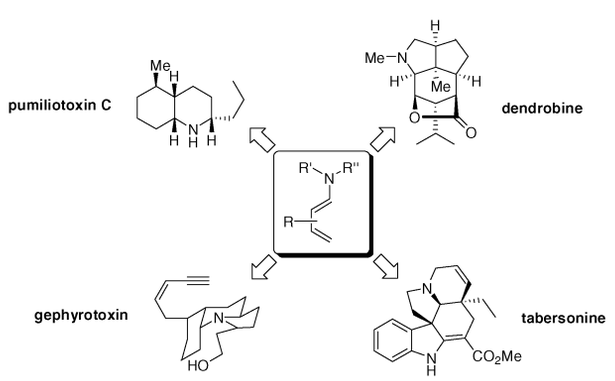
Received 10th December 2003, Accepted 14th January 2004
First published as an Advance Article on the web 16th February 2004

The acid-catalyzed condensation of aldehydes and acetamide has been shown to provide a pool of diverse equilibrating species. For the first time, the synthesis of substituted 1-*N*-acylamino-1,3-butadienes has been accomplished directly in moderate yields upon telomerization of two molecules of aldehyde with one molecule of carboxamide. Detailed spectroscopic and computational investigations establish the favourable formation of all-*trans* aminodienes under the reaction conditions. Employment thereof as diene building blocks in Diels–Alder reactions allows for the synthesis of carbocyclic molecules with high stereocontrol.

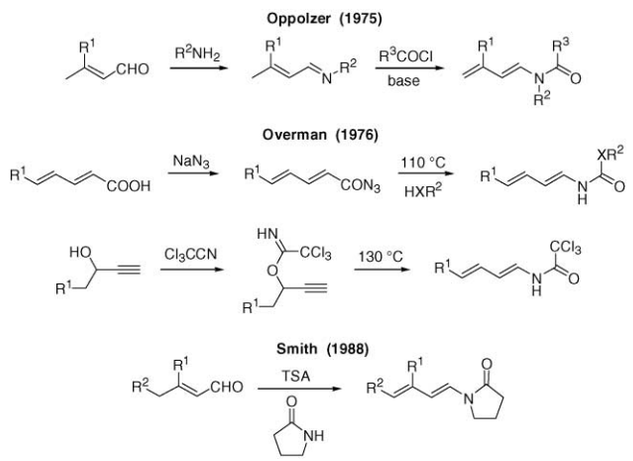
Introduction

The versatility of the Diels–Alder reaction, one of the most powerful tools for the synthesis of six-membered ring systems, has been significantly increased with the advent of available heteroatom-substituted dienes. By comparison with their purely 'carbonic' counterparts, heteroatom-substituted dienes not only exhibit higher reactivity in most cases but also give functionalized products which arguably are useful for further manipulation.[1] While alkoxy-substituted dienes have been studied intensively, applications of amino-substituted dienes are scarce because of their elaborate synthesis. Nevertheless, the 1-carbamoyl-substituted Oppolzer–Overman dienes represent an important class of amino-substituted diene building blocks.[2] Several groups have elegantly demonstrated the synthetic versatility of 1-acylamino-1,3-dienes for Diels–Alder chemistry.[3] Prominent examples in which the pivotal aminodiene-based Diels–Alder reactions constitute particularly attractive solutions for the construction of six-membered carbocyclic subunits with high attendant regio- and stereoselectivity include the total syntheses of pumiliotoxin C,[4] gephyrotoxin,[5] dendrobine,[6] and tabersonine[7] (Scheme 1).



Scheme 1 1-*N*-Acylaminodienes as building blocks in natural product syntheses.

Several synthetic approaches to Oppolzer–Overman-type dienes and related 1-acylamino-1,3-butadiene derivatives have been reported in the literature (Scheme 2).[2] Oppolzer reported on a two-step synthesis starting from crotonaldehydes. Upon



Scheme 2 Literature syntheses of 1-*N*-acylaminobutadienes.

condensation with an amine and subsequent acylation, 1-*N*-acylaminodienes are obtained.[2b] Overman accomplished the synthesis of related compounds *via* two alternative strategies. Dienoic acid is converted into the azide derivative which gives an intermediate isocyanate *via* a modified Curtius rearrangement under pyrolysis conditions. Subsequent trapping with an amine or alcohol affords the acylaminodiene.[2c] Another approach uses propargylic trichloroacetimidates which are prepared by base-catalyzed addition of the corresponding propargylic alcohol and trichloroacetonitrile. Claisen rearrangement at elevated temperatures gives the desired trichloroacetamido-1,3-dienes.[2d] In the late 1980's, Smith reported on the preparation of *N*-dienyl lactams by simple acid-catalyzed condensation of lactams and substituted crotonaldehydes.[2e] In addition two other aminodiene syntheses have to be noted: a strategy based upon double lithiation of *N*-acyl tosylmethylamines has been reported on by Yus,[2f] while Katritzky[2g] utilized auxiliary benzotriazole to introduce *N*-dienyl substituents into amides. Both routes represent rather special procedures, and generality has not been shown. In general, the aforementioned routes are multi-step procedures and afford moderate yields of the targeted aminodienes (mostly 30–60%).

Dependent on the specific procedure, different acylamine equivalents can be attached to the diene. The Oppolzer route[2b]

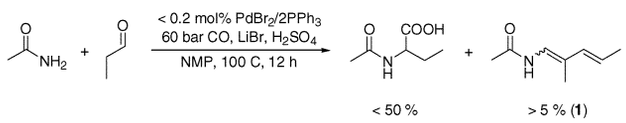
DOI: 10.1039/b316026b

allows the introduction of a secondary acylamine endcapped *via* consecutive amination and acylation whereas Smith[2e] prepared analogous compounds from lactams. The Overman dienes bear further functionalized acyl groups (–CCl_3 or –NR_2/–OR/–SR).[2c,d] The exclusive utilization of olefinic starting materials in all aforementioned procedures clearly limits their generality and scope. Herein, we present a one-step procedure for the synthesis of substituted 1-*N*-acylamino-butadienes that relies upon a simple condensation reaction of carboxamides and aldehydes.[8a]

Results and discussion

Aminodienes

Discovery. Over the past years, we have investigated the palladium-catalyzed amidocarbonylation of aldehydes with carboxamides and CO for the synthesis of *N*-acyl α-amino acids.[9] Detailed mechanistic studies on the nature of the employed amide–aldehyde mixture proved the formation of (1*E*,3*E*)-1-*N*-acylamino-2,4-dialkyl-1,3-butadienes (**1a**) as by-products under amidocarbonylation conditions (Scheme 3 and Fig. 1).[10] Obviously, **1a** does not form *via* a palladium-catalyzed reaction path but upon simple condensation of two molecules of aldehyde with the carboxamide.



Scheme 3 Palladium-catalyzed amidocarbonylation of propionaldehyde with acetamide at low catalyst loadings.

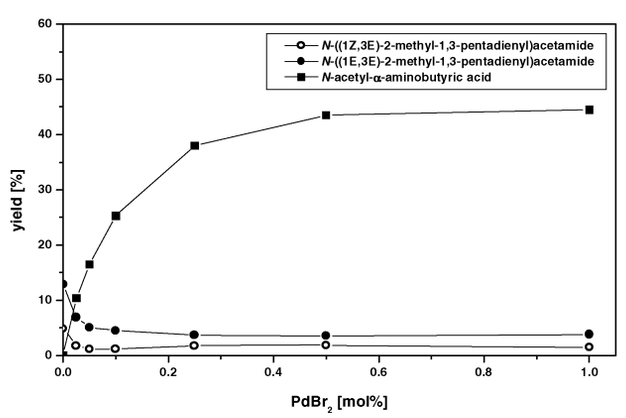
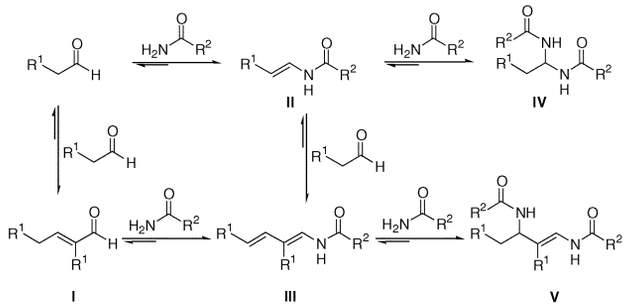


Fig. 1 Aminodienes as byproducts in the palladium-catalyzed amidocarbonylation of aldehydes.

Our interest in this class of 1-*N*-acylamino-2,4-dialkyl-1,3-butadienes (**1**) was largely fueled by two reasons. Firstly, we considered the inherent aminodiene structure an important building block for organic synthesis as the 1-*N*-acylamino-1,3-butadiene system obviously bears a conceptual relationship to the established Oppolzer–Overman dienes.[2] Secondly, the underlying one-pot procedure is unique in that it merely involves mixing of cheap carboxamide and aldehyde at elevated temperature.

Optimization. Studies on the condensation chemistry of amide–aldehyde mixtures indicated that both amidocarbonylation and aminodiene routes share the intermediacy of the same pool of equilibrating amide–aldehyde adducts (Scheme 4).[11] The generation of aminodienes of type **III** can generally proceed *via* intermediate α,β-unsaturated aldehyde or enamide species. The all-*trans* (1*E*,3*E*)-*N*-acylamino-2,4-dialkyl-1,3-butadiene (**III**) as the major product is usually accompanied by small amounts of the corresponding 1*Z*-isomer. The corresponding unsaturated aldehyde (**I**) and enamide (**II**) species are the most reactive compounds and only isolable from the reaction mixture when bearing bulky substituents on the amide or aldehyde. The 1,1-bis(amido) species (**IV**, amidal) is preferentially formed in less polar solvents such as chloroform and toluene. The 1,3-bis(amido)alkenes (**V**), that form upon amide addition to the intermediate *N*-acylimines at high temperatures, are generally very stable compounds.[12]



Scheme 4 Equilibrating amide–aldehyde condensation adducts.

On account of the presence of several equilibrating amide–aldehyde isomers, the optimization of the general procedure with respect to higher yields and selectivity toward the targeted aminodiene species was the prime objective of our research activities, as was the realization of generality by extending the scope of the reaction to other starting materials. Further investigations focused on the model reaction of acetamide with propionaldehyde. In screening experiments, principal reaction parameters such as temperature, reaction time, solvent, additives, ratio of reactants *etc.* were varied in order to ascertain their effect on the overall yield of aminodiene **1**. The presence of catalytic amounts of *p*-toluenesulfonic acid (TSA) and stoichiometric amounts of acetic anhydride (Ac_2O) were shown to be beneficial, with the latter almost doubling the yield. Fig. 2 illustrates the significantly higher yields under optimized conditions with 1 mol% *p*-TSA and 1 equivalent of Ac_2O.

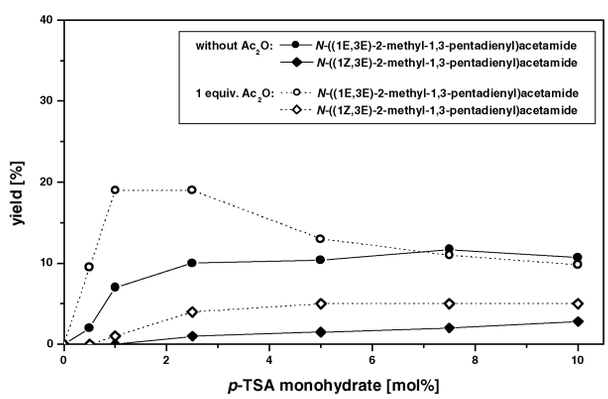
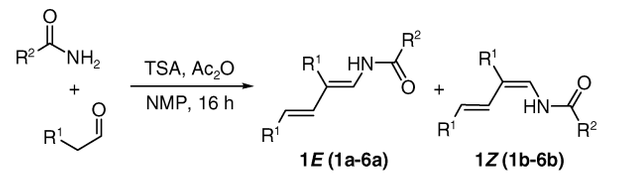


Fig. 2 Beneficial effect of stoichiometric Ac_2O and catalytic TSA.

Common Lewis acids were also employed in this protocol, but gave no superior results. Surprisingly, alternative dehydrating agents such as $HC(OMe)_3$, $(CF_3CO_2)O$, and Na_2SO_4 gave lower yields. The addition of extra water was found to reduce conversion by driving the equilibria back to the reactant side. Further screening experimentation revealed a strong influence of the reactant ratio. Hence, increasing the amide/aldehyde ratio from 1 : 1 to 3 : 1 in the presence of 1 equivalent of Ac_2O almost doubled the yield of *trans*-aminodiene **1a** (Fig. 3). The high reactivity of the aldehyde toward oligomerization likely accounts for the excess of acetamide required.

Interestingly, a strong solvent dependence was established. Solvents such as toluene, chloroform, and ethanol afforded the corresponding aminal (**IV**) as the main product under the aforementioned optimized reaction conditions, whereas amino-

Table 1 Synthesized 1-*N*-acylamino-2,4-dialkyl-1,3-butadienes



Entry	R^1	R^2	T/°C	(1*E*) : (1*Z*)	Σ yield [%]
1	Me	Me	100	8.2 : 1	42
2	Et	Me	100	4.2 : 1	39
3	*i*-Pr	Me	120	1 : 1.5	52
4	*n*-Hex	Me	120	5.3 : 1	53
5	Bn	Me	120	2.1 : 1	47
6	Et	Ph	120	1 : 1	42

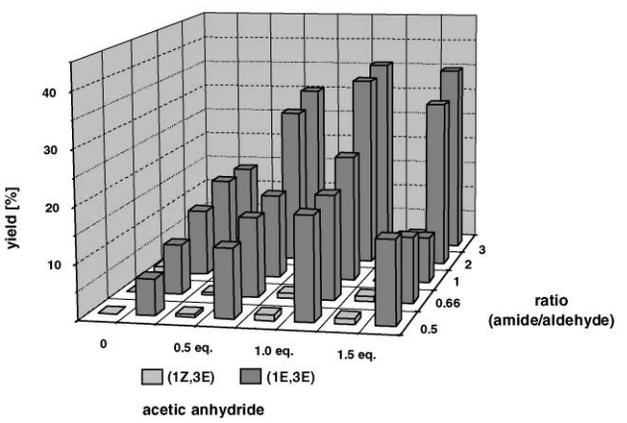


Fig. 3 Optimized yields with amide/aldehyde = 2 : 1.

diene formation was merely reduced in DMF and THF solution (< 20%). Employment of NMP (*N*-methyl-2-pyrrolidinone) proved pivotal and gave model compound **1a** in moderate yield (42% GC; 36% isolated).

An alternative route toward 1-*N*-acylamino-1,3-butadienes starting from α,β-unsaturated aldehydes parallels Smith's procedure for the synthesis of *N*-dienyl lactams. Model studies on the reaction of acetamide with 2-methyl-2-pentenal (the homo aldol condensation adduct of propionaldehyde) proved the presence of TSA was essential (2–3 mol%). Unlike with simple propionaldehyde, acetic anhydride was shown to significantly decrease the yield of aminodiene **1a**.[12b]

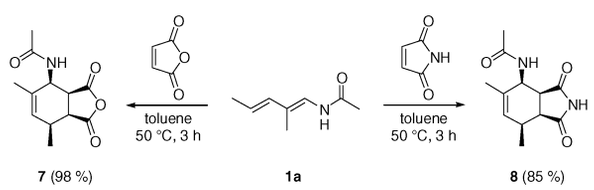
Synthesis. With the optimized set of conditions, a small series of 1,3-dialkyl substituted *N*-acylamino dienes were prepared by mixing aldehyde and amide at elevated temperature (Table 1). In all cases, two double bond isomers with respect to the enamide moiety (1*E*,1*Z*) were obtained. The overall yields cluster between 40–50% which is due to the presence of several other equilibrating amide–aldehyde adducts (see Scheme 4).

The bulkiness of the alkyl substituents significantly affects the observed *trans*/*cis* (1*E*/1*Z*) ratio. Linear alkyl substituents favor formation of the 1*E*-isomer, with isomer ratios ranging from 2 : 1 to 8 : 1. Bulky isopropyl groups were found to reverse the geometrical preference (entry 3). However, employment of benzamide and butyraldehyde afforded an equimolar ratio of both isomers (entry 6).

Computations. In addition to our experimental observations, we subjected double bond isomers of model compounds **1** and **3** to DFT-level full geometry optimizations.[13] Table 2 shows the data for the (1*E*) and (1*Z*) double bond isomers in their s-*cis* and s-*trans* conformations. The calculated enthalpies support the observed preferential formation of the all-*trans* isomer **1a**. The ΔE value of 0.6 kcal mol^{-1} between s-*trans* isomers of (1*E*,3*E*)- and (1*Z*,3*E*)-aminodienes results in a theoretical 2.7 : 1 ratio at 80 °C (referenced to thermodynamic equilibration). Although this suggests a significantly lower isomer ratio due to the neglect of solvent, stability, and other effects, it aligns with our experimental findings that rendered all-*trans* **1a** the major isomer. For bulkier acyl and alkyl substituents, the all-*trans* isomer is thermodynamically less favored, which is in full accord with the isomer ratios observed for dienes **3**, **5**, and **6**. Calculations on rotamers of isopropyl derivative **3** exhibit a significant preference for the 1*Z*,3*E* isomer which is due to steric repulsion.

Diels–Alder reactions

Synthesis. Encouraged by the advantageous use of substituted 1-aminodienes in Diels–Alder reactions for the synthesis of complex cyclic molecules, we set out to investigate model Diels–Alder additions in the presence of electron-deficient dienophiles. We thus subjected maleimide and maleic anhydride as powerful dienophiles to Diels–Alder conditions in the presence of all-*trans* *N*-acetylamino-2-methyl-1,3-pentadiene (**1a**). After 3 h at 50 °C, almost quantitative yields of the desired cyclohexene adducts **7** and **8** were isolated by silica gel chromatography (Scheme 5). The adducts were found to contain the fused rings in an *endo* configuration. In neither case were hetero Diels–Alder adducts observed. Owing to the *endo* addition of the dienophile to the all-*trans* (1*E*,3*E*)-amidodiene, all substituents on the cyclohexene ring adopt a *syn* position. Equivalent structures have been crystallographically confirmed.[8]



Scheme 5 Diels–Alder reaction of **1a** with maleic anhydride and maleimide.

Computations. DFT calculations[13] were performed on the model reaction of **1a** with maleimide. The calculated course of the reaction is in full agreement with the experimental data. The boat-like *endo* transition state is about 8 kcal mol^{-1} more stable than the corresponding *exo* TS, kinetically favoring the *endo* pathway by ~10^6. Furthermore, the *endo* adduct is also thermodynamically stabilized with respect to the *exo* isomer (Fig. 4).

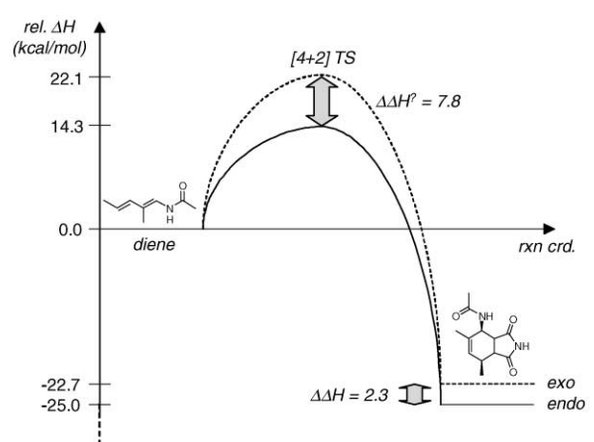
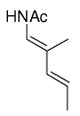
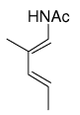
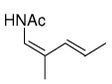
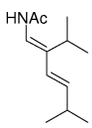
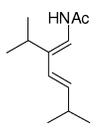
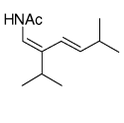
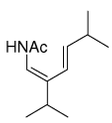


Fig. 4 DFT calculations on the reaction of **1a** with maleimide.

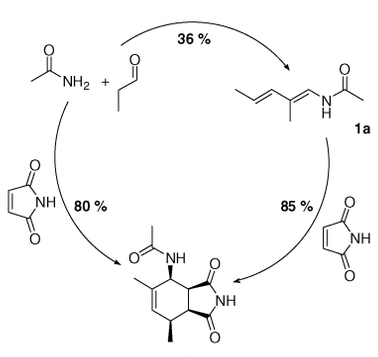
Multicomponent reactions. Over the last decades, an extensive amount of research has been dedicated to multicomponent reactions based on Diels–Alder chemistry which have spawned numerous examples of ravishing complex organic target syntheses.[14]

Table 2 DFT calculations on isomers of aminodiene **1**

				
Isomer	s-*trans*-1*E*,3*E*	s-*cis*-1*E*,3*E*	s-*trans*-1*Z*,3*E*	s-*cis*-1*Z*,3*E*
E_{tot} (au)	−442.64834	−442.64386	−442.64732	−442.64406
E_{rel} (kcal mol^{-1})	0.0	2.8	0.6	2.7
				
Isomer	s-*trans*-1*E*,3*E*	s-*cis*-1*E*,3*E*	s-*trans*-1*Z*,3*E*	s-*cis*-1*Z*,3*E*
E_{tot} (au)	−599.89543	−599.89264	−599.89691	−599.89746
E_{rel} (kcal mol^{-1})	0.0	1.8	−0.9	−1.3

As the preparation of 1-*N*-acylaminodiene species was regarded as rather troublesome with respect to the isolation procedure and yield, we looked for more efficient one-pot protocols which would obviate the isolation of the 1-*N*-acylaminodiene intermediate. Following our initial observations that acylaminodiene systems of type **1a** irreversibly undergo facile Diels–Alder additions to electron-deficient dienophiles, we investigated the corresponding one-pot process in the presence of aldehyde, carboxamide, and dienophile. Since the several equilibrium steps that are involved in the formation of the 1-*N*-acylaminodiene likely account for the moderate yields, a perturbation of the equilibria (Scheme 4) by *in situ* trapping of the aminodiene derivative with suitable dienophiles may have a beneficial effect on the overall yield.[11] Although all equilibrating aminodiene isomers can principally act as the diene component in Diels–Alder reactions, the minimal steric hindrance might kinetically favor consumption of the all-*trans* isomer.[15]

The synthesis of 4-(*N*-acylamino)-5,7-dialkyl-1,3-dioxo-*cis*-2,3,3a,4,7,7a-hexahydro-1*H*-isoindoles (**8**), *via* both the two-step and one-pot routes (Scheme 6), served as a model system. The stepwise procedure involved the isolation of **1a** followed by Diels–Alder addition to maleimide and gave an overall yield of 30% which is significantly impaired by the moderate yield of isolated **1a** (36%). Verifying our expectations, the multicomponent route afforded directly **8** in 80% yield. With more than doubled yield, this one-pot approach significantly outperforms the two-step route in efficiency as well as simplicity and involves nearly quantitative formation of intermediate aminodiene **1a** in *quasi* steady-state manner.



Scheme 6 Two-step *vs.* one-pot synthesis of adduct **8**.

As expected from kinetic considerations, the preparative studies on a series of multicomponent adducts revealed the preferential (> 95%) formation of the all-*syn* adducts *via* an *endo*-facial Diels–Alder reaction of the all-*trans* aminodiene isomer.[8]

Mechanistic investigations

In order to clarify the role of the different equilibrating species NMR experiments were performed with 1-^{13}C-propionaldehyde in the presence of acetamide, TSA, and Ac_2O. The sample was heated to 140 °C. Upon appearance of the resonances of 1,3-^{13}C-**1a**, maleimide was added which resulted in a clean conversion of the multicomponent mixture to the desired cycloadduct **8**. Fig. 5 illustrates selected recorded spectra.[16] The decrease of resonance intensity of 1-^{13}C-propionaldehyde (***A***; 203.6 ppm) obviously accounts for the appearance of several condensation adducts including 2-methyl-2-pentenal (***B***; 195.2 ppm, d, 6.68 Hz; 156.5 ppm, d, 6.68 Hz) and 1,1-bis(acetylamino)propane (***F***; 57.3 ppm). However, the latter and unassigned signals at 122 and 124 ppm disappear in favor of the aminodiene (**1a**) signals (***D***; 133.5 ppm, d, 5.72 Hz; 122.1 ppm, d, 5.72 Hz). Upon addition of maleimide (***C***; 172.8 ppm; 135.2 ppm), the spectra exhibit the almost exclusive formation of cycloadduct **8** (***E***; 126.4 ppm, d, 1.91 Hz; 48.2 ppm, d, 1.91 Hz) after 24 h (***S***, solvent resonances).

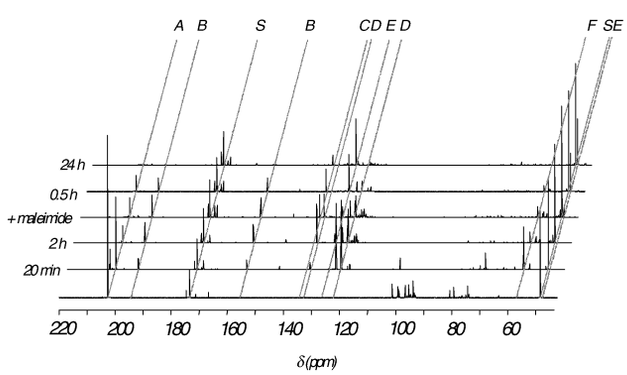


Fig. 5 NMR experiments with 1-^{13}C-propionaldehyde.

This and further experiments testify to the *quasi* steady-state behavior of the intermediate *N*-acetylamino-2-methylpentadiene (**1a**). While the primary condensation adducts (aldol, enamide, aminal *etc.*) were formed in the absence and presence of dienophilic maleimide, the latter conditions showed the formation of the desired cycloadduct in high yields, although only minor aminodiene formation has been observed by NMR.

Summary

The developed synthesis of substituted 1-acylamino-1,3-butadienes is unique in that aliphatic, non-olefinic starting materials (simple aldehydes, carboxamides) are employed for the construction of the diene backbone. The multicomponent one-pot synthesis is straightforward and exhibits noteworthy simplicity. The inherent selective telomerization of two aldehydes with one

amide molecule is especially remarkable when considering side reactions which are likely to proceed under the applied reaction conditions (further aldol condensations, oligomerizations *etc.*). The starting materials are among the most fundamental and widespread reagents in organic synthesis. They are commercially available, cheap, and easy to handle. Furthermore, the reaction tolerates the employment of off-shelf reactants, additives, and solvents without prior purification, as it does not require an inert atmosphere. However, the overall yields are still not satisfactory but *in situ* cycloaddition reactions with suitable dienophiles have been shown to proceed with high selectivity and excellent yields.[11]

Experimental

All reactions were run in ACE pressure tubes from Aldrich. NMP was distilled from CaH_2 and stored over 3 Å molecular sieves. Unless otherwise noted, all reagents were used as received from commercial suppliers.

Silica gel column chromatography was performed with 230–400 mesh ASTM silica gel from Merck. Mp were recorded on a Galen III (Cambridge Instruments) and are uncorrected. IR spectra of solids were recorded as KBr pellets on a Nicolet Magna 550, liquids were analyzed capillarily. MS were obtained on AMD 402/3 of AMD Intectra (EI, 70 eV). MA were performed by the Microanalytical Laboratory, Department of Chemistry at the University of Rostock on a C/H/N/S analyzer by Leco. NMR data were recorded on a Bruker ARX 400 with QNP probe head (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C. GC analyses were performed on an HP 6890 equipped with an HP-5 capillary column (5% phenylmethylsiloxane, L = 30 m, d = 250 µm, d_{film} = 0.25 µm) and an FID detector. Quantitative GC analyses were referenced to internal diethylene glycol dibutyl ether.

General procedure for preparation of amidodienes 1–6

Aldehyde (15 mmol), amide (15 mmol), acetic anhydride (1.45 mL, 15 mmol), and *p*-TSA·H_2O (29 mg, 1 mol%) were heated for 16 h at elevated temperature (see Table 1). Silica gel chromatography (*n*-heptane–ethyl acetate) afforded *N*-((1*E*,3*E*)- (**1**–**6a**) and *N*-((1*Z*,3*E*)-2-alkyl-1,3-butadienyl)amides (**1**–**6b**).

N-(2-Methyl-1,3-pentadienyl)acetamides (1)

***N*-((1*E*,3*E*)-2-Methyl-1,3-pentadienyl)acetamide (1a).** Yield: 36% (white solid); R_f: 0.33 (H/EA 1 : 2). Mp: 53 °C (MA). IR (KBr): 3301 vs, 1664 vs, 1638 vs, 1508 vs, 1368 s, 1266 vs, 1236 vs, 1167 s, 960 vs, 717 m, 604 m. MS (EI): 139 ([**1a**]$^+$, 100%); 97 ([**1a**-Ac]$^+$, 55%); 82 ([**1a**-AcNH]$^+$, 76%); 57 ([AcNH]$^+$, 12%); 43 ([Ac]$^+$, 42%); no other peaks of > 10%. HRMS for $C_8H_{13}NO$: calcd. 139.0997; found 139.0966. MA for $C_8H_{13}NO$: calcd. C, 69.03; H, 9.41; N, 10.06; found C, 69.4; H, 9.21; N, 10.11%.

^{1}H (DMSO-d_6): δ 9.30 (d, 1H, 10.5 Hz, N*H*); 6.60 (d, 1H, 10.5 Hz, C*H*NH); 6.03 (d, 1H, 15.3 Hz, *H*C=CHMe); 5.44 (td, 1H, 5.8/15.3 Hz, C*H*Me); 1.96 (s, 3H, *Me*CO); 1.71 (d, 3H, 5.8 Hz, *Me*CH); 1.70 (s, 3H, *Me*C=). ^{13}C{^{1}H} (DMSO-d_6): δ 167.4 (*C*O); 133.5 (*C*H=CHMe); 122.1 (*C*HNH); 120.4 (*C*HMe); 115.8 (Me*C*=); 22.6 (*Me*CO); 18.1 (*Me*CH); 11.3 (*Me*C=).

***N*-((1*Z*,3*E*)-2-Methyl-1,3-pentadienyl)acetamide (1b).** Yield: 5% (colorless oil); R_f: 0.38 (H/EA 1 : 2). IR (KBr): 3269 vs, 2964 s, 2931 s, 1738 vs, 1659 vs, 1513 vs, 1450 vs, 1371 m, 1274 vs, 1222 m, 1173 m, 1069 m, 1011 s. MS (EI): 139 ([**1b**]$^+$, 93%); 97 ([**1b**-Ac]$^+$, 100%); 82 ([**1b**-AcNH]$^+$, 85%); 57 ([AcNH]$^+$, 22%); 43 ([Ac]$^+$, 65%); no other peaks of > 10%. HRMS for $C_8H_{13}NO$: calcd. 139.0997; found 139.0974. MA for $C_8H_{13}NO$: calcd. C, 69.03; H, 9.41; N, 10.06; found C, 69.41; H, 9.01; N, 10.22%.

^{1}H (DMSO-d_6): δ 9.51 (d, 1H, 10.5 Hz, N*H*); 6.62 (d, 1H, 15.0 Hz, *H*C=CHMe); 6.41 (d, 1H, 10.5 Hz, C*H*NH); 5.54 (dt, 1H, 6.6/15.0 Hz, HC=C*H*Me); 1.94 (s, 3H, *Me*CO); 1.78 (d, 3H, 6.6 Hz, *Me*CH=); 1.67 (s, 3H, *Me*C=). ^{13}C{^{1}H} (DMSO-d_6): δ 167.0 (*C*O); 128.6 (*C*H=CHMe); 124.8 (*C*HNH); 121.9 (=*C*HMe); 119.2 (Me*C*=); 22.5 (*Me*CO); 22.1 (*Me*CH=); 13.8 (*Me*C=).

N-(2-Ethyl-1,3-hexadienyl)acetamides (2):

***N*-((1*E*,3*E*)-2-Ethyl-1,3-hexadienyl)acetamide (2a).** Yield 31% (white solid); R_f: 0.43 (H/EA 2 : 1). Mp: 58 °C (MA). IR (KBr): 3280 s, 2966 s, 2932 m, 2872 m, 1666 s, 1644 vs, 1626 s, 1515 vs, 1371 m, 1270 s, 1161 m, 961 m, 869 w, 604 w. MS (EI): 167 ([**2a**]$^+$, 44%); 125 ([**2a**-Ac]$^+$, 25%); 124 ([**2a**-Ac]$^+$, 37%); 110 ([**2a**-AcNH]$^+$, 100%); 96 ([**2a**-Ac-Et]$^+$, 64%); 43 ([Ac]$^+$, 60%); no other peaks of > 10%. HRMS for $C_{10}H_{17}NO$: calcd. 167.1310; found 167.1317. MA for $C_{10}H_{17}NO$: calcd. C, 71.81; H, 10.25; N, 8.37; found C, 71.48; H, 10.22; N, 8.00%.

^{1}H (DMSO-d_6): δ 9.32 (d, 1H, 10.7 Hz, N*H*); 6.57 (d, 1H, 10.7 Hz, C*H*NH); 5.88 (d, 1H, 15.6 Hz, *H*C=CHEt); 5.51 (dt, 1H, 6.6/15.6 Hz, C*H*Et); 2.23 (q, 2H, 7.5 Hz, CH_2C=); 2.06 (dt, 2H, 0.8/7.5 Hz, CH_2CH=); 1.97 (s, 3H, *Me*CO); 0.95 (t, 3H, 7.5 Hz, *Me*CH$_2$CH=); 0.93 (t, 3H, 7.5 Hz, *Me*CH$_2$C=). ^{13}C{^{1}H} (DMSO-d_6): δ 167.4 (*C*O); 129.7 (*C*H=CHEt); 127.0 (*C*HEt); 121.8 (Et*C*=); 121.4 (*C*HNH); 25.5 (*C*H$_2$CH); 22.6 (*Me*CO); 17.9 (*C*H$_2$C=); 14.0 (*Me*CH$_2$CH); 13.0 (*Me*CH$_2$C=).

***N*-((1*Z*,3*E*)-2-Ethyl-1,3-hexadienyl)acetamide (2b).** Yield: 8% (colorless oil); R_f: 0.50 (H/EA 2 : 1). IR (KBr): 3289 vs, 3015 m, 2961 s, 2930 s, 2871 m, 1662 vs, 1644 vs, 1632 vs, 1522 vs, 1371 m, 1274 vs, 1222 m, 1163 m, 963 s, 872 m, 728 m, 609 m. MS (EI): 167 ([**2b**]$^+$, 37%); 125 ([**2b**-Ac]$^+$, 25%); 124 ([**2b**-Ac]$^+$, 37%); 110 ([**2b**-AcNH]$^+$, 100%); 96 ([**2b**-Ac-Et]$^+$, 67%); 43 ([Ac]$^+$, 91%); no other peaks of > 10%. HRMS for $C_{10}H_{17}NO$: calcd. 167.1310; found 167.1296. MA for $C_{10}H_{17}NO$: calcd. C, 71.81; H, 10.25; N, 8.37; found C, 71.13; H, 10.39; N, 7.83%.

^{1}H (DMSO-d_6): δ 9.48 (d, 1H, 10.5 Hz, N*H*); 6.49 (d, 1H, 15.5 Hz, *H*C=CHEt); 6.44 (d, 1H, 10.5 Hz, C*H*NH); 5.53 (dt, 1H, 6.8/15.5 Hz, C*H*Et); 2.08–2.14 (m, 4H, CH_2); 1.95 (s, 3H, *Me*CO); 1.04–0.95 (m, 6H, *Me*CH$_2$). ^{13}C{^{1}H} (DMSO-d_6): δ 167.2 (*C*O); 130.2 (*C*HEt); 123.8 (*C*H=CHEt); 119.6 (Et*C*=); 118.6 (*C*HNH); 25.9 (*C*H$_2$CH); 23.7 (*C*H$_2$C=); 22.6 (*Me*CO); 14.0 (*Me*CH$_2$CH); 13.7 (*Me*CH$_2$C=).

