Synthesis of *N*-Methylbenzo[*d,e*]quinolines

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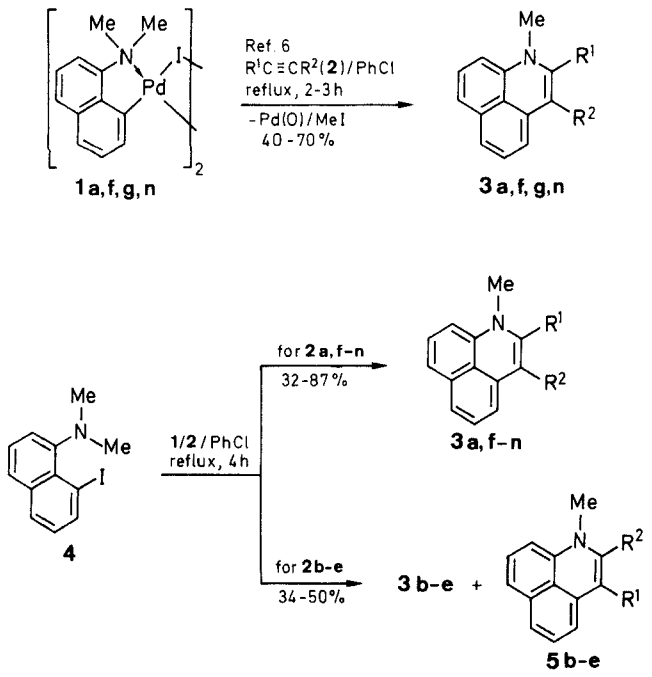
The reaction between internal alkynes and 1-iodo-8-dimethylaminonaphthalene in the presence of catalytic amounts of a cyclopalladated compound provides a new route to *N*-methylbenzo[*d,e*]quinolines.

Aporphine derivatives form a class of alkaloids which display important biological activities and which are useful either for the treatment of Parkinsonism or in cancer chemotherapy.[1] Most of the nonbiogenetic syntheses of these polycyclic compounds involve the reduction of *N*-methylbenzo[*d,e*]quinoline derivatives.[2] However, there are only a few synthetic methods for these compounds which do not use isoquinolines as starting materials: the reaction between amidines and 1,3,6,8-tetranitronaphthalene,[3] the photodecomposition of triazaphenalenes in the presence of vinyl bromide[4] or the reaction of dimethyl butynedioate with 1,4-dihydronaphthalene-1,4-imines.[5] More recently it was shown that the palladium derivative of 1-dimethylaminonaphthalene **1**, afforded stoichiometrically a new class of 2,3-disubstituted benzo[*d,e*]quinolines **3** by a reaction with disubstituted alkynes **2**.[6]

We now report the synthesis of a series of compounds **3** (Table 1), which is based on the palladium-catalyzed addition of 1-iodo-8-dimethylaminonaphthalene **(4)** to disubstituted alkynes **2**; a process that is derived from the Heck reaction.[7] The results are presented in the tables 1 and 2, and the Scheme.

The only active palladium catalyst was compound **1**. All attempts with other palladium compounds, i.e. $Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd(OAc)_2$or $PdCl_2(PhCN)_2$, did not lead to any detectable amount of **3**. Thus, when calculating the total amount of alkyne required for the reaction, the amount of **4** in the catalyst present must also be considered. The best yields of compound **3** were obtained when the 1-iodo-8-dimethylaminonaphthalene **(4)** was slowly added at reflux temperature to a chlorobenzene solution containing a catalytic amount of **1** and the disubstituted alkyne **2**. The use of 1-alkynes or even of trimethylsilyl protected moieties did not lead to any



2,3,5	R^1	R^2	2,3,5	R^1	R^2
a	Ph	Ph	**h**	Ph	Me
b	Ph	4-$NO_2C_6H_4$	**i**	Ph	$CH(OEt)_2$
c	Ph	4-MeC_6H_4	**j**	Et	Et
d	Ph	4-$MeOC_6H_4$	**k**	Ph	CO_2Me
e	Ph	3-$CF_3C_6H_4$	**l**	Ph	CHO
f	Ph	CO_2Et	**m**	Ph	COMe
g	CO_2Me	CO_2Me	**n**	CF_3	CF_3

Scheme

Table 1. *N*-Methylbenzo[*d,e*]quinolines **3a**, **3f–m** and the Regioisomeric Mixtures **3b–e**, **5b–e** Prepared

Product	Catalyst **1** (%)	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b] or Lit. mp (°C)
3a[6]	5	87	196–198 (pentane)	201[6]
3b, **5b**[c]	5	48	198–200 (Et_2O/hexane)[c]	$C_{25}H_{18}N_2O_2$ (378.4)
3c, **5c**[c]	5	50	136–138 (pentane)[c]	$C_{26}H_{21}N$ (347.5)
3d, **5d**[c]	5	34	238 (Et_2O/hexane)[c]	$C_{26}H_{21}NO$ (363.5)
3e, **5e**[c]	5	35	188–190 (hexane)[c]	$C_{26}H_{18}NF_3$ (401.4)
3f[6]	5	70	116–117 (Et_2O/hexane)	117[6]
3g[6]	5	43	84–86 (Et_2O/hexane)	92[6]
3h	20	53	118–120 (pentane)	$C_{20}H_{17}N$ (271.4)
3i[d]	50	80	n.d.	$C_{24}H_{25}NO_2$ (359.5)
3j[e]	50	47	88–89 (Et_2O/pentane)	$C_{17}H_{19}N$ (237.3)
3k	5	59	110–112 (Et_2O/pentane)	$C_{21}H_{17}NO_2$ (315.7)
3l	5	50	190–192 (Et_2O/pentane)	$C_{20}H_{15}NO$ (285.3)
3m	5	32	124–126 (Et_2O/pentane)	$C_{21}H_{17}NO$ (299.4)

[a] Yield of isolated product based on **4** and the amount of catalyst **1** used for the reaction, after chromatographic separation.
[b] Satisfactory microanalyses: C ±0.48, H ±0.34, N ±0.24, except for **3i**.
[c] This products are inseparable mixtures of the regioisomeric compounds **3** and **5**; melting points are taken from the mixtures.
[d] Very sensitive to hydrolysis which affords the corresponding aldehyde, **3l**.
[e] Unstable in solution and in the presence of light.

identifiable products. The results reported in Table 1 show that the use of alkynes substituted by aryl units or electron withdrawing groups such as carboxylates gives better yields. Lower yields of **3** were obtained with electron rich alkynes such as 3-hexyne **(2j)**, 1-phenyl-1-propyne **(2h)** or 3,3-diethoxy-1-phenyl-1-propyne **(2i)**. However, by increasing the amount of palladium catalyst these latter reactions afforded reasonable yields of **3h–j**.

There was no regioselectivity observed when the asymmetric diarylalkynes **2b–e** were used. In these cases the products were a 1:1-mixture of the regioisomeric compounds **3** and **5** with the exception of **3b** and **5b**, which has a ratio of 1:2, according to the ^{1}H- or ^{19}F-NMR spectroscopic data. This is an argument in favor of the reaction being controlled by steric effects of the alkynyl substituents rather than by electronic factors as stated earlier.[6] However, with the other asymmetric alkynes only one regioisomer was found. We suggest that in these cases the phenyl groups are always on the carbon which is linked to the nitrogen atom, a result which is in concert with our previous observations on the insertion of alkynes into the Pd-C bonds of cyclopalladated compounds.[6] This feature was also confirmed by a NOE ^{1}H-NMR study on compound **3h** which showed that the alkynyl methyl group and the naphthyl unit are adjacent to each other.

The likely reaction path by which these quinolines are formed should involve initial insertion of the alkyne into the Pd–C bond of the catalyst **1**, followed by reductive elimination of Pd(0) which leads to the formation of the C–N bond. The catalyst is then regenerated by oxidative addition of the 1-iodo-8-dimethylaminonaphthalene.

In conclusion we have expanded a convenient route to otherwise unavailable *N*-methylbenzo[*d,e*]quinolines functionalized at the 2- and 3-positions, that will provide an interesting entry into a new class of functionalized aporphine derivatives. Further work in this latter direction are in progress.

