Synthesis of Substituted 7,7'-bis-Indolizines via 1,3-Dipolar Cycloaddition under Microwave Irradiation

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Abstract
An efficient method for preparation of substituted 7,7'-bis-indolizines, based on 1,3-dipolar cycloaddition of 4,4'-bipyridinium ylides generated *in situ* with activated alkynes, is proposed. The reaction was carried out in good yields by microwave irradiation and KF/alumina under solvent-free conditions.

Introduction

The synthesis of N-heteroaromatic compounds like indolizine derivatives attracts continuously the attention of synthetic chemists (1), since, for example, they are useful intermediates in the synthesis of cycl[3.2.2]azine (2).

The 1,3-dipolar cycloaddition of pyridinium and related heteroaromatic ylides with acetylenes is one of the most important and efficient methods of synthesis, although generally the reaction yields are very low (3). In addition, this procedure often suffers from drawbacks and limitations: for example it requires very long reaction times and the presence of environmentally hazards solvents such as benzene (4).

We have previously described that 4,4-bipyridinium ylides react with activated alkynes in benzene (or *N*-methylpyrrolidone) