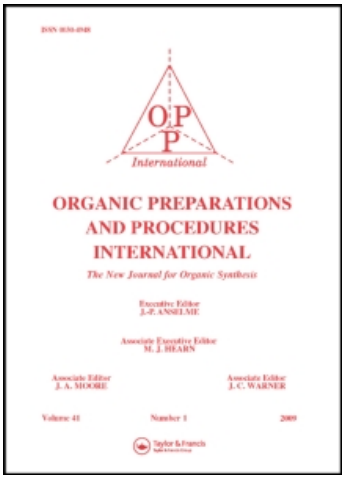

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Nicolas Tesson[a]; Sandrine Deshayes[a]
[a] Laboratoire des Réactions Séectives Sur Supports, ICMO, Université Paris-Sud, Orsay, FRANCE

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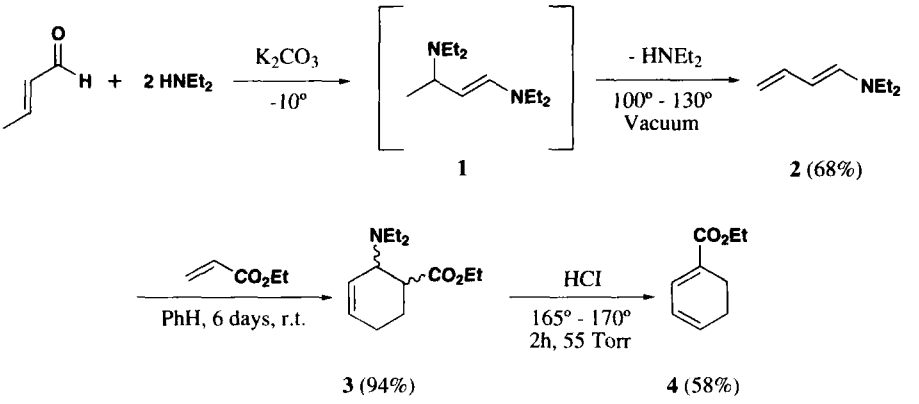
IMPROVED AND EXPEDITIOUS MICROWAVE SYNTHESIS OF ETHYL 1,3-CYCLOHEXADIEN-1-CARBOXYLATE

Nicolas Tesson and Sandrine Deshayes*

Laboratoire des Réactions Sélectives Sur Supports, ICMO
Université Paris-Sud, Bât. 410, 91405 Orsay, FRANCE

Ethyl 1,3-cyclohexadien-1-carboxylate (**4**) has often been used in Diels-Alder reactions with various dienophiles to build 1,4-disubstituted bicyclo[2.2.2] octanes,[1] to synthesize aromatic esters (by cycloaddition to alkynes followed by aromatization of adducts)[2] and to prepare molecules of biological interest such as tabtoxin (the exotoxin from *Pseudomonas tabaci*)[3] and sirenin (a female sexual pheromone of the aquatic fungus, *Allomyces*).[4]

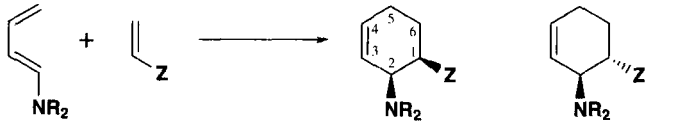
The critical step in the synthesis of **4** originally described by Hünig and Kahanek[5] and modified by Grob *et al.*,[6] is the preparation of the dienamine **2** in good yield as extensive polymerization occurs during distillation. The major drawbacks for this synthesis are long reaction times (15 days), the use of toxic solvents (benzene), multiple distillations, and poor reproductibility with an optimal yield of 30%. This article describes an improved procedure for the synthesis of compound **4** employing microwave activation coupled with dry media techniques, which are known to give rapid, clean and economical reactions in improved yields.[7]



The 1,3-diamino alkene **1** was prepared according to the known procedure (crotonaldehyde was added dropwise to diethylamine dissolved in dry diethyl ether at -10° in presence of anhydrous potassium carbonate). After evaporation of solvent under reduced pressure, the elimination of diethy-

lamine was carried out at atmospheric pressure in a focused microwave reactor with measurement and control of temperature and power. Thus **1**, under solvent-free microwave irradiations (8 minutes at 110°) gave dienamine **2** in 75% yield. The reaction performed under the same conditions in an oil bath at 110° for 8 minutes, gave a lower yield (53%) and more contamination by diethylamine. Under microwave irradiation, removal of small volatile polar molecules such as diethylamine is facilitated. The crude product is sufficiently pure for the next step but must be used rapidly; the shorter reaction times under microwave irradiation leads to a noticeable diminution of polymerization.

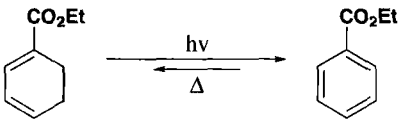
1-Amino-1,3-butadienes react easily with various olefins bearing an electron-withdrawing group (Z = NO_2, CHO, CO_2R, CN) to furnish exclusively the corresponding "*ortho*" aminocyclohexenes.[8] The ratio of the resulting stereoisomeric cyclohexenes (*cis* or *trans* resulting from *endo* or *exo* addition, respectively) depends on the size of the amine substituent, *cis* being the major stereoisomer.[9]



a (*endo* or *cis*) **b** (*exo* or *trans*)

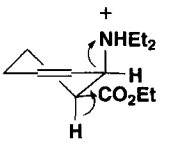
Upon standing in benzene or ether for six days at ambient temperature, a mixture *N,N*-diethyl-1,3-butadienylamine **(2)** and ethyl acrylate was reported[5] to give only the *"ortho"*-adducts of *cis*-configuration in 94% yield; in fact, a mixture of both *cis* and *trans* is probably obtained. Diels-Alder cycloadditions have already successfully studied under microwave irradiation with[10] or without solvents.[11] We therefore performed the cycloaddition between dienamine **2** and ethyl acrylate under microwave irradiation for 30 minutes at 70° without solvent and obtained a 60/40 ratio non-separable mixture of the *endo* **3a** and the *exo* isomer **3b** (determined by GC analysis), isolated in 90% yield by acidic extraction of the crude mixture. Classical heating under the same conditions (30 minutes at 70°) did not affect the selectivity but the yield is lower (62%). While stable adduct **3b** has been isolated by acidic treatment of reaction mixture, adduct **3a** undergoes loss of diethylamine to give the dihydrobenzene derivative.

Compound **4** was obtained from a mixture of **3a** and **3b** by elimination of diethylamine by thermolysis in partial vacuum under acidic conditions in 58% yield, this procedure which requires successive heating at different pressure,[6] is poorly reproductible due to photoisomerization of product into the hexatriene (Scheme 3).[12] The elimination of diethylamine was performed by impregnation of

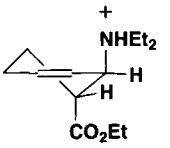


the mixture of **3a** and **3b** on an acidic support such as montmorillonite K-10 irradiated under microwave for 20 minutes at 100°. After extraction from support by simple elution with diethyl ether, **4** was recovered in 50% yield, together with unreacted **3b** (40%), indicating that only adduct of *cis*

configuration **3a** had reacted; this suggests a *trans* diaxial elimination (Scheme 4) to give **4**, which was obtained in high purity without distillation, after acidic extraction to remove the unreacted amine **3b**. Adduct **3b** can be subsequently epimerized under basic conditions to give the thermodynamic mixture 60/40 of **3a** and **3b**. The use of more acidic montmorillonite KSF at the same temperature led to a lower yield due to enhanced polymerization under these conditions.



3a *cis*



3b *trans*

In conclusion, synergy between microwave irradiation and solvent-free conditions allowed the preparation of ethyl 1,3-cyclohexadien-1-carboxylate **(4)** in good reproductibility within 2 days in 35% overall yield instead of 15 days using classical procedures. Each one of the three steps is performed under microwave, leading to products of high purity, thus avoiding further purification.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded at 200 or 250 MHz on Brucker AC-200 and AC-250 spectrometers. Chemical shifts are reported in ppm (δ) using $CDCl_3$ as standard and coupling constants value J are given in Hz. Microwave irradiations were carried out in a Pyrex tube 15 cm high (Prolabo) at ambient pressure with mechanical stirring using a Prolabo Synthewave S402 monomode reactor (2450 MHz, 300W, available from Prolabo, 54 rue Roger Salengro, 94126 Fontenay-sous-Bois, France) fitted with a variable speed stirring system. The irradiation was monitored by a PC computer, infrared measuring system and continuous feedback temperature control (adjusted and controlled). The power was continuously emitted throughout the reaction and modulated in order to maintain the temperature at a limited imposed value.[13] GC analysis was performed using an OV-1 12 m capillary column on a Carlo Erba CG 8000 (flame ionization) apparatus; helium carrier gas (p=0.4 kPa); oven temperature was programmed from 80 to 280° at 10° per min; injector and detector temperatures were 250°.

Synthesis of 1,3-Diaminoalkene 1.- Freshly distilled crotonaldehyde (59.1 g, 0.8 mole) was added dropwise with stirring to 117 g (1.6 mole) of diethylamine and anhydrous potassium carbonate in dry ether (60 mL) at -10°. The mixture are stirred at 0° for 1 h and 4 h at room temperature until the crotonaldehyde was totally consumed. The reaction mixture was filtered and diethyl ether removed under reduced pressure to give **1** as a yellow oil (150 g, 95%).

