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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8383–8387

From the study of naturally occurring *N*-allylated phenazines towards new Pd-mediated transformations

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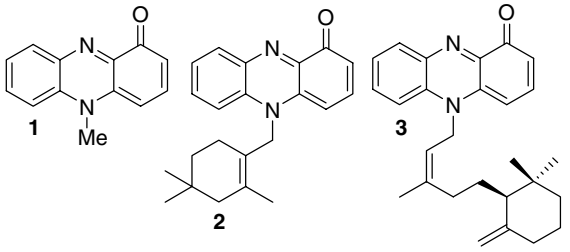
Received 18 June 2007; revised 27 August 2007; accepted 7 September 2007
Available online 12 September 2007

Abstract—New Pd-mediated reductive heteroannulations of *N*-allyl diphenylamines accessible through Pd-catalyzed N-arylation and of *O*-allylethers are reported.

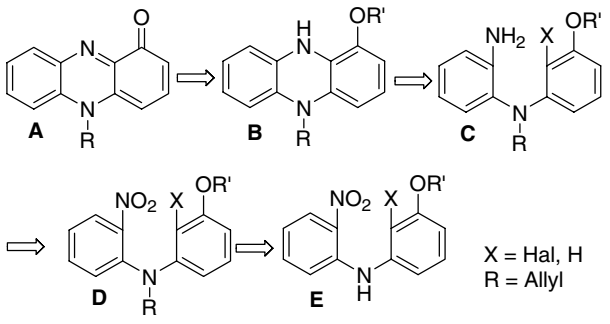
Currently we know more than 100 naturally occurring phenazines, which, due to the diversity of their biological activities, have gained a lot of popularity.[1] Most of them are C-substituted compounds. In addition, a small number of naturally occurring *N*-alkylated and *N*-allylated phenazine derivatives are known. Apart from the *N*-alkylated phenazinones represented by the structurally most simple pyocyanin **1**,[2] there are, in particular, the *N*-allylated phenazinones like lavanducyanin (WS-9659 B) **2**[3] and phenazinomycin **3**.[4] The latter was isolated by Ōmura et al. from the mycelial extracts of *Streptomyces* sp. WK-2057.[4a] It exhibits in vivo antitumour activity against experimental murine tumour cells and cytotoxic activity against adriamycin resistant P388 leukaemia cells.[4b] The total synthesis of **3** was reported by Kitahara, using low-yield N-allylation under high pressure conditions.[5]



Against this background we envisaged performing an alternative synthesis of *N*-allylated phenazinones according to the retrosynthesis depicted in Scheme 1. The initial idea was to start the synthesis with a diphenylamine **E**, which was to be *N*-allylated. The reduction of **D** (X = Hal) was expected to deliver **C** (X = Hal), which in turn should be transformed into **B** by intramolecular N-arylation according to Buchwald–Hartwig.[6] Alternatively, the reductive cyclization of **D** (X = H) according to the method described by Holliman[7] would deliver **B** in one synthetic step. Deprotection of the phenolic OH group, followed by oxidation, should finally give the *N*-allylated phenazinone **A**.

First, we focussed on the synthesis of the tertiary *o*-nitro-substituted diphenylamines **4a–c** and their conversion into the corresponding anilines **5a–c**.

Intermolecular N-arylation reactions of the Buchwald–Hartwig type[6] were used to synthesize the secondary



Scheme 1. Retrosynthesis of *N*-allylated phenazinones.

Keywords: Pd-catalysis; CO; Domino reactions; Benzoxazine; Heterocycles.
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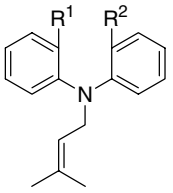
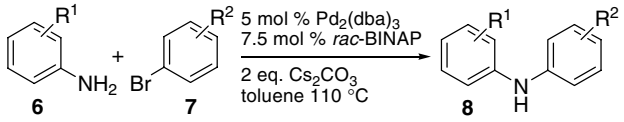
doi:10.1016/j.tetlet.2007.09.045