The alkynes used in this study were from commercial sources (Aldrich or Lancaster) except the asymmetric diarylacetylenes which were synthesized according to a slightly modified literature procedure[8] from phenylacetylene and the corresponding iodoaryl

Table 2. Spectral Data of *N*-Methylbenzo[*d,e*]quinolines **3** and **3, 5**

Product	UV-Vis(CH_2Cl_2) λ_{max}(nm) (log ε)	IR (KBr) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS m/z (%)
3a	472 (sh), 439 (sh), 419 (3.58), 356 (4.23), 225 (4.41)	1620 (vs), 1575 (vs), 768 (vs), 751 (vs), 698 (vs)	–[6]	333 (–)[d]
3b, 5b[a]	497 (3.25), 366 (sh), 352 (4.22), 242 (sh), 225 (4.40)	1512 (s), 1342 (vs), 775 (s), 752 (s), 708 (s)	8.10–6.04 (m, 15H_{arom}), 2.91, 2.89 (2s (1:2), 3H, NCH_3)	–
3c, 5c[a]	440 (sh), 419 (3.59), 371 (sh), 356 (4.26), 226 (4.46)	1625 (vs), 1574 (vs), 768 (vs), 707 (vs)	7.26–6.15 (m, 15H_{arom}), 2.88 (s, 3H, NCH_3), 2.25, 2.24 (2s (1:1), 3H, CH_3)	–
3d, 5d[a]	470 (sh), 441 (sh), 420 (3.58), 3.56 (4.25), 229 (4.46)	1573 (vs), 1250 (vs), 870 (vs), 708 (vs)	7.26–6.12 (m, 15H_{arom}), 3.74, 3.73 (2s (1:1), 3H, OCH_3), 2.89, 2.88 (2s (1:1), 3H, NCH_3)	–
3e, 5e[a]	441 (sh), 418 (3.64), 358 (4.32), 226 (4.53)	1168 (vs), 1120 (vs), 1075 (vs)	7.38–6.08 (m, 15H_{arom}), 2.90 (s, 3H, NCH_3)[b]	–
3f	418 (sh), 367 (sh), 352 (4.28), 236 (4.47)	1710 (vs), 768 (vs), 702 (s)	–[6]	329 (–)[d]
3g	434 (3.34), 363 (sh), 348 (4.28), 235 (4.54)	1732 (s), 1690 (vs), 757 (s), 732 (s)	–[6]	297 (–)[d]
3h	432 (sh), 413 (3.67), 358 (4.19), 250 (4.20), 230 (4.25)	1570 (vs), 758 (vs), 702 (vs)	7.54–6.20 (m, 11H_{arom}), 2.86 (s, 3H, NCH_3), 1.65 (s, 3H, CCH_3)	271 (29)[e]
3i[c]	–	–	7.61–6.15 (m, 11H_{arom}), 4.64 (s, 1H, $CH(OEt)_2$), 3.35 (m, 4H, CH_2), 2.77 (s, 3H, NCH_3), 1.10 (t, 6H, J = 7.1, CCH_3)	
3j	432 (sh), 412 (sh), 366 (sh), 354 (3.26), 251 (3.29), 219 (3.48)	1575 (vs), 1352 (s), 767 (vs)	7.51–6.17 (m, 6H_{arom}), 3.18 (s, 3H, NCH_3), 2.62, 2.49 (2q, 4H, J = 7.5, CH_2), 1.22, 1.15 (2t, 6H, J = 7.5, CH_3)	237 (14)[e]
3k	422 (sh), 368 (sh), 353 (3.59), 236 (3.80), 218 (3.79)	1695 (vs), 1260 (vs), 772 (vs)	7.46–6.88 (m, 10H_{arom}), 6.28 (d, 1H_{arom}), 3.34 (s, 3H, CO_2CH_3), 2.89 (s, 3H, NCH_3)	315 (34)[e]
3l	438 (3.23), 373 (3.84), 347 (3.89), 2.39 (4.29), 219 (4.16)	1618 (vs), 1368 (vs)	9.11 (s, 1H, CHO), 8.67 (dd, 1H_{arom}), 7.59–7.20 (m, 8H_{arom}), 6.56 (dd, 1H_{arom}), 3.00 (s, 3H, NCH_3)	285 (23)[e]
3m	436 (sh), 380 (sh), 357 (3.28), 240 (3.54), 2.19 (3.56)	1673 (s), 1572 (vs), 770 (vs)	7.50–7.04 (m, 8H_{arom}), 6.74 (dd, 1H_{arom}), 6.29 (d, 1H_{arom}), 2.93 (s, 3H, NCH_3), 1.76 (s, 3H, $COCH_3$)	299 (30)[e]

