Microwave-Assisted Reductive Cyclization of *N*-Allyl 2-Nitroanilines: A New Approach to Substituted 1,2,3,4-Tetrahydroquinoxalines

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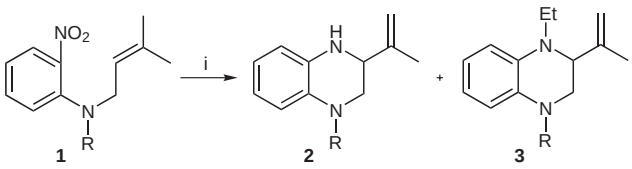
Abstract: *N*-Allyl 2-nitrophenyl amines can be efficiently cyclized to yield alkenyl-1,2,3,4-tetrahydroquinoxalines in a single reaction step by means of a new microwave-assisted reductive domino process.

Key words: cyclizations, domino reactions, ene reactions, microwaves, tetrahydroquinoxalines

The applications of 1,2,3,4-tetrahydroquinoxalines as promising prostaglandin D2 receptor antagonists[1] and vasopressin V2 receptor antagonists[2] underline the importance of this heterocyclic skeleton for the development of new pharmaceuticals. Due to their role as model compounds for tetrahydrofolic acid the synthesis of 1,2,3,4-tetrahydroquinoxalines is also important in the field of bioorganic chemistry.[3]

Despite the marked interest in 1,2,3,4-tetrahydroquinoxalines there are only a limited number of synthetic methods available. A classic strategy to 1,2,3,4-tetrahydroquinoxalines is the reduction of suitably substituted quinoxalines.[4] Alternatively, more recent approaches to 1,2,3,4-tetrahydroquinoxalines include the metal-mediated reaction between substituted 1,2-diaminobenzenes with 1,4-butene diol or acetates[5] as well as the Lewis acid promoted addition of allyl stannanes to *o*-quinonediimines.[6] Suitably substituted nitroarenes are not only used as a substrate for tetrahydroquinoxaline syntheses in a domino reduction/Michael addition,[7] but are also employed in other domino processes.[8–10]

Altogether there is a strong demand for new and efficient methods for the synthesis of the 1,2,3,4-tetrahydroquinoxaline skeleton. Recently, we discovered a new domino process that allows the transformation of allyl 2-nitrophenyl ethers into substituted 3,4-dihydro-2*H*-1,4-benzoxazines in a single synthetic operation.[11] Whether a new synthetic method is able to gain major importance will greatly depend on its scope and limitations. Here we report on the successful application of this new reductive domino process to the preparation of substituted 1,2,3,4-tetrahydroquinoxalines. First, the easily accessible protected *N*-allyl 2-nitroanilines **1a**–**d** were reacted with triethyl phosphite [$(EtO)_3P$] under argon. After heating under reflux for 2–12 hours the 3-isopropenyl-1,2,3,4-tetrahydroquinoxalines **2a**–**d**[12] were isolated as the main products with yields ranging from 55% to 60% (Scheme 1, Table 1).



Scheme 1 Reductive cyclization of protected *N*-prenyl 2-nitroanilines **1** under thermal conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) $(EtO)_3P$ (6 equiv), reflux 2–12 h.

Table 1 Synthesis of 3-Isopropenyl-1,2,3,4-tetrahydroquinoxalines **2** and **3** under Thermal Conditions in Neat $(EtO)_3P$

Entry	**1**	R	Time (h)	**2**	Yield (%) of **2**	**3**	Yield (%) of **3**
1	**a**	CO_2Me	2	**a**	60	**a**	6
2	**b**	CO_2Bn	2	**b**	59	**b**	4
3	**c**	CO_2t-Bu	2	**c**	55[a]	**c**	–
4	**d**	Ph	12	**d**	57	**d**	<2

[a] In addition, **4** (12%, Figure 1) was isolated.

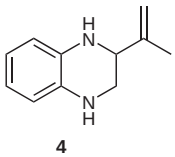


Figure 1

In these reactions, 4-ethyl-3-isopropenyl-1,2,3,4-tetrahydroquinoxalines **3a**,**b**,**d**[13] were also formed as side products in small amounts (2–6%) (Scheme 1, Table 1). It is assumed that the formation of these N-ethylated compounds is due to the ethylation of **2** with $(EtO)_3PO$, which is produced during the reaction by oxidation of $(EtO)_3P$. The conversion of *tert*-butyl carbamate **1c** is unusual since the Boc group is partially cleaved under the reaction conditions. Apart from 55% of **2c**, an additional 12% of 2-isopropenyl-1,2,3,4-tetrahydroquinoxaline (**4**; Figure 1) was isolated.