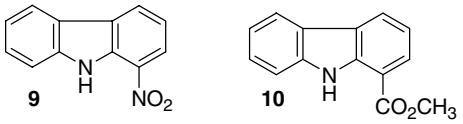
4a $R^1 = NO_2$, $R^2 = Br$
4b $R^1 = NO_2$, $R^2 = Cl$
4c $R^1 = NO_2$, $R^2 = H$

5a $R^1 = NH_2$, $R^2 = Br$
5b $R^1 = NH_2$, $R^2 = Cl$
5c $R^1 = NH_2$, $R^2 = H$

diphenylamines **8a–c**, the precursors of anilines **5a–c** and **4a–c**, respectively. The reactions between *o*-substituted anilines **6a–e** and aryl bromides **7a–d** were achieved by combining the catalyst $Pd_2(dba)_3$, the ligand *rac*-BINAP, the base Cs_2CO_3 and toluene as a solvent. Under these conditions, diphenylamines **8** were isolated with yields ranging from 57% to 99% (Table 1).[8] Reaction times varied between 12 and 17 h.



6 **7** **8**



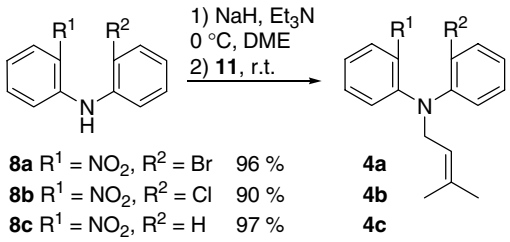
9 **10**

In two cases, cyclization to the corresponding carbazoles was observed.[9] Most noticeably, the reaction between **6d** and **7b** exclusively produces nitrocarbazole **9** in 90% yield. In contrast, the reaction of **6d** and **7d** yields a mixture of diphenylamine **8e** (80%) and carbazole **10** (15%).

Then the secondary diphenylamines **8a–c** were transformed into the corresponding tertiary amines **4a–c** by N-allylation-with prenyl bromide **11** in yields from 90% to 97% (Scheme 2).

This transformation was achieved by deprotonation of **8a–c** with a slight excess of NaH in dimethoxyethane at 0 °C followed by treatment with an excess of prenyl bromide **11** at room temperature.[10]

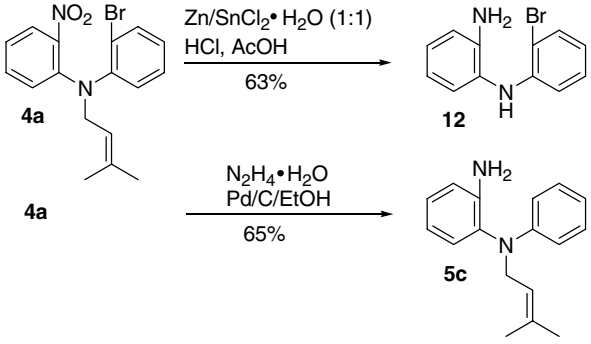
The next goal was to reduce the nitro compounds **4a–c** to the corresponding anilines **5a–c**. However, unexpected problems occurred with the reduction of the nitro groups of **4a** and **4b**. For example, treatment of 1 equiv of **4a** with 2.5 equiv of a 1:1-mixture of Zn and $SnCl_2 \cdot 2H_2O$ as reducing agents under acidic conditions[11] (37% HCl in concd CH_3CO_2H) did not only lead to the reduction of the nitro group but also to N-deallylation. The *o*,*o*′-disubstituted diphenylamine **12** was formed exclusively in a yield of 63% (Scheme 3). On the other hand, the reaction of 1 equiv of **4a** with a large excess of $N_2H_4 \cdot H_2O$ (13 equiv) in the presence of 2.5 mol % Pd/C[12] resulted in both reduction of the nitro group and cleavage of the bromo substituent, so compound **5c** was isolated in 65% yield (Scheme 3).



8a $R^1 = NO_2$, $R^2 = Br$ 96 % **4a**
8b $R^1 = NO_2$, $R^2 = Cl$ 90 % **4b**
8c $R^1 = NO_2$, $R^2 = H$ 97 % **4c**

Scheme 2. Synthesis of tertiary diphenylamines **4a–c**.

