Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2829-2832, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00494-2

Construction of the Tricyclic Benzoquinolizine Ring System by Combination of a Tandem Mannich-Michael Reaction with a Heck Reaction

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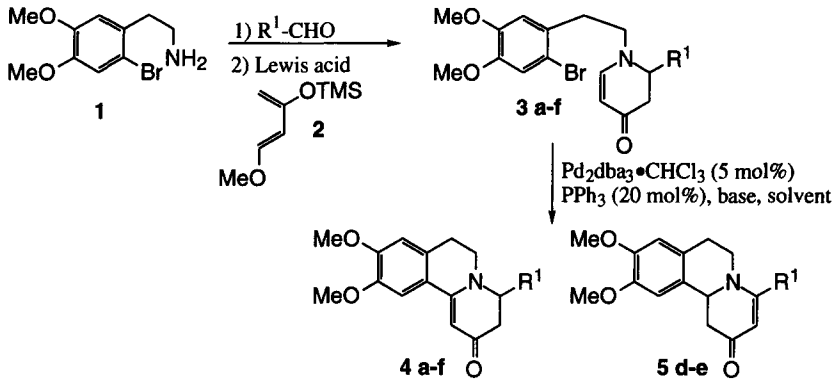
Abstract: Tetrahydro- and hexahydrobenzo[a]quinolizinones can be built up efficiently by means of a two step reaction sequence consisting of a tandem Mannich-Michael reaction and a Heck reaction.

Polycyclic N-heterocycles form the basic frameworks of numerous natural products and physiologically active drugs. For instance, the benzoquinolizine system occurs in various alkaloids, e.g. of the berberine type[1] and the benzo[a]quinolizinone[2] structure is found in psychoactive drugs like tetrabenazine.[2c,d] Benzo-[a]quinolizinones may bind to the benzodiazepine receptor and thereby mimic the physiological effects mediated by benzodiazepine drugs.[3] In the light of these biological properties and due to the challenge which the construction of complex alkaloids offers, the development of new methods for the stereoselective synthesis of these nitrogen heterocycles is of great relevance to organic synthesis in general and to natural product, heterocyclic and medicinal chemistry in particular.

We have previously shown, that indolo[2,3-a]quinolizinones can be built up efficiently by a short reaction sequence in which a tandem Mannich-Michael reaction between an electron-rich silyloxydiene and an indolylethylamine-derived Schiff base is followed by a Lewis acid mediated Bischler-Napieralski type ring closure reaction.[4,5] The purpose of this paper is to report that benzo[a]quinolizinones like **4/5** and **13** are accessible by a similarly short and efficient two step reaction sequence which employs a Heck reaction as the key step for the generation of the polycyclic ring system.

The Heck reaction, i.e. the Pd(0)-mediated coupling of an aryl halide with an olefin has proven to be a powerful tool for the construction of nitrogen heterocycles.[6] In order to investigate if this organometallic transformation can advantageously be combined with the construction of enaminones,[7] which are viable precursors for the generation of polycyclic nitrogen heterocycles,[4,5,7] the 2-bromo homoveratrylamine **1** was converted to the vinylogous amides **3** by means of imine formation and subsequent tandem Mannich-Michael reaction with the electron-rich silyloxydiene **2** (Scheme 1, Table 1). In accordance with earlier observations,[8] for aromatic Schiff bases and the formaldehyde imine the highest yields were obtained if $ZnCl_2$ in THF at 0°C was employed as Lewis acid, whereas aliphatic imines gave the best results if aluminium Lewis acids in CH_2Cl_2 at -78°C were used to promote the reaction.

