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A FACILE AND CONVENIENT SYNTHESIS OF 1,2,3,6-TETRAHYDROPYRIDAZINES USING AZODICARBOXYLATES UNDER LANTHANUM TRIFLATE CATALYSIS

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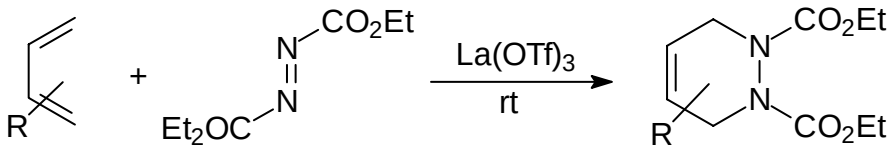
Abstract - The hetero-Diels-Alder reaction catalyzed by lanthanum triflate hydrate using diethyl azodicarboxylate as dienophile, yielding differently substituted 1,2,3,6-tetrahydropyridazines, is described.

The Diels-Alders reaction is one of the most useful method in synthetic organic chemistry. The use of azo compounds in this process has been known for over seventy years and different types of cyclic and acyclic azodienophiles have been widely employed.[1] In particular, azodicarboxylates are very reactive and have been used in combination with many kinds of dienes to synthetize pyridazine heterocycles. The reaction of diethyl azodicarboxylate (DEAD) with cyclopentadiene, described by Diels and coworkers in 1925, is of historical importance as it is one of the first examples of a [4+2] cycloaddition process.[2] Generally the hetero-Diels-Alder reactions between dienes and azodicarboxylate dienophiles are thermally or photochemically promoted;[1-3] during the last decades it has also been reported that microwave irradiation accelerates reaction rates and yields.[4]

In the last fifteen years lanthanide triflates have been found as unique Lewis acids, able to effectively promote several carbon-carbon and carbon-heteroatom bond formation reactions in aqueous media.[5] $Sc(OTf)_3$ has been employed in the Diels-Alder reaction,[6] while other $Ln(OTf)_3$ has been successfully employed for aza-Diels-Alder reactions, using different dienes and imines, generated *in situ* from aldehydes and benzylamine hydrochloride or phenylalanine methyl ester, as dienophiles.[7] More recently lanthanide complexes other than triflates, including chiral ones, have been also employed for the same purpose.[8]

As a part of our ongoing efforts to investigate the use of $Ln(OTf)_3$ as catalysts in solvent-free conditions, we recently reported the high yielding synthesis of 1,5-benzodiazepine derivatives catalyzed by $Yb(OTf)_3$.[9] Herein we wish to report the application of $La(OTf)_3$ hydrate catalysis to the hetero-Diels-Alder reaction using DEAD as dienophile to synthetize differently substituted 1,2,3,6-tetrahydropyridazines, whose structure is incorporated in a lot of natural and biologically active compounds (Scheme 1).[10]



Scheme 1

The reaction was carried out in solvent-free conditions for 30 min using diene (1.0 mmol) and DEAD (1.0 mmol) in the presence of $La(OTf)_3$ hydrate (0.02 mmol) at room temperature. The results are summarized in the Table 1. The importance of adding the catalyst becomes evident when considering that, carrying out a trial experiment mixing DEAD and 2,3-dimethyl-1,3-butadiene alone under the same reaction conditions, after 30 min the Diels-Alder adduct was obtained in less than 15 % yield.