In contrast, the transformation of the unprotected *N*-prenyl 2-nitroaniline (**5a**) with $(EtO)_3P$ under thermal condi-

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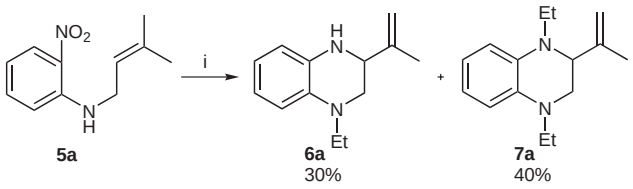
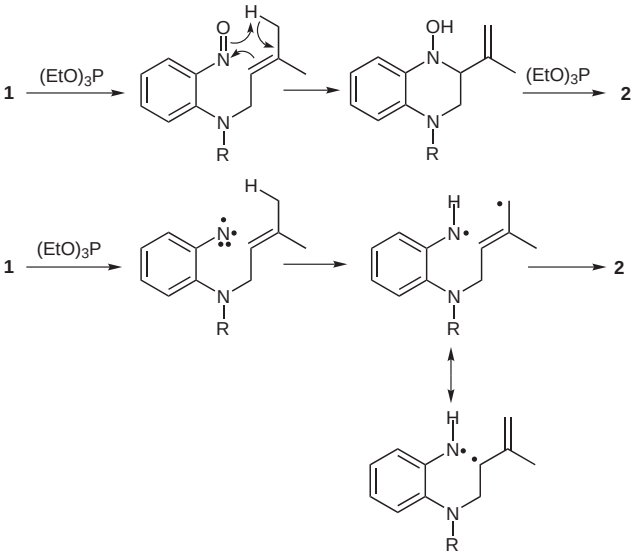
tions exclusively gave N-ethylated products, namely 1-ethyl-3-isopropenyl-1,2,3,4-tetrahydroquinoxaline (**6a**, 30%) and 1,4-diethyl-2-isopropenyl-1,2,3,4-tetrahydroquinoxaline (**7a**, 40%) (Scheme 2).



Scheme 2 Reductive cyclization of the unprotected *N*-prenyl 2-nitroaniline (**5a**) under thermal conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) $(EtO)_3P$ (6 equiv), reflux, 12 h.

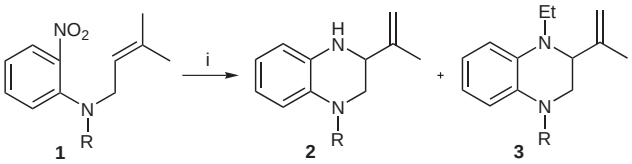
Both an intramolecular nitroso ene reaction[14] and the reaction of a nitrene[15] may be considered as the reaction mechanism (Scheme 3). With a nitroso ene reaction, we may assume that the reaction of the protected *N*-prenyl 2-nitroanilines **1** with phosphite begins with the reduction of the nitro group. The nitroso group so formed then undergoes an intramolecular ene reaction with the 2-methylpropenyl group of the molecule, resulting in the formation of a cyclic hydroxyl amine that is finally reduced by the phosphite to yield the cyclic amine **2** (Scheme 3). In the case of a nitrene mechanism, we assume that the nitro group is first reduced to the corresponding nitrene, which then abstracts a hydrogen atom from the 2-methylpropenyl group and yields both an NH radical and a mesomerically stabilized propenyl radical, which undergo intramolecular cyclization to give **2** (Scheme 3).[16]



Scheme 3 Possible reaction mechanisms

On the basis of these results we examined whether (a) the reaction times of the reductive cyclization and, (b) the proportion of N-ethylated products could be decreased by conducting the domino reactions of **1** and **5** under microwave conditions.[17a] Recently, Dehaen et al. have reported on the Cadogan cyclization under microwave conditions.[17b]

It turned out that indeed the reaction times of the reductive cyclization of *N*-allyl 2-nitroanilines could be dramatically shortened in some cases (Scheme 4, Table 2 and Scheme 5, Table 3). For example, the reaction time required to transform **1d** could be reduced from 12 hours to 30 minutes (Scheme 4, Table 2, entry 4).



Scheme 4 Reductive cyclization of protected *N*-prenyl 2-nitroanilines **1** under microwave conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) $(EtO)_3P$ (6 equiv), MW (300 W), 200 °C.