The *ortho* bromo arylethyl substituted enaminones **3** were then subjected to a Heck cyclization. In the presence of aromatic substituents R^1 in **3**, the desired tetrahydrobenzo[a]quinolizinones **4** were obtained in good yields (Table 1, entries 1-3). For **4a** and **4b** the best results were recorded if 5 mol% of $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol% of PPh_3 were employed at 120°C in DMF in the presence of K_2CO_3 and NEt_4Cl, i.e. under heterogeneous conditions.[9] The use of *i*-Pr_2NEt in homogeneous solution or CH_3CN as solvent gave inferior results. In the case of **4c**, however, the highest yield was recovered if *i*-Pr_2NEt was employed as base. The Heck cyclization of the enaminones **3d** and **3e**, which are derived from aliphatic Schiff bases (R^1=aliphatic), in the presence of K_2CO_3 unexpectedly yielded not only the benzoquinolizinones **4d** and **4e** but also the isomers



Scheme 1

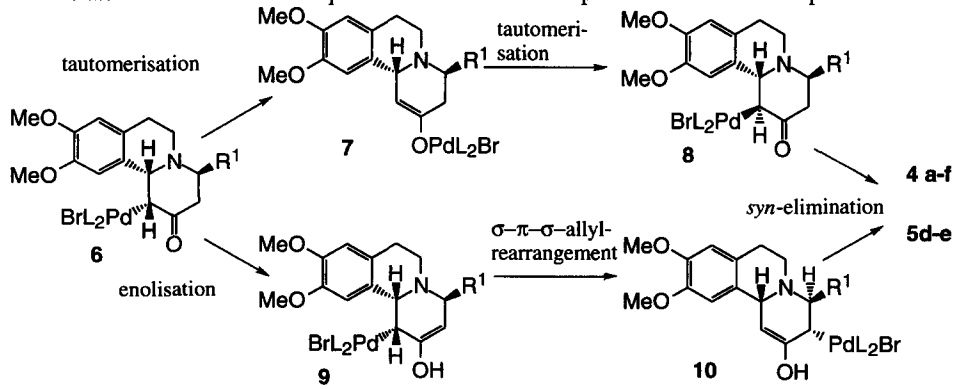
Table 1: Results of the synthesis of the enaminones **3** and their Heck cyclization to give the tetrahydrobenzo[a]quinolizinones **4** and **5**.

entry	3,4,5	R^1	Lewis acid/ solvent[a]	yield 3 [%]	base (equiv.)	solvent	temp [°C]	time	yield [%] 4	5
1	**a**	Ph	$ZnCl_2$/THF	43	K_2CO_3 (1.5)	DMF[b]	120	3h	87	-
2	**b**	4-OMe-Ph	$ZnCl_2$/THF	66	K_2CO_3 (1.5)	DMF[b]	120	3h	76	-
3	**c**	2-NO_2-Ph	$ZnCl_2$/THF	20	$NEtiPr_2$ (2)	DMF	100	25h	65	-
4	**d**	*i*-Pr	$EtAlCl_2/CH_2Cl_2$	65	K_2CO_3 (10)	toluene[b]	120	16h	30	60
5	**e**	*n*-Pr	$EtAlCl_2/CH_2Cl_2$	43	K_2CO_3 (1.5)	DMF[b]	120	5h	26	42
6	**f**	H	$ZnCl_2$/THF	47	K_2CO_3 (1.5)	DMF[b]	120	5h	33	-

a) $ZnCl_2$/THF at 0°C, 2eq.; $EtAlCl_2/CH_2Cl_2$ at -78°C, 2 eq. b) 1.0-1.2 eq. of NEt_4Cl was added.

5d and **5e** (Scheme 1, Table 1, entries 4 and 5). **4** and **5** are readily separeted by simple flash chromatography. In the presence of *i*-Pr_2NEt only the isomers **4** were formed, but only in low yield. If the formaldehyde derived enaminone **3f** was subjected to the Heck cyclization, only the underlying unsubstituted benzo[a]quinolizinone **4f** (Table 1, entry 6) could be isolated.