Clean conversion of **4a–b** into **5a–b** also failed with various other reducing agents, including $NH_4OH/(NH_4)_2Fe(SO_4)_2$,[13] $Cu(acac)_2/NaBH_4$,[14] In/NH_4Cl,[15] Zn/CH_3CO_2H,[16] Fe/HCl,[17] $FeCl_3 \cdot 6H_2O/NH_2–N(CH_3)_2$[18] and SmI_2.[19] Thus, we focussed on the reduction of **4c** to **5c** and the reductive cyclization of **4c**, respectively. A classical procedure for the reductive cyclization of *o*-nitrodiphenylamines to phenazines in a single step is Holliman's method[7] using a mixture of $NaBH_4$ and NaOEt in excess as the reducing agent. Surprisingly, no phenazine was formed when **4c** was treated with



4a **12**

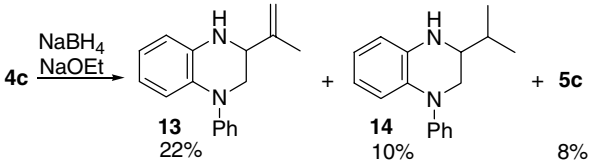
4a **5c**

Scheme 3. Reductions of **4a**.

Table 1. Synthesis of diphenylamines **8a–f**

Entry	6	R^1	7	R^2	8	Yield **8** (%)
1	**a**	*o*-NO_2	**a**	*o*-Br	**a**	68
2	**b**	*o*-Cl	**b**	*o*-NO_2	**b**	99
3	**c**	*o*-H	**b**	*o*-NO_2	**c**	98
4	**d**	*o*-Br	**b**	*o*-NO_2	—[a]	—
5	**d**	*o*-Br	**c**	*p*-NO_2	**d**	58
6	**d**	*o*-Br	**d**	*o*-CO_2CH_3	**e**[b]	80
7	**e**	*o*-Br-*p*-CN	**b**	*o*-NO_2	**f**	57

[a] 1-Nitrocarbazole (**9**) was isolated in 90% yield.
[b] In addition, 15% of **10** was isolated.



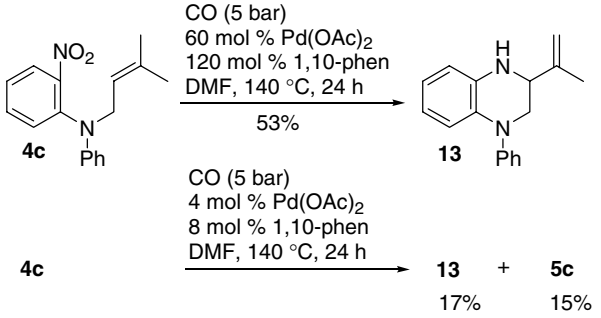
Scheme 4. Reductive cyclization of **4c** using $NaBH_4$/NaOEt as a reagent.

2.5 equiv $NaBH_4$ and a 5 N ethanolic solution of NaOEt. Instead, a mixture of 3-isopropenyl-1-phenyl-1,2,3,4-tetrahydroquinoxaline **13** (22%), 3-isopropyl-1-phenyl-1,2,3,4-tetrahydroquinoxaline **14** (10%) and amine **5c** (8%) was isolated (Scheme 4).

Despite the modest yield of 22% of 3-isopropenyl-1-phenyl-1,2,3,4-tetrahydroquinoxaline **13** the conversion of an ω-nitroalkene into an alkenyl-substituted N-heterocycle in a single synthetic step is of general interest as this transformation represents a new reductive domino process.[20] In the course of our studies we tried to establish reagents and reaction conditions capable of increasing the yields of the annulation products. This objective was reached by using phosphites as the reagents.[21] For example, compound **13** was obtained in a yield of 57% upon heating **4c** with $(EtO)_3P$ under reflux. In this and all the other cases investigated, $(EtO)_3P$ had to be used in excess. It was this excess that triggered the search for catalytic alternatives.

The past years have shown that the synthesis of N-heterocycles can be achieved by transition metal-catalyzed N-heteroannulations of aromatic nitro compounds in the presence of CO.[22] Particularly well known is the Pd-catalyzed reductive N-heteroannulation of *o*-nitrostyrenes to indoles.[22,23] Even if this annulation can be performed with complexes of other metals like Ru,[22,24] Rh[22,25] or Fe,[22] it is the Pd complexes that are undoubtedly the most important catalysts. So we set out to investigate the reductive cyclization of ω-nitroalkene **4c** into the saturated N-heterocycle **13** by Pd-catalyzed reactions with CO. First we concentrated on the combination of $Pd(OAc)_2$ as a catalyst, 1,10-phenanthroline as a ligand and CO as a reductant. We found that reductive cyclization of ω-nitroalkene **4c** can be realized in a single step by using 60 mol % of $Pd(OAc)_2$, 120 mol % of 1,10-phenanthroline and CO (5 bar).[26] Under these conditions 1,2,3,4-tetrahydroquinoxaline **13** was isolated in 53% yield (Scheme 5). But although we managed a reduction of $Pd(OAc)_2$ to 4 mol % and of 1,10-phenanthroline to 8 mol %, the product yield dropped: only 17% of **13** was formed under these conditions, accompanied by 15% of the tertiary diphenylamine **5c** (GC–MS) (Scheme 5).

In order to find out whether this new one-step Pd-mediated N-heteroannulation of ω-nitroalkenes can also be applied to the synthesis of other heterocycles, we turned our attention to the conversion of allyl 2-nitrophenyl ethers. Reaction of 3,3-dimethylallyl-2-nitrophenyl ether **15** with CO (5 bar, 140 °C) in the presence of 60 mol % $Pd(OAc)_2$ and 120 mol % 1,10-phenanthroline produced

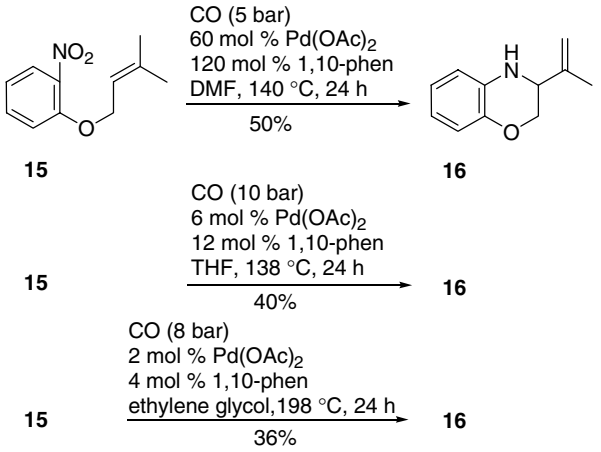


Scheme 5. Pd-mediated N-heteroannulation of **4c**.

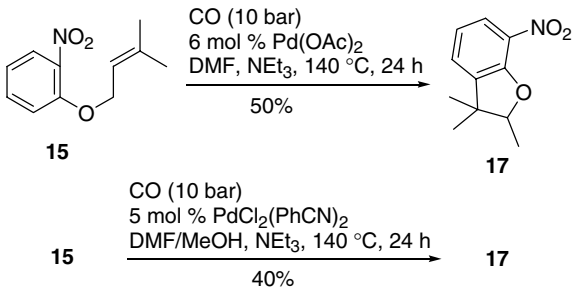
3-isopropenyl-3,4-dihydro-2*H*-1,4 benzoxazine **16** in 50% yield (Scheme 6).

In the case of **15** the amounts of $Pd(OAc)_2$ and 1,10-phenanthroline could be reduced to 6 mol % and 12 mol %, respectively, when the reaction was performed with CO (10 bar) in tetrahydrofuran (138 °C). Under these conditions **16** was obtained in 40% yield. With ethylene glycol as the solvent as little as 2 mol % $Pd(OAc)_2$ and 4 mol % 1,10-phenanthroline were sufficient to catalyze the reductive cyclization of **15** with CO (8 bar). After 24 h at 198 °C **16** was isolated in 36% yield. The remarkably strong influence of the solvent on the course of this reaction is supported by the finding that no cyclization occurred in xylene (145 °C, 10 bar CO), and many products were formed (TLC) in acetonitrile (140 °C, 10 bar CO).