[a] See footnote c, Table 1.
[b] ^{19}F-NMR (376.05 MHz, $COCl_3/CFCl_3$): δ = –60,86, –64.61 (2s (1:1), CF_3).
[c] This compound was always contaminated by the presence of variable amounts of EtOH and the corresponding aldehyde derivative, **21**.
[d] Recorded on a Thomson THN 208 spectrometer (70 eV).
[e] Recorded on a VG ZAB-HF spectrometer (FAB).

derivative. 1-Lithio-8-dimethylaminonaphthalene[9] and compound **1**[6] were obtained as described in the literature, 1-naphthylamine being purchased from Aldrich. The solvents were dried and distilled under nitrogen prior to use. Chromatographic separation of the products was achieved on Al_2O_3 90,70–230 mesh (Merck).

Melting points were measured by the Kofler method or with a Büchi apparatus and are uncorrected. The compounds being placed in open capillaries. Analyses were performed by the Service d'analyses du CNRS, Strasbourg. ^{1}H- and ^{19}F-NMR spectra were run with a Bruker SY200 and AM400 spectrometer in $CDCl_3$ with TMS and $CFCl_3$ as internal standard, respectively. IR spectra were run with a Perkin-Elmer 398 Infrared spectrometer on KBr pellets; UV-Vis spectra were run with a Shimadzu UV-260 spectrometer on CH_2Cl_2 solution. Mass spectra were measured by the Laboratoire de Spectroscopie de Masse, Strasbourg.

1-Iodo-8-dimethylaminonaphthalene (4):
To a stirred suspension of 1-lithio-8-dimethylaminonaphthalene (11.11 g, 44.26 mmol) in Et_2O (40 mL) under N_2 at 0 °C is slowly added a solution of I_2 (11.33 g, 44.6 mmol) in Et_2O (60 mL). After 1 h stirring the obtained light-brown solution is washed with a solution of $Na_2S_2O_3$ (1 g) in H_2O (40 mL). The organic layer is dried ($MgSO_4$) and the solvent is removed under reduced pressure to afford a brown oil. The product is then chromatographed on a silica gel column (20 cm × 3 cm; 70–230 mesh) using hexane as eluent (300 mL) to give **4** as a pale yellow liquid; yield: 10.29 g (72%).

^{1}H-NMR ($CDCl_3$/TMS): δ = 8.17, 7.76, 7.50, 7.25 (4 dd, 4 H_{arom}, J = 7.5–8.0 Hz, J = 1.0–1.5 Hz), 7.41, 7.02 (2t, 2 H_{arom}, J = 8.0 Hz, J = 7.5 Hz), 2.68 (s, 6 H, $N(CH_3)_2$), in accord to the values reported in literature.[10]

Synthesis of the *N*-methylbenzo[*d,e*]quinolines; General Procedure:
A solution of 1-iodo-8-dimethylaminonaphthalene (**4**; 1.188 g, 4 mmol) in PhCl (20 mL) was slowly added to a solution of the alkyne **2** (4.2 mmol) and compound **1** (0.080 g, 0.2 mmol) in PhCl (20 mL) at reflux temperature within 1 to 2 h. The resulting solution is then refluxed further 2 h. After removal of the solvent under reduced pressure the compound is chromatographed on a column of alumina (20 cm × 3 cm). Elution with pentane (500–1000 mL) eliminates the unreacted reagents whereas elution with Et_2O (200–500 mL) affords compounds **3** and the mixtures **3** and **5** which are then recrystallized (Table 1). This procedure can be used for all alkynes except of dimethyl butynedioate **2g** for which the temperature of the reaction should not exceed 85 °C in order to avoid extensive polymerisation of the alkyne.

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