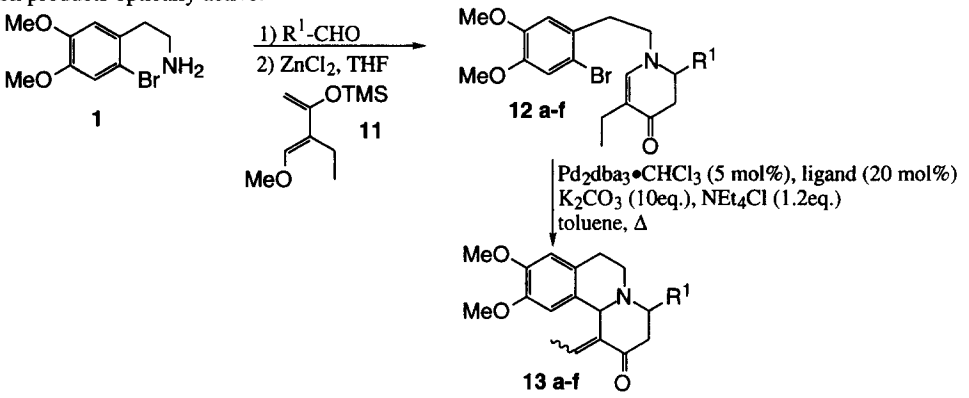
To account for the formation of both **4** and **5** we propose the mechanistic rationalization depicted in Scheme 2. After insertion of the Pd(0)-catalyst into the aryl-Br bond in **3** the resulting arylpalladium intermediate adds to the double bond of the enaminone to give the *cis* σ-palladium complex **6**. **6** may be regarded as a tautomer of the palladium enolate[10] **7** which is also in equilibrium with the Pd complex **8**. Whereas from **6** palladium can not be



Scheme 2

eliminated to complete the catalytic cycle, in **8** *syn* hydrogen H-11b is available for this purpose and the benzoquinolizinones **4** are formed by reductive *syn* elimination. This pathway is followed exclusively if R^1 is aromatic or hydrogen (Table 1). If R^1 is aliphatic, however, an alternative reaction pathway is accessible. Enolization of the ketone present in **6** which probably for steric or conformational reasons does not occur in the case of aromatic substituents R^1 gives rise to the intermediate **9**. This palladium complex now may undergo a σ-π-σ 1,3-shift of the palladium to generate **10** which after enolization and *syn* elimination of the palladium gives the heterocycles **5**.

In our previous investigations on the combination of the tandem Mannich-Michael reaction between imines and electron-rich dienes with a Bischler-Napieralski type cyclization, we had pointed out, that additional substituents may efficiently be introduced into the 1- and the 3-position of the polycyclic N-heterocycles by using appropriately substituted silyloxydienes.[5] In order to investigate if this principle can also be realized via the Heck cyclization route described above, the ethyl-substituted enaminones **12** were built up as depicted in Scheme 2 by employing the diene **11** instead of the unsubstituted diene **2**. Upon treatment of the enaminones **12** with $Pd_2(dba)_3$•$CHCl_3$ and an additional phosphine in refluxing toluene with K_2CO_3 as base and NEt_4Cl as additive the hexahydrobenzo[a]quinolizidinones **13** embodying an exocyclic double bond were formed in moderate yield (Scheme 3, Table 2). As proposed above, the initially formed arylpalladium intermediate in these cases too undergoes a *syn* addition to the double bond of **12**, but due to the presence of the additional ethyl substituent the addition product which is analogous to **6** then can directly eliminate the palladium again by formation of an exocyclic double bond. Since in **13** a new stereocenter is created in the course of the Heck cyclization, asymmetric induction might occur in the presence of a chiral phosphine ligand. Therefore, (*R*)-BINAP which had already proven to be an efficient mediator of chirality in enantioselective Heck reactions[11] was employed instead of PPh_3 or P(*o*-Tol)$_3$ as additive in the Pd(0)-mediated reaction. However, unfortunately, in no case were the reaction products optically active.