Finally, the Pd-catalyzed transformation of **15** with CO (10 bar) was also examined under basic conditions with NEt_3 (10 equiv) in DMF or DMF/MeOH. Surprisingly, 2,3,3-trimethyl-7-nitro-2,3-dihydro-benzofuran **17** was the only cyclization product formed. Yields ranged from 40% to 50% (Scheme 7).[27] Formation of **17** implicates that the cyclization proceeds without the participation of the nitro group in **15**. As a side product 2-nitrophenol was isolated with yields of 10% and 15%, respectively. It probably originates from deallylation of **15**.



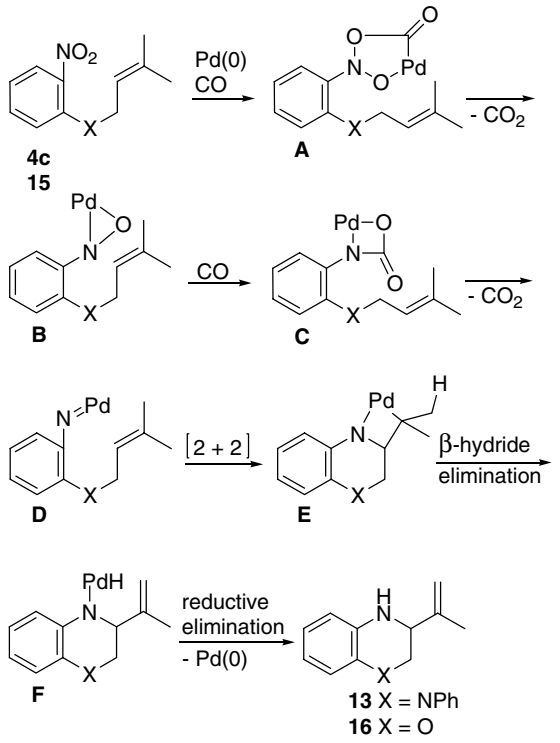
Scheme 6. Synthesis of benzoxazine **16**.



Scheme 7. Synthesis of benzofuran **17**.

Currently, we can only speculate on the mechanism of the Pd-mediated reductive N-heteroannulation of ω-nitroalkenes with CO.[28]

We assume that the process starts with the metal-mediated deoxygenation of **4c** and **15**, respectively. Reaction of the nitro group with CO would first yield **A** leading to the metal-bound nitrosamine **B** and the formation of CO_2. Repeated insertion of CO would give the metallacyclobutanone **C**, which in turn decomposes to yield the metal-bound nitrene **D** and CO_2. A formal intramolecular [2+2] cycloaddition between the Pd-bound nitrene and the alkene would give tricycle **E**. The next step involves the formation of the bicyclic intermediate **F** by means of β-hydride elimination. Finally, reductive elimination would not only deliver products **13** and **16**, respectively, but also regenerate the Pd(0) catalyst (Scheme 8).



Scheme 8. Possible reaction mechanism for the Pd-mediated N-heteroannulation.

In summary, new Pd-mediated reductive heteroannulations have been achieved starting from *N*-allyl diphenylamines and *O*-allylethers yielding saturated heterocycles.

Acknowledgements

We thank Dr. J. Conrad, Ms. S. Mika, Dr. R. Frank and Ms. I. Klaiber for recording of NMR, UV and MS spectra.

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26. *General procedure for the cyclization reaction with CO*. A Berghof PTFE liner was charged with (0.166 g, 0.589 mmol) **4c** dissolved in 5 mL DMF and inserted into a Berghof pressure reactor HR-100. A mixture of $Pd(OAc)_2$ (80 mg, 0.356 mmol) and 1,10-phenanthroline (128 mg, 0.71 mmol) dissolved in 50 mL DMF was added. The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (5 bar) and heated at 140 °C for 24 h. The reaction mixture was cooled to rt, the catalyst filtered off and washed with H_2O. Extraction with EtOAc (3×50 mL) was followed by drying of the organic phase over $MgSO_4$ and removal of the solvent under reduced pressure. The residue was purified by flash column chromatography (PE/EtOAc = 20:1).
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