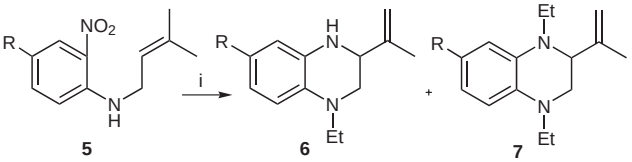
Table 2 Synthesis of 3-Isopropenyl-1,2,3,4-tetrahydroquinoxalines **2** and **3** under Microwave Conditions in Neat $(EtO)_3P$

Entry	**1**	R	Time (min)	**2**	Yield (%) of **2**	**3**	Yield (%) of **3**
1	**a**	CO_2Me	35	**a**	60	**a**	4
2	**b**	CO_2Bn	35	**b**	58	**b**	4
3	**c**	CO_2t-Bu	35	**c**	36[a]	**c**	–
4	**d**	Ph	30	**d**	56	**d**	<2

[a] In addition, **4** (28%, Figure 1) was isolated.

In contrast, the formation of the N-ethylated products could not be suppressed by using microwaves, as can be shown by the cyclizations of **1a–d** and, even more noticeably, by the transformation of **5a–d** which exclusively yielded the mono- and diethylated products **6a–d** and **7a–d**, respectively (Scheme 5, Table 3).

The reactions of **5a–d** also demonstrate that the reductive domino process tolerates substrates that are substituted at the aromatic nucleus.



Scheme 5 Reductive cyclization of the unprotected *N*-prenyl 2-nitroanilines **5a–d** under microwave conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) $(EtO)_3P$ (6 equiv), MW (300 W), 200 °C.

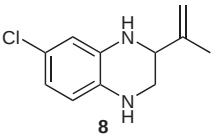
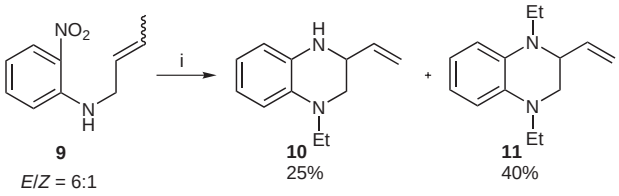


Figure 2

Table 3 Synthesis of Substituted 1,2,3,4-Tetrahydroquinoxalines **6** and **7** under Microwave Conditions in Neat $(EtO)_3P$

Entry	**5**	R	Time (min)	**6**	Yield (%) of **6**	**7**	Yield (%) of **7**
1	**a**	H	35	**a**	40	**a**	23
2	**b**	Me	35	**b**	46	**b**	21
3	**c**	OMe	35	**c**	45	**c**	17
4	**d**	Cl[a]	35	**d**	26	**d**	4

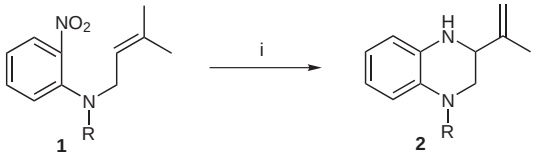
[a] In addition, **8** (38%; Figure 2) was isolated.



Scheme 6 Reductive cyclization of the unprotected *N*-crotyl 2-nitroaniline (**9**) under thermal conditions in neat $(EtO)_3P$. *Reagents and conditions*: (i) $(EtO)_3P$ (6 equiv), reflux, 12 h.

Furthermore the question arose whether the presence of a dimethyl allyl group is essential to the cyclization process or whether it can be achieved with a crotyl group instead. Heating the *N*-crotyl 2-nitroaniline (**9**) with triethyl phosphite led to the formation of 1-ethyl-3-vinyl-1,2,3,4-tetrahydroquinoxaline (**10**) in 25% yield and 1,4-diethyl-2-vinyl-1,2,3,4-tetrahydroquinoxaline (**11**) in a yield of 40% (Scheme 6). This clearly demonstrates that variation of the allylic component also works.

Finally, the influence of solvents on the reaction was studied. After some experimentation $(EtO)_3P$ in toluene was identified as the most suitable combination for this



Scheme 7 Reductive cyclization of protected *N*-prenyl 2-nitroanilines **1** in $(EtO)_3P$–toluene. *Reagents and conditions*: (i) $(EtO)_3P$ (6 equiv), toluene, MW (300 W), 200 °C.

Table 4 Synthesis of Substituted 3-Isopropenyl-1,2,3,4-tetrahydroquinoxalines **2a**–**d** under Microwave Conditions in $(EtO)_3P$–Toluene

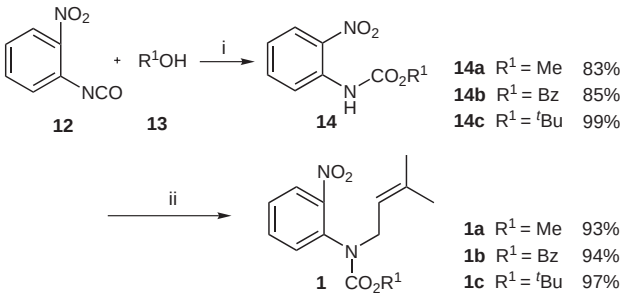
Entry	**1**	R	Time (min)	**2**	Yield (%) of **2**
1	**a**	CO_2Me	35	**a**	70
2	**b**	CO_2Bn	35	**b**	67
3	**c**	CO_2t-Bu	35	**c**	36[a]
4	**d**	Ph	35	**d**	60

[a] In addition, **4** (28%, Figure 1) was isolated.

type of cyclization. When, for example, **1a** was reacted with $(EtO)_3P$ in toluene under microwave conditions, the heterocycle **2a** was isolated in good yield (70%) after 35 min. These reaction conditions[18] led to the exclusive production of **2a**, while formation of the N-ethylated side product **3a** was completely suppressed (Scheme 7, Table 4, entry 1).

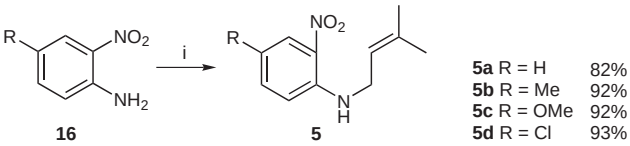
Similarly good results were observed with the reductive cyclizations of **1b**–**d** (Scheme 7, Table 4, entries 2–4). Again, the cyclization of **1c** was an exception since partial cleavage of the Boc group of **2c** also occurred under these reaction conditions (Scheme 7, Table 4, entry 3). Surprisingly, the secondary 2-nitroanilines **5a**–**d** did not react under these conditions at all; the substrates could be retrieved unchanged after one hour irradiation at 200 °C. The same holds true for the *N*-crotyl 2-nitroaniline (**9**).

Another benefit of the novel tetrahydroquinoxaline synthesis is the easy accessibility of the substrates. Compounds of type **1** could be obtained in high yields by reacting 2-nitrophenylisocyanate (**12**) with the alcohols **13a**–**c** (MeOH, BnOH, *t*-BuOH) to give **14a**–**c**,[19] followed by allylation of the carbamates **14a**–**c** with prenyl bromide (**15**)[20,21] (Scheme 8).



Scheme 8 Preparation of protected *N*-prenyl 2-nitroanilines **1a**–**c**. *Reagents and conditions*: (i) petroleum ether, reflux; (ii) NaH, DME, 0 °C or *t*-BuOK, THF, –78 °C, **15**, r.t.

The approach to the secondary amines **5a**–**d** is even simpler in that they can be obtained in one step by reaction of the corresponding substituted 2-nitroanilines **16a**–**d** with prenyl bromide (**15**) in very good yields (Scheme 9).[22]



Scheme 9 Preparation of unprotected secondary 2-nitroanilines **5a**–**d**. *Reagents and conditions*: (i) benzene, reflux, 50% NaOH, **15**, $PhCH_2N^+Et_3Cl^-$.

In summary, the efficient conversion of *N*-allyl 2-nitroanilines into substituted 1,2,3,4-tetrahydroquinoxalines by means of a $(EtO)_3P$-mediated reductive domino reaction has been presented.

Acknowledgment

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References and Notes

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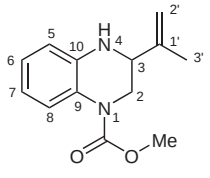
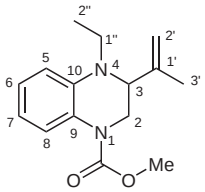
(12) **Selected Data for 2a** (Figure 3):
R_f 0.40 (PE–EtOAc, 20:1). IR (ATR): 3376 (NH), 2952, 2854 (Me, CH_2), 1691 (C=O), 1604, 1501 (C=C), 1435, 1382, 1372 (COO^-), 1232, 1211, 1146, 1061 (=COC), 900, 760, 741 cm^{-1}. UV–Vis (EtOH): λ_{max} (log ε) = 307 (2.48), 253 (2.40), 220 (2.34) nm. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3 H, 3′-Me), 3.58 (dd, ^2J = 12.3 Hz, ^3J = 6.2 Hz, 1 H, 2-H), 3.81 (s, 3 H, OMe), 3.98 (dd, ^3J = 3.4, 6.2 Hz, 1 H, 3-H), 4.02 (dd, ^2J = 12.3 Hz, ^3J = 3.3 Hz, 1 H, 2-H), 4.98 (br s, 1 H, 2′-H), 5.05 (br s, 1 H, 2′-H), 6.65 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1 H, 5-H), 6.70 (ddd, ^3J = 7.4, 8.2 Hz, ^4J = 1.5 Hz, 1 H, 7-H), 6.97 (ddd, ^3J = 7.4, 7.9 Hz, ^4J = 1.4 Hz, 1 H, 6-H), 7.48 (br s, 1 H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.57 (C-3′), 45.25 (C-2), 53.24 (OMe), 56.72 (C-3), 112.87 (C-2′), 114.4 (C-5), 116.9 (C-7), 123.9 (C-9), 124.61 (C-8), 125.4 (C-6), 137.09 (C-10), 144.3 (C-1′), 155.3 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 232 (100) [M^+], 218 (8), 199 (14), 191 (40), 173 (21), 157 (18), 131 (40), 106 (7), 77 (7). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.43; H, 7.01; N, 11.99.



2a

Figure 3



3a

Figure 4

(13) **Selected Data for 3a** (Figure 4):
R_f 0.59 (PE–EtOAc, 20:1). IR (ATR): 2980, 2958 (Me, CH_2), 1702 (C=O), 1602, 1504 (C=C), 1438, 1375, 1344 (COO^-), 1217, 1190, 1145, 1062 (=COC), 899, 733 cm^{-1}. UV–Vis (EtOH): λ_{max} (log ε) = 310 (2.49), 258 (2.41), 223 (2.35) nm. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, ^3J = 7.1 Hz, 3 H, 2′′-Me), 1.80 (s, 3 H, 3′-Me), 3.15–3.27 (overlapped, 2 H, 1′′-CH_2), 3.52 (dd, ^2J = 13.1 Hz, ^3J = 7.1 Hz, 1 H, 2-H), 3.76 (s, 3 H, OMe), 3.94 (t, ^3J = 7.1 Hz, 1 H, 3-H), 4.37 (dd, ^2J = 12.9 Hz, ^3J = 7.1 Hz, 1 H, 2-H), 4.81 (br s, 1 H, 2′-H), 4.93 (br s, 1 H, 2′-H), 6.62 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 1 H, 5-H), 6.75 (ddd, ^3J = 7.8, 8.1 Hz, ^4J = 1.2 Hz, 1 H, 7-H), 7.06 (ddd, ^3J = 7.8, 8.1 Hz, ^4J = 1.2 Hz, 1 H, 6-H), 7.4 (br s, 1 H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.76 (C-2′′), 19.60 (C-3′), 43.50 (C-1′′), 43.82 (C-2), 53.12 (OMe), 62.76 (C-3), 110.56 (C-2′), 113.5 (C-5), 115.1 (C-7), 124.3 (C-9), 124.7 (C-8), 125.8 (C-6), 137.9 (C-10), 143.06 (C-1′), 155.4 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 260 (100) [M^+], 245 (16), 231 (26), 219 (58), 213 (12), 190 (34), 171 (20), 159 (30), 131 (27), 119 (6), 92 (3), 77 (12), 41 (3), 28 (3). HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{20}N_2O_2$: 260.1525; found: 260.1507.
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(16) Scheme 3 shows a mechanism involving a triplet nitrene. However, the occurrence of a singlet nitrene cannot be ruled out.
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(18) **General Procedure for the Synthesis of Alkenyl-1,2,3,4-tetrahydroquinoxalines under Microwave Conditions:**
A solution of **1a** (1 mmol), $(EtO)_3P$ (6 mmol) and toluene (3 mL) in a 10-mL septum-sealed reaction vial was irradiated with microwaves (Discover™ by CEM; 2450 MHz; 300 W; 200 °C). After removal of $(EtO)_3P$ and $(EtO)_3PO$ (10^{-1} mbar) the residue was taken up in EtOAc (25 mL) and washed with brine (3 × 20 mL). The residue obtained after drying over $MgSO_4$ and after concentration in vacuo was purified by flash chromatography on silica gel (PE–EtOAc, 20:1).
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