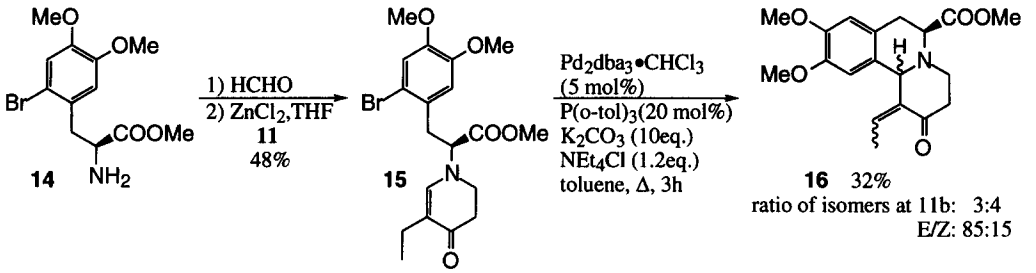


Scheme 3

Table 2: Results of the synthesis of the 3-ethyl substituted enaminones **12** and their Heck cyclization to give the hexahydrobenzo[a]quinolizinones **13**.

entry	**12,13**	R^1	yield **12** [%]	ligand	time	yield **13** [%]	E/Z ratio
1	**a**	Ph	45	PPh_3	26h	53	3:1
2	**b**	4-OMe-Ph	52	R-(+)-BINAP	6.5h	53	3:1
3	**c**	4-NO_2-Ph	73	P(*o*-tol)$_3$	5h	41	3:1
4	**d**	*i*-Pr	27	R-(+)-BINAP	21h	34	>20:1
5	**e**	Heptyl	22	R-(+)-BINAP	48h	40	1:1
6	**f**	H	64	PPh_3	6h	27	>20:1

As an alternative approach to the stereoselective construction of hexahydrobenzo[a]quinolizinones, the use of an enantiomerically pure amino acid in the Mannich-Michael/Heck sequence was investigated. To this end, the bromo substituted (S)-amino acid ester **14**[12] was converted to the enaminone **15**, which was then subjected to the Heck cyclization (Scheme 4). In the course of this transformation, the cyclic amino acid derivatives **16** were formed in 32% yield as a mixture of diastereomers (ratio of isomers at H-11b 3:4; ratio of E and Z isomer 85:15).



Scheme 4

In conclusion, the results detailed above demonstrate that tetrahydrobenzoquinolizinones and hexahydroquinolizinones can be built up in a straightforward manner by means of a short two step reaction sequence consisting of a tandem Mannich-Michael reaction and a Heck cyclization. This method should open up new routes for the construction of alkaloids and analogues thereof.

Acknowledgement: This research was supported by the Fonds der Chemischen Industrie.

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12. *(S)-(2-Bromo-4,5-dimethoxy-phenyl)alanine-methylester* **14** was prepared from L-DOPA by bromination (Br_2, AcOH, quant.), esterification ($SOCl_2$, MeOH, quant.), Boc protection (MeOH, NEt_3, Boc_2O, 69%), methylation (CH_2N_2, CH_2Cl_2, 74%), and Boc deprotection (TFA, quant.): yellowish oil; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.02 (s, 1H, CH-3), 6.75 (s, 1H, CH-6), 3.85 (2s, 6H, OCH_3), 3.83 (dd, $J_{vic,CH2a}$=5.7 Hz, $J_{vic,CH2b}$=8.6 Hz, 1H, CH-COOMe), 3.72 (s, 3H, $COOCH_3$), 3.18 (dd, J_{vic}=5.7 Hz, J_{gem}=13.7 Hz, 1H, CH_{2a}), 2.90 (dd, J_{vic}=8.5 Hz, J_{gem}=13.7 Hz, 1H, CH_{2b}), 1.65 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 175.3 (COOMe), 148.6, 148.4 (2C, C-OMe), 128.8 (ipso-C), 115.7 (CH-3), 114.8 (C-Br), 114.0 (CH-6), 56.2, 56.1 (2C, OCH_3), 54.7 (CH-COOMe), 52.2 ($COOCH_3$), 30.9 (CH_2) ppm; **14**•TFA $[\alpha]_D^{20}$ = +10.6 (*c*=1.18, MeOH).

(*Received in Germany* 11 *February* 1997; *accepted* 8 *March* 1997)