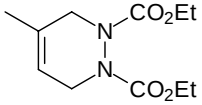
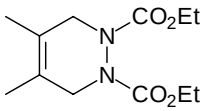
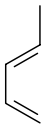
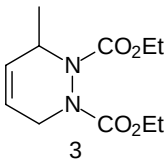
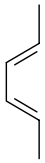
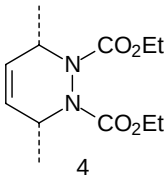
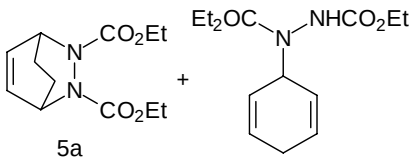
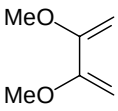
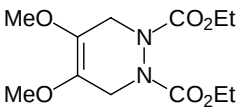
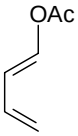
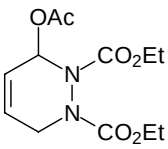
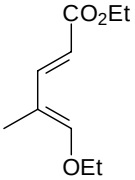
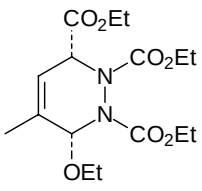
It's noteworthy that we obtained nearly quantitative yields in all cases and in particular in using alkoxy- and acetoxybutadienes: the corresponding Diels-Alder adducts (**6)** and (**7)** are in fact important intermediates for the synthesis of cyclitols, carbohydrates and related natural products.[11] Another synthon of natural and natural-derived biologically active compounds is the 1,2,3,6-tetrahydropyridazincarboxylate (**8)**; compounds of such a structure have been employed as precursors of 2,3,4,5-tetrahydropyridazine-3-carboxylic acids, constituents of antrimycins, aurantimycins, luzopeptins, quinoxapeptins and their semi-synthetic analogues, peptides and despeptides with antibiotic, antiviral and antitumour activities.[10a]

Using 1,3-cyclohexadiene as diene we obtained an equimolar mixture of the Diels-Alder adduct (**5a**) and (**5b**), derived from an ene reaction. This kind of reactivity of cyclohexadienes towards azodicarboxylates is however well documented in the literature.[3a,12]

Best results were obtained using just 0.02 equivalents of $La(OTf)_3$ hydrate: upper loading had no significant improvements. The catalyst, recovered by filtration from the reaction media could be reused several times without any loss of activity; the reaction to yield compound (**1)** has been repeated three

more times, through the catalyst washed with CH_2Cl_2 and dried at 70 °C for 2 h, with the following yields: 98%, 99%, 97%.

Table 1. $La(OTf)_3$ hydrate catalyzed hetero-Diels-Alder reaction

Diene	Product	Yield %[a]
	 1	99
	 2	99
	 3	99
	 4	98
	 5a + 1:1 5b	99
	 6	98
	 7	98
	 8	89

[a]Yields of pure isolated products, characterized by IR, GC-MS, ^1H NMR and ^{13}C NMR.

In summary an easy work-up procedure, mild conditions, short reaction times, the low loading and the complete recyclability of the catalyst and nearly quantitative yields make our methodology a valid and alternative contribution to the existing processes in the field of azo dienophiles based hetero-Diels-Alder reactions.

ACKNOWLEDGEMENT

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EXPERIMENTAL

General procedure: A mixture of diene (1.0 mmol) and diethyl azodicarboxylate (1.1 mmol) was well stirred with $La(OTf)_3$ hydrate (0.02 mmol) at rt for 30 min; CH_2Cl_2 was added to get $La(OTf)_3$ crystallized; the catalyst was filtered under reduced pressure and the residue purified by silica gel column chromatography using CH_2Cl_2 as eluent, yielding pure tetrahydropyridazine.

Diethyl 4-methyl-1,2,3,6-tetrahydro-1,2-pyridazincarboxylate (1): colorless oil; IR (cm^{-1}) 1710; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, 6H, *J* = 7.1 Hz), 1.73 (s, 3H), 3.59-3.88 (m, 2H), 4.11-4.25 (m, 2H), 4.32 (q, 4H, *J* = 7.1 Hz), 5.44-5.56 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.8, 155.7, 130.94, 117.61, 62.6, 62.4, 47.3, 47.0, 19.9, 14.5, 14.4; GC/MS: M^+ = 242. Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.56; H, 7.48; N, 11.58.

Diethyl 4,5-dimethyl-1,2,3,6,-tetrahydro-1,2-pyridazincarboxylate (2): colourless oil; IR; ^1H NMR;[13] ^{13}C NMR.[14] Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.87; N, 10.93. Found: C, 56.25; H, 7.85; N, 10.91.

Diethyl 3-methyl-1,2,3,6-tetrahydro-1,2-pyridazincarboxylate (3): colorless oil; IR (cm^{-1}) 1709; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17-1.35 (m, 9H), 3.66-3.79 (m, 2H), 4.07-4.25 (m, 4H), 4.35-4.41 (m, 1H), 5.61-5.83 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.8, 155.7, 129.12, 122.32, 62.0, 61,8, 50.1, 42.3, 18.2, 14.5, 14.4; GC/MS: M^+ = 242. Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.54; H, 7.46; N, 11.59.

Diethyl *cis*-3,6-dimethyl-1,2,3,6-tetrahydro-1,2-pyridazincarboxylate (4): colourless oil; IR (cm^{-1}) 1710; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19-1.38 (t, 6H, *J* = 7.0 Hz), 1.51-1.65 (d, 6H, *J* = 6.7 Hz), 4.03-4.28 (q, 4H, *J* = 7.0 Hz), 4.69-4.82 (m, 2H), 5-43-5.56 (m, 1H), 5.75-5.89 (m, 1H); ^{13}C NMR;[14] M^+ = 256. Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.87; N, 10.93. Found: C, 56.27; H, 7.84; N, 10.90.

Diethyl 2,3-diazabicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate (5a): colorless oil; IR; ^1H NMR;[12] ^{13}C NMR.[15] Anal. Calcd. for $C_{12}H_{20}N_2O_6$: C, 49.99; H, 6.99; N, 9.72. Found: C, 49.96; H, 7.01; N, 9.72.

Diethyl *N*-2,5-cyclohexadienylhydrazino-*N,N*-dicarboxylate (5b): white solid, mp 52-53 °C; IR; ^{1}H NMR;[12] ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.9, 156.8, 132.2, 131.9, 129.0, 128.8, 62.2, 62.0, 50.1, 20.4, 14.4, 14.3; GC/MS: M^+ = 256. Anal. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.69; H, 7.12; N, 11.01.

Diethyl 4,5-dimethoxy-1,2,3,6-tetrahydro-1,2-pyridazincarboxylate (6): colorless oil; IR (cm^{-1}) 1711; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23-1.36 (t, 6H, *J* = 7.0 Hz), 3.71 (s, 6H), 4.15-4.32 (q, 4H, *J* = 7.0 Hz), 4.33-4.51 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.1, 134.3, 62.8, 58.6, 47.9, 14.5; GC/MS: M^+ = 288. Anal. Calcd. for $C_{12}H_{20}N_2O_6$: C, 49.99; H, 6.99; N, 9.72. Found: C, 49.96; H, 7.01; N, 9.72.

Diethyl 3-methylcarbonyloxy-1,2,3,6-tetrahydro-1,2-pyridazincarboxylate (7): colorless oil; IR (cm^{-1}) 1740, 1710; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18-1.26 (t, 6H, *J* = 7.0 Hz), 2.12 (s, 3H), 4.15-4.25 (q, 4H, *J* = 7.0 Hz), 4.35-4.48 (m, 2H), 5.60-5.74 (m, 1H), 5.76-5.83 (m, 1H), 6.18-6.27 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 155.1, 155.0, 134.5, 125.7, 69.3, 62.4, 62.2, 20.7, 14.4, 14.3; GC/MS: M^+ = 286. Anal. Calcd. for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.33; H, 6.32; N, 9.82.

Triethyl *cis*-6-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,3-pyridazinetricarboxylate (8): colorless oil; IR (cm^{-1}) 1745, 1716; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23-1.35 (m, 9H), 1.66 (t, 3H, *J* = 7.0 Hz), 1.76 (s, 3H), 3.43-3.62 (m, 2H), 4.05-4.25 (m, 8H), 5.52-5.64 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 154.6, 154.4, 135.7, 120.6, 79.5, 67.2, 62.6, 61.4, 60.6, 20.6, 15.3, 14.5, 14.3, 14.2; GC/MS: M^+ = 358. Anal. Calcd. for $C_{16}H_{26}N_2O_7$: C, 53.62; H, 7.31; N, 7.82. Found: C, 53.60; H, 7.31; N, 7.84.

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