N-(5-Methyl-2-isopropyl-1,3-hexadienyl)acetamides (3)

***N*-((1*E*,3*E*)-5-Methyl-2-isopropyl-1,3-hexadienyl)acetamide (3a).** Yield: 21% (white solid); R_f: 0.29 (H/EA 1 : 2). Mp: 69–71 °C. IR (KBr): 3282 s, 2956 s, 2931 s, 2869 m, 1661 vs, 1626 vs, 1509 vs, 1465 m, 1374 s, 1276 s, 1175 m, 1063 m, 966 m. MS (EI): 195 ([**3a**]$^+$, 26%); 152 ([**3a**-Ac]$^+$, 53%); 138 ([**3a**-Ac-NH]$^+$, 100%); 121 ([**3a**-74]$^+$, 96%); 110 ([**3a**-Ac-isopropyl]$^+$, 75%); 93 ([**3a**-AcNH-isopropyl]$^+$, 45%); 68 (18%); 43 ([Ac]$^+$, 39%); no other peaks of > 10%. HRMS for $C_{12}H_{21}NO$: calcd. 195.1623; found 195.1622.

^{1}H (DMSO-d_6): δ 9.26 (d, 1H, 10.5 Hz, N*H*); 6.54 (d, 1H, 10.5 Hz, C*H*NH); 5.79 (d, 1H, 15.7 Hz, *H*C=CH–iPr); 5.60 (dd, 1H, 6.9/15.7 Hz, =C*H*-iPr); 2.93 (sept, 1H, 6.9 Hz, Me$_2$C*H*C=); 2.28 (oct, 1H, 6.7 Hz, Me$_2$C*H*CH=); 1.95 (s, 3H, *Me*CO); 1.00 and 0.96 (d, 12H, 6.7 Hz, *Me*$_2$CH). ^{13}C{^{1}H} (DMSO-d_6): δ 167.5 (*C*O); 135.1 (=*C*H-iPr); 125.4 (=*C*-iPr); 124.5 (*C*H=CH–iPr); 117.7 (*C*HNH); 31.0 (Me$_2$*C*HCH=); 25.9 (Me$_2$*C*HC=); 22.6 (*Me*CO); 22.5 and 20.7 (*Me*$_2$CH).

***N*-((1*Z*,3*E*)-5-Methyl-2-isopropyl-1,3-hexadienyl)acetamide (3b).** Yield: 31% (white solid); R_f: 0.35 (H/EA 2 : 1). Mp: 57–60 °C. IR (KBr): 3241 s, 2963 vs, 2930 s, 2867 m, 1659 vs, 1638 vs, 1620 vs, 1527 vs, 1465 s, 1371 s, 1288 vs, 1235 w, 1182 s, 1066 s, 983 s, 972 s, 863 m. MS (EI): 195 ([**3b**]$^+$, 58%); 152 ([**3b**-Ac]$^+$, 58%); 138 ([**3b**-AcNH]$^+$, 95%); 121 ([**3b**-74]$^+$, 100%); 110 ([**3b**-

Ac-isopropyl]$^+$, 68%); 93 ([**3b**-AcNH-isopropyl]$^+$, 68%); 68 (68%); 43 ([Ac]$^+$, 91%); no other peaks of > 10%. HRMS for $C_{12}H_{21}NO$: calcd. 195.1623; found 195.1618.

^{1}H (DMSO-d_6): δ 9.42 (d, 1H, 10.3 Hz, N*H*); 6.47 (d, 1H, 10.3 Hz, C*H*NH); 6.44 (d, 1H, 15.6 Hz, C*H*=CH–iPr); 5.66 (dd, 1H, 7.3/15.6 Hz, C*H*–iPr); 2.57 (sept, 1H, 6.7 Hz, Me_2CHC=); 2.38 (oct, 1H, 6.7 Hz, Me_2CHCH); 1.96 (s, 3H, *Me*CO); 1.01 (d, 12H, 6.7 Hz, Me_2CH). ^{13}C{^{1}H} (DMSO-d_6): δ 167.3 (*C*O); 135.3 (=*C*H–iPr); 123.8 (=*C*–iPr); 121.7 (*C*H=CH–iPr); 117.4 (*C*HNH); 31.6 (Me_2*C*HCH); 27.2 (Me_2*C*HC=); 22.6 (*Me*CO); 22.8 and 22.4 (Me_2CH).

N-(2-n-Hexyl-1,3-decadienyl)acetamides (4)

***N*-((1*E*,3*E*)-2-n-Hexyl-1,3-decadienyl)acetamide (4a).** Yield: 44% (white solid); R_f: 0.45 (H/EA 1 : 2). Mp: 68 °C (MA). IR (KBr): 3299 s, 2965 vs, 2941 vs, 2870 vs, 1739 m, 1647 vs, 1515 vs, 1467 vs, 1374 s, 1270 vs, 960 s, 724 w. MS (EI): 279 ([**4a**]$^+$, 60%); 236 ([**4a**-Ac]$^+$, 67%); 166 ([**4a**-Ac-C_5H_{11}]$^+$, 92%); 149 ([**4a**-Ac-C_6H_{13}]$^+$, 45%); 43 ([Ac]$^+$, 100%); no other peaks of > 10%. HRMS for $C_{18}H_{33}NO$: calcd. 279.2562; found 279.2559.

^{1}H (acetone-d_6): δ 8.64 (d, 1H, 10.1 Hz, N*H*); 6.73 (d, 1H, 10.1 Hz, C*H*NH); 5.94 (d, 1H, 15.5 Hz, *H*C=CHCH$_2$); 5.52 (dt, 1H, 6.9/15.5 Hz, =C*H*CH$_2$); 2.24 (dd, 2H, 7.8/7.8 Hz, CH_2C=); 2.08 (m, 2H, C$H_2C_5H_{11}$); 1.95 (s, 3H, *Me*CO); 1.45–1.25 (bm, 16H, MeC$_4H_8$); 0.86 (m, 6H, *Me*CH$_2$). ^{13}C{^{1}H} (acetone-d_6): δ 167.6 (*C*O); 131.9 (=*C*HCH$_2$); 126.6 (*C*H=CHCH$_2$); 122.6 (*C*HNH); 121.4 (CH$_2$*C*=); 33.5, 32.5, 32.3, 30.4, 30.1, 28.9, and 26.0 (Me*C*$_4$H$_8$); 23.2 and 23.1 (*C*H$_2$C$_5$H$_{11}$); 22.8 (*Me*CO); 14.2 (*Me*CH$_2$).

***N*-((1*Z*,3*E*)-2-n-Hexyl-1,3-decadienyl)acetamide (4b).** Yield: 9% (colorless oil); R_f: 0.5 (H/EA 1 : 2). IR (KBr): 3313 w, 2961 vs, 2935 vs, 2870 vs, 1739 m, 1679 s, 1654 vs, 1521 m, 1466 s, 1376 s, 1246 m, 724 w. MS (EI): 279 ([**4b**]$^+$, 40%); 236 ([**4b**-Ac]$^+$, 46%); 166 ([**4b**-Ac-C_5H_{11}]$^+$, 46%); 149 ([**4b**-Ac-C_6H_{13}]$^+$, 26%); 43 ([Ac]$^+$, 100%); no other peaks of > 10%. HRMS for $C_{18}H_{33}NO$: calcd. 279.2562; found 279.2560.

^{1}H (acetone-d_6): δ 8.82 (bs, 1H, N*H*); 6.59 (d, 1H, 10.1 Hz, C*H*NH); 6.41 (d, 1H, 15.5 Hz, C*H*=CHC$_6$H$_{13}$); 5.69 (dt, 1H, 6.8/15.5 Hz, =C*H*C$_6$H$_{13}$); 2.08–2.20 (m, 4H, C$H_2C_5H_{11}$); 1.98 (s, 3H, *Me*CO); 1.50–1.20 (bm, 16H, MeC$_4H_8$); 0.88 (m, 6H, *Me*CH$_2$). ^{13}C{^{1}H} (acetone-d_6): δ 167.3 (*C*O); 130.1 (=*C*HCH$_2$); 125.0 (*C*H=CHCH$_2$); 119.9 (*C*HNH); 119.1 (CH$_2$*C*=); 34.7, 32.9, 32.8, 32.7, 30.8, 30.3, 30.2, and 30.0 (Me*C*$_4$H$_8$); 23.2 and 23.1 (*C*H$_2$C$_5$H$_{11}$); 22.6 (*Me*CO); 14.2 (*Me*CH$_2$).

N-(2-Benzyl-5-phenyl-1,3-pentadienyl)acetamides (5)

***N*-((1*E*,3*E*)-2-Benzyl-5-phenyl-1,3-pentadienyl)acetamide (5a).** Yield: 32% (white solid); R_f: 0.31 (H/EA 2 : 1). Mp: 102 °C (EA). IR (KBr): 3292 m, 3026 w, 2928 w, 1654 vs, 1522 vs, 1495 vs, 1371 s, 1274 m, 747 m, 699 vs. MS (EI): 291 ([**5a**]$^+$, 97%); 248 ([**5a**-Ac]$^+$, 22%); 232 ([**5a**-AcNH]$^+$, 37%); 200 ([**5a**-Bn]$^+$, 28%); 158 ([**5a**-Ac-Bn]$^+$, 100%); 141 ([**5a**-AcNH-Bn]$^+$, 37%); 128 (18%); 91 ([Bn]$^+$, 70%); 43 ([Ac]$^+$, 24%); no other peaks of > 10%. HRMS for $C_{20}H_{21}NO$: calcd. 291.1623; found 291.1637.

^{1}H (DMSO-d_6): δ 9.70 (d, 1H, 11 Hz, N*H*); 7.10–7.30 (bm, 8H, *o*- and *m*-Ph); 6.99 (d, 2H, 6.9 Hz, *p*-Ph); 6.92 (d, 1H, 11 Hz, C*H*NH); 6.09 (d, 1H, 15.2 Hz, C*H*=CHCH$_2$); 5.49 (dt, 1H, 6.9/15.2 Hz, =C*H*CH$_2$); 3.67 (s, 2H, CH_2C=); 3.28 (d, 2H, 6.9 Hz, =CHCH_2); 1.99 (s, 3H, *Me*CO). ^{13}C{^{1}H} (DMSO-d_6): δ 167.8 (*C*O); 140.6 and 139.6 (*ipso*-Ph); 132.2, 128.2, 128.1, and 127.9 (*o*-Ph); 125.7 and 125.4 (*m*-Ph); 124.4 (*p*-Ph); 118.1 (CH$_2$*C*=); 38.3 (=CH*C*H$_2$); 30.8 (*C*H$_2$C=); 22.6 (*Me*CO).

***N*-((1*Z*,3*E*)-2-Benzyl-5-phenyl-1,3-pentadienyl)acetamide (5b).** Yield: 15% (colorless oil); R_f: 0.42 (H/EA 2 : 1). Mp: 91–93 °C (MA). IR (KBr): 3237 s, 3025 m, 1664 s, 1645 vs, 1628 vs, 1517 vs, 1493 vs, 1452 vs, 1369 s, 1288 vs, 1147 s, 983 vs, 738 vs, 728 vs, 696 vs. MS (EI): 291 ([**5b**]$^+$, 82%); 248 ([**5b**-Ac]$^+$, 21%); 232 ([**5b**-AcNH]$^+$, 35%); 200 ([**5b**-Bn]$^+$, 27%); 158 ([**5b**-Ac-Bn]$^+$, 100%); 141 ([**5b**-AcNH-Bn]$^+$, 37%); 128 (20%); 91 ([Bn]$^+$, 73%); 43 ([Ac]$^+$, 26%); no other peaks of > 10%. HRMS for $C_{20}H_{21}NO$: calcd. 291.1623; found 291.1639.

^{1}H (DMSO-d_6): δ 9.69 (d, 1H, 10.5 Hz, N*H*); 7.10–7.30 (bm, 8H, *o*- and *m*-Ph); 7.03 (d, 2H, 6.9 Hz, *p*-Ph); 6.73 (d, 1H, 15.5 Hz, C*H*=CHCH$_2$); 6.56 (d, 1H, 10.5 Hz, C*H*NH); 5.68 (dt, 1H, 7.4/15.5 Hz, =C*H*CH$_2$); 3.45 (s, 2H, CH_2C=); 3.38 (d, 2H, 7.4 Hz, =CHCH_2); 1.99 (s, 3H, *Me*CO). ^{13}C{^{1}H} (DMSO-d_6): δ 167.4 (*C*O); 140.4 and 140.3 (*ipso*-Ph); 128.3 and 128.1 (*o*-Ph); 126.0, 125.9, and 125.8 (*m*- and *p*-Ph); 122.0 (*C*HNH); 116.9 (CH$_2$*C*=); 38.8 (=CH*C*H$_2$); 37.0 (*C*H$_2$C=); 22.6 (*Me*CO).

N-((3*E*)-2-Ethyl-1,3-hexadienyl)benzamides (6)

Yield: 42% (inseparable 1 : 1 mixture of (1*E*) and (1*Z*) isomers, yellowish paste); R_f: 0.45 (H/EA 1 : 2). IR (KBr): 3316 br vs, 3066 w, 2964 vs, 2933 m, 2874 m, 1717 m, 1644 vs, 1602 w, 1579 m, 1508 m, 1483 m, 1377 w, 1277 m, 1169 w, 1070 m, 1027 w, 963 w, 797 w, 710 m, 692 m. MS (EI): 229 ([**6**]$^+$, 28%); 200 ([**6**-Et]$^+$, 5%); 174 (7%); 124 ([**6**-Bz]$^+$, 31%); 105 ([Bz]$^+$, 100%); 77 ([Ph]$^+$, 73%); 51 (16%). HRMS: calcd. for $C_{15}H_{19}NO$: 229.14666; found 229.14636.

^{1}H (DMSO-d_6): δ 9.82 (d, 1H, 9.7 Hz, N*H*); 9.62 (d, 1H, 10.1 Hz, N*H*); 7.88 and 7.86 (2d, 4H, 7.9/7.9 Hz, *o*-Ph); 7.55 (m, 2H, *p*-Ph); 7.48 (m, 4H, *m*-Ph); 6.81 (d, 1H, 10.1 Hz, C*H*NH); 6.71 (d, 1H, 14.6 Hz); 6.67 (d, 1H, 9.4 Hz); 5.99 (d, 1H, 15.6 Hz); 5.73–5.57 (m, 2H); 2.40 (q, 2H, 7.4 Hz); 2.23–2.08 (m, 6H); 1.06 (t, 3H, 7.4 Hz); 1.00 and 0.98 (2t, 6H, 7.2/7.2 Hz, *Me*). ^{13}C{^{1}H} (DMSO-d_6): δ 164.9 and 164.8 (*C*O); 134.0 (*ipso*-Ph); 131.5, 131.4, 130.6, 129.7, 128.1, 128.0, 127.9, 127.8, 124.6 (*C*H); 124.3 and 122.4 (Et*C*=); 121.8 and 119.0 (*C*H); 25.9, 25.5, 24.0, 18.1 (*C*H$_2$); 14.0, 13.9, 13.7, and 13.1 (*Me*). ^{15}N{^{1}H} (DMSO-d_6): δ −252.6 and −251.4.

3-(*N*-Acetylamino)-4,6-dimethyl-*cis*-1,2,3,6-tetrahydrophthalic anhydride (7)

Yield: 98% (white solid). R_f: 0.25 (H/EA 1 : 2). Mp: 143 °C (EA). IR (KBr) 3411 s, 2974 m, 2942 m, 2918 w, 2882 w, 1771 s, 1681 s, 1530 s, 1179 s, 979 s, 920 s. MS (CI): 238 ([**7**]$^+$, 99%); 196 ([**7**-Ac]$^+$, 100%); no other peaks of > 8%. HRMS for $C_{12}H_{15}NO_4$: calcd. 237.10050. Found: 237.10011.

^{1}H ($CDCl_3$) 6.88 (d, 8.6 Hz, 1H, N*H*); 5.48 (m, 1H, C*H*=C); 4.80 (m, 1H, NHC*H*); 3.46 (dd, 5.3/9.4 Hz, 1H, NHCHC*H*); 3.32 (dd, 7.5/9.5 Hz, 1H, CH$_3$CHC*H*); 2.55 (m, 1H, CH$_3$-C*H*CH); 2.12 (s, 3H, C*H*$_3$CO); 1.71 (s, 3H, C*H*$_3$C=CH); 1.36 (d, 7.4 Hz, 3H, C*H*$_3$CHCH). ^{13}C{^{1}H} 173.9 (CH$_3$*C*O); 170.2 and 170.0 (*C*OO*C*O); 138.4 (*C*=CH); 127.7 (C=*C*H); 47.1 (NH*C*H); 45.9 and 45.0 (NCH*C*H and CH$_3$CH*C*H); 30.0 (CH$_3$*C*HCH); 23.2 (*C*H$_3$CO); 18.5 (*C*H$_3$C=CH); 16.4 (*C*H$_3$CHCH).

4-(*N*-Acetylamino)-5,7-dimethyl-1,3-dioxo-*cis*-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole (8)

Yield: 85% (white solid). R_f: 0.40 (H/EA 1 : 2). Mp: 218 °C (EA). IR (KBr): 3387 s, 3135 m, 3045 s, 2771 m, 1773 m, 1712 vs, 1657 vs, 1522 vs, 1358 m, 1333 m, 1177 m. MS (EI): 236 ([**8**]$^+$, 3%); 193 ([**8**-Ac]$^+$, 100%); 122 ([**8**-Ac-CONHCO]$^+$, 36%); 97 ([maleimide]$^+$, 13%); 43 ([Ac]$^+$, 20%); no other peaks of > 10%. HRMS for $C_{12}H_{16}N_2O_3$: calcd. 236.1160; found 236.1150.

^{1}H (DMSO-d_6): 11.20 (s, 1H, CON*H*CO); 7.71 (d, 8.9 Hz, 1H, CH$_3$CON*H*); 5.35 (s, 1H, C=C*H*); 4.48 (m, 1H, NHC*H*); 3.16 (dd, 5.9/8.5 Hz, 1H, NHCHC*H*); 2.99 (dd, 7.5/8.5 Hz, 1H, CH$_3$CHC*H*); 2.39 (m, 1H, CH$_3$C*H*CH); 1.96 (s, 3H, C*H*$_3$-CO); 1.59 (s, 3H, C*H*$_3$C=CH); 1.21 (d, 7.3 Hz, 3H, C*H*$_3$CHCH). ^{13}C{^{1}H} 180.2 and 178.6 (*C*ONH*C*O); 169.3 (CH$_3$*C*O); 137.5 (*C*=CH); 126.9 (C=*C*H); 47.6 (NH*C*H); 45.1 and 45.2 (NHCH*C*H and CH$_3$CH*C*H); 29.6 (CH$_3$*C*HCH); 22.8 (*C*H$_3$CO); 18.3 (*C*H$_3$C=CH); 16.8 (*C*H$_3$CHCH).

NMR experiments

A screw-cap NMR tube was cooled to 0 °C and charged with acetamide (30 mg, 0.5 mmol), *p*-TSA (2 mg, 2 mol%), NMP (0.5 mL), DMSO-d_6 (0.05 mL), Ac_2O (47 μL, 0.5 mmol), and 1-^{13}C-propionaldehyde (30 mg, 0.5 mmol). The mixture was heated to 140 °C, and intervallic ^{13}C NMR spectra were recorded at 25 °C. Upon appearance of the *N*-acetylaminodiene resonances (~ 4 h), maleimide (74 mg, 0.75 mmol) was added, and the mixture was further heated and intervallic NMR spectra were recorded.

Acknowledgements

We thank S. Giertz and Dr C. Fischer (both IfOK) for excellent technical assistance. Generous financial support from the state of Mecklenburg-Western Pomerania and the BMBF is gratefully acknowledged.

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12 For synthesis and characterization of other amide–aldehyde adducts, see: (*a*) A. Jacobi von Wangelin, PhD thesis, Universität Rostock, 2002; (*b*) D. Gördes, PhD thesis, Universität Rostock, 2002.

13 All geometries were first optimized at the *ab initio* HF/3-21G level of theory and then refined at the B3LYP/6-31G(d) density functional level of theory. Optimized stationary points on the potential energy surface were characterized as energy minima with only real frequencies order, transition state with only one imaginary frequency at the HF/3-21G level. This frequency calculation provides also the zero-point energies (ZPE, scaled by 0.89) for correcting the calculated relative energies. The final energies for discussion are the single-point energies at the B3LYP/6-311+G(d,p) level with the B3LYP/6-31G(d) geometries, including the ZPE corrections. All calculations were performed using the Gaussian 98 program. For further details, see Supporting Information of ref. 8*a*.

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15 Although thermodynamics favor isopropyl-substituted aminodiene **3** in its 1*Z*-isomeric form, multicomponent Diels–Alder additions to maleimide resulted in the exclusive formation of the all-*syn* product, thus testifying to the kinetic preference for the 1*E*-aminodiene. See also ref. 8*a*.

16 Intervallic ^{13}C NMR experiments were performed at 25 °C. For details, see Experimental section.