^{1}H-NMR ($CDCl_3$): δ 1.05 (12H, m, 4 x C<u>H</u>$_3$CH$_2$), 2.4 (4H, m, 2 x C<u>H</u>$_2$-N), 2.9 (q, 4H, 2 x C<u>H</u>$_2$N), 3.15 (1H, m, CH-C<u>H</u>(CH$_3$)(NEt$_2$)), 4.10 (1H, dd, J 8.3 and 13.7, CH-C<u>H</u>=CH), 5.85 (1H, d, J 13.7, CH=C<u>H</u>-NEt$_2$).

This product was used without purification in the next step.

Synthesis of *N,N*-Diethyl-1,3-butadienylamine (2).- Compound **1** (0.5 g, 2.5 mmoles) in a Pyrex tube was irradiated for 8 minutes at 110° to give the dienamine **2** directly. The yellow oil obtained

(0.24 g, 75%) was sufficiently pure (^{1}H NMR) and was used immediatly for the following step to avoid polymerization.

^{1}H-NMR ($CDCl_3$): δ 1.05 (t, 6H, J 7, 2 x $C\underline{H}_3CH_2$), 3.05 (q, 4H, J 7, 2 x CH_2-N), 4.40 (dd, 1H, J 10.4 and 1, C<u>H</u>=), 4.70 (dd, 1H, J 16.8 and 1, C<u>H</u>=), 5.05 (dd, 1H, J 13.4 and 10.4, C<u>H</u>=), 6.20 (d, 1H, J 13.4, =C<u>H</u>-N), 6.25 (dt, 1H, J 16.8 and 10.4, =C<u>H</u>-).

Synthesis of Ethyl 2-Diethylamino-3-cyclohexen-1-carboxylate (3).- In a Pyrex tube containing dienamine **2** (0.24 g, 1.9 mmole) was added ethyl acrylate (0.23 g, 2.28 mmole). The mixture was then placed in the MW reactor and irradiated for 30 minutes at 70°. The reaction mixture was cooled and 40 mL diethyl ether added. The product was extracted with aqueous 2M hydrochloric acid (3 x 50 mL). After neutralization with aqueous NaOH solution, the product was extracted with diethyl ether (3 x 50 mL). After drying ($MgSO_4$), the solvent was evaporated under vacumm to give a yellow oil (0.38 g, 89%). Analysis of the crude mixture by GC-mass revealed the presence of two products with close retention times (tr = 7.23 and tr = 7.74 mn) of identical molecular weight [M^+ = 226] by chemical ionization (NH_3) and same fragmentation by electronic impact, the two adducts **3a** and **3b** could not be separated. In our case, only one of the two isomers has been isolated after acidic treatment of the crude mixture, diethylamine elimination only occuring from **3a** under these conditions.

^{1}H-NMR ($CDCl_3$): δ 0.9 (6H, m, 2 x $C\underline{H}_3CH_2N$), 1.2 (3H, m, $C\underline{H}_3CH_2CO$), 1.7-1.9 ($2H_6$, m, CH-$C\underline{H}_2$-CH_2), 1.9-2.1 ($2H_5$, m, CH_2-$C\underline{H}_2$-CH), 2.5 (5H, m, H_1 $C\underline{H}CO_2Et$ + 2 x N-$C\underline{H}_2CH_3$), 3.6 ($1H_2$, m, C<u>H</u>-NEt_2), 4-4.2 (2H, m, $CO_2C\underline{H}_2CH_3$), 5.75 ($2H_3$-H_4, m, C<u>H</u>=C<u>H</u>).

Synthesis Ethyl 1,3-Cyclohexadien-1-carboxylate (4).- The mixture of adducts **3a** and **3b** (1 g, 4.4 mmoles) was impregnated on montmorillonite K-10 (3 g) and vigorously stirred in a Pyrex tube. The reaction mixture was irradiated in the focused MW reactor for 20 minutes at 100°. The product was desorbed with diethyl ether. The etheral layer was washed with aqueous hydrochloric acid solution (2N) to remove unreacted amine adduct **3b** and diethylamine. After drying over Na_2SO_4, the ether layer was evaporated. The crude product obtained (0.34 g; 50%) is pure, bp. 95-98°/13 Torr, *lit.*[5] bp. 90-92°/11 Torr.

^{1}H-NMR ($CDCl_3$): δ 1.20 (3H, t, J 7, $CO_2CH_2C\underline{H}_3$), 2.20 (2H, m, $C\underline{H}_2CH_2$), 2.4 (2H, m, $CH_2C\underline{H}_2CH$), 4.2 (2H, q, J 7.3, $CO_2C\underline{H}_2CH_3$), 6.10 (2H, m, C<u>H</u>=CH-C<u>H</u>=), 7.00 (1H, dd, J 5.2, CH=C<u>H</u>-CH=).

^{13}C-NMR ($CDCl_3$): δ 14.23 (CH_3), 20.66 and 22.78 (CH_2), 60.25 (OCH_2), 123.90 (<u>C</u>-CO), 127.35, 132.94 and 133.33 (-CH=), 167.45 (CO).

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