Facile Synthesis of Substituted Fumaronitriles and Maleonitriles: Precursors to Soluble Tetraazaporphyrins

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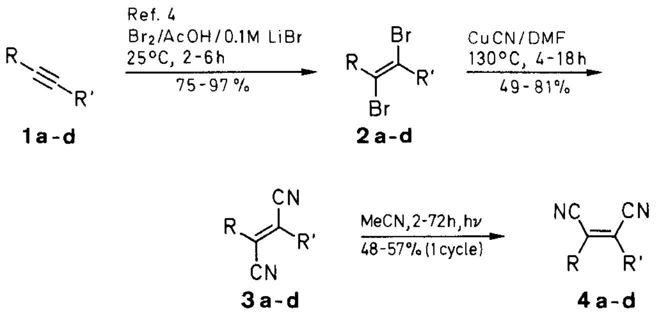
Alkynes are converted in good yield to alkyl and/or aryl substituted fumaronitriles and maleonitriles, a rich source of precursors to soluble tetraazaporphyrins.

Tetraazaporphyrins[1], macrocyclic ligands composed of four pyrrole rings bridged by aza nitrogens, are easily prepared from fumaronitriles or maleonitriles via Linstead's template cyclization.[2] However, alkyl or aryl substituted fumaronitriles and maleonitriles, necessary as precursors to the soluble tetraazaporphyrins of interest in our work, are not readily available.[3]

We report herein an efficient, general synthesis of alkyl and/or aryl substituted fumaronitriles and maleonitriles starting from commercially available alkynes. To demonstrate that these dinitriles may be cyclized into tetraazaporphyrins, we also report the synthesis of octaethyltetraazaporphyrin.

Treatment of either internal or terminal alkynes, **1**, with one equivalent of bromine, in the presence of bromide ion, produces *trans*-dibromoalkenes, **2**.[4] These vinylic dibromides are converted to fumaronitriles, **3**, via the Rosenmund-von Braun reaction, a reaction which typically has been applied only to aryl bromides.[5] The fumaronitriles, **3**, may be photoisomerized to the corresponding maleonitriles, **4**, using a modified form of the procedure of Turro.[6]

All steps proceed in moderate to good yields except the photoisomerizations which reach photostationary states consisting of approximately equal amounts of *cis*- and *trans*-dinitriles. These isomers are easily separated by fractional vacuum distillation, allowing the fumaronitrile to be recycled. The assignment of stereochemistry to the dinitriles is based on either literature data or measured dipole moments; the fumaronitriles have dipole moments between 0.0 and 2.0 D and the maleonitriles have dipole moments between 5.5 and 6.0 D.



1-4	R	R'	1-4	R	R'
a	Et	Et	**c**	Ph	H
b	Bu	H	**d**	Ph	Ph

The synthesis of substituted fumaronitriles and maleonitriles described above is a significant improvement over methods in the literature. Linstead's oxidative coupling of substituted acetonitriles is a low yield process applicable only to the synthesis of diarylfumaronitriles.[2] More recent modifications have increased the yield but at a cost of additional synthetic steps with no gain in the generality of the reaction.[7] Mixtures of alkyl and/or aryl substituted fumaronitriles and maleonitriles may be produced in

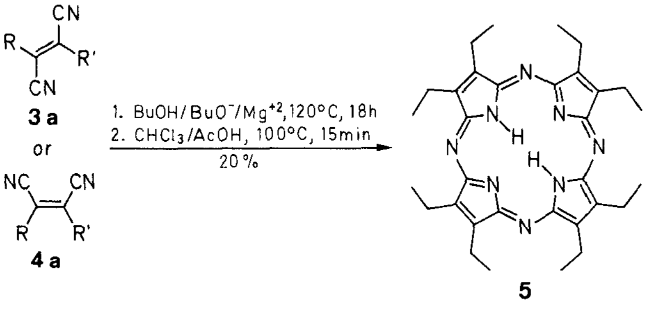
Table. Compounds 3 and 4 Prepared

Compound	Reaction Time (h)	Yield[a] (%)	mp (°C)[b] or bp (°C)/mbar	Molecular Formula[c] or Lit. Data	IR (neat)[d] ν (cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[e] δ
3a	18	78	64–65/8	$C_8H_{10}N_2$ (134.2)	2960, 2920, 2855, 2200, 1445, 1370, 1045, 945	1.23 (t, 6H), 2.59 (q, 4H)
3b	4	60	50–51/3	$C_8H_{10}N_2$ (134.2)	3070, 2980, 2945, 2880, 2240, 1470, 1380, 860	0.99 (t, 3H), 1.42 (m, 2H), 1.66 (m, 2H), 2.61 (t, 2H), 5.96 (s, 1H)
3c	4	49	87.5–88	89–90[8]	3060, 2225, 1575, 1455, 1340, 1265, 860, 770, 690[f]	6.39 (s, 1H), 7.55 (m, 3H), 7.66 (m, 2H)
3d	4	81	160–161	159–160[7]	3080, 3045, 2230, 1585, 1500, 1450, 1255, 1010, 760, 700[f]	7.56 (m, 6H), 7.85 (m, 4H)
4a	72	50	108–110/8	$C_8H_{10}N_2$ (134.2)	2990, 2945, 2890, 2230, 1460, 1390, 1060, 955	1.25 (t, 6H), 2.42 (q, 4H)
4b	72	48	87–88/3	$C_8H_{10}N_2$ (134.2)	3070, 2960, 2880, 2240, 1615, 1470, 1390, 1110, 855	0.95 (t, 3H), 1.40 (m, 2H), 1.62 (m, 2H), 2.43 (t, 2H), 5.88 (s, 1H)
4c	2	57	40.5–41	42–43[8]	3060, 2230, 1595, 1575, 1450, 1370, 1210, 845, 780, 695[f]	6.14 (s, 1H), 7.57 (m, 3H), 7.92 (m, 2H)
4d	1	~0	134	134[11]	3080, 3040, 2230, 1600, 1590, 1490, 1450, 1310, 770, 700[f]	7.31 (m, 6H), 7.39 (m, 4H)

[a] Yield of isolated product.
[b] Uncorrected, measured on a Thomas-Hoover apparatus.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, N ±0.35.
[d] Recorded on a Perkin-Elmer 1320 Infrared Spectrophotometer.
[e] Recorded on a General Electric QE 300 Spectrometer.
[f] KBr pellet

moderate yields from less readily available β-oxonitriles in a three-step process reported by Beech and Piggott.[8] The preparative utility of this method is limited by the final step, a pyrolysis at 480 °C. One drawback to the method reported here is its inapplicability to the synthesis of diarylmaleonitriles. Attempts to photoisomerize diarylfumaronitriles result in formation of the corresponding dihydrophenanthrene.[9]

Both 2,3-diethylfumaronitrile (**3a**) and 2,3-diethylmaleonitrile (**4a**) may be converted to octaethyltetraazaporphyrin, **5**, via modified literature procedures.[10]



Yields are significantly higher when the maleonitrile starting material is used. This is to be expected because, in order to cyclize, the two nitrile groups must be *cis* to each other. It is not clear if thermal isomerization occurs in the free dinitrile or in an intermediate prior to macrocycle formation. The fact that diphenylmaleonitrile may be isolated from cyclization reactions in which the fumaronitrile was used as the starting material suggests that isomerization occurs in the free dinitrile.

All reagents except 3-hexyne were purchased from Aldrich Chemical Co. 3-Hexyne was purchased from Lancaster Synthesis Ltd. All reagents were of commercial quality except the DMF, which was purchased as "anhydrous", and the 1-butanol, which was distilled from magnesium prior to use. All *trans*-dibromoalkenes were prepared as described in the literature.[4] Analytical TLC plates and TLC grade silica gel (for flash chromatography columns) were purchased from J.T. Baker Co. Samples were submitted to Galbraith Laboratories for elemental analyses. ^{1}H-NMR spectra and IR spectra were recorded on a General Electric QE300 spectrometer and a Perkin-Elmer 1320 spectrometer, respectively. Dinitrile mixtures were analyzed on a Hewlett-Packard 5890 capillary gas chromatograph using a flame ionization detector.

Fumaronitriles 3; General Procedure:

A 500 mL round bottom flask, fitted with a magnetic stirrer, a condensor and a nitrogen inlet tube, is charged with copper(I) cyanide (44 g, 0.50 mol) and dry DMF (250 mL). This stirred mixture is heated to reflux for 1 h and then allowed to cool to r.t. under a N_2 atmosphere. *trans*-Dibromoalkene (0.20 mol) is added and the stirred solution is heated in an oil bath maintained at 130 °C between 4 and 18 h. Temperature control is critical in this reaction; heating at the reflux temperature causes catastrophic decreases in yield. The cooled mixture is poured into 6 M aq NH_3 (1.5 L); the resulting blue solution is stirred for 1 h and then vaccum filtered. The precipitate is washed with Et_2O (3 × 50 mL) and the filtrate is extracted with Et_2O (3 × 100 mL). All the ether portions are combined, washed once with water (100 mL), once with sat. aq NaCl (100 mL), dried ($MgSO_4$), filtered and reduced on a rotary evaporator. The pure product was obtained either by vacuum distillation or recrystallization.

Maleonitriles 4; General Procedure:

A stirred solution of substituted fumaronitrile (0.15 mol) in MeCN (500 mL) is irradiated with unfiltered light from a 450 W medium pressure mercury lamp while being degassed with a slow stream of N_2. The reaction, as monitored by both TLC (silica gel GF, 1/1 to $CHCl_3$/hexanes) and capillary GC (crosslinked methyl silicone, He flow rate = 20.0 mL/min, T = 100 °C (5 min), 5 °C/min, 125 °C (10 min)) reaches a photostationary state within 2 and 72 h of irradiation. The solvent is removed from the mixture on a rotary evaporator and the resulting crude product is purified by either fractional vacuum distillation or recrystallization.

Octaethyltetraazaporphyrin (5):

To a suspension of Mg (0.50 g, 20 mmol) in dry BuOH (25 mL) is added I_2 (2.61 g, 10 mmol). This mixture is heated at reflux under N_2 overnight or until all the Mg metal has been consumed. Once prepared, this solution is allowed to cool to r.t., 2,3-diethylmaleonitrile (2.75 g, 20 mmol) is added, and the solution is heated back to the reflux temperature. Reflux is maintained for 18 h when the solution is allowed to cool and the resulting mass is dissolved in EtOH (200 mL). *Addition of this solution to water (800 mL) causes* crude magnesium octaethyltetraazaporphyrin to precipitate; this is collected by vacuum filtration and dried under vacuum. The tetraazaporphyrin is separated from some insoluble tar by Soxhlet extraction into $CHCl_3$ (250 mL). Removal of the solvent followed by chromatography of the resulting residue (10 × 4 cm; TLC grade) using CH_2Cl_2/Et_2O (10:1) as eluent afforded crude magnesium *octaethyltetraazaporphyrin (0.58 g)*. Removal of magnesium from the tetraazaporphyrin is accomplished by heating at reflux in a $CHCl_3/AcOH$ (20:1) solution (200 mL) for 15 minutes. The cooled solution is poured into water (200 mL) which is made basic by the addition of NaOH. The organic layer is separated, washed once with 10% aq NaOH (50 mL), dried (Na_2SO_4), and filtered. The tetraazaporphyrin is adsorbed onto silica gel by suspending TLC grade silica gel (30 g) in the filtrate and removing the solvent on a rotary evaporator. The coated silica gel is loaded onto a silica gel column (10 × 4 cm; TLC grade) and eluted with CH_2Cl_2/hexanes (1:1). Slow evaporation of the solvent gives a microcrystalline solid which could be recrystallized by slow diffusion of benzene into a $CHCl_3$ solution of the tetraazaporphyrin; yield: 0.55 g (20%); mp > 300 °C.

$C_{32}H_{42}N_8$	calc.	C 71.34	H 7.86	N 20.80
(538.7)	found	71.50	7.89	20.92

UV-vis (CH_2Cl_2): λ_{max} (nm) (log ε) = 340 (4.9), 515 (sh), 558 (4.6), 600 (3.9), 627 (4.8).

^{1}H-NMR ($CDCl_3$): $\delta = -2.11$ (s, 2H, NH), 1.86 (t, 24H, J = 7.7 Hz, CH_3), 3.98 (q, 16H, J = 7.7 Hz, $C\underline{H}_2CH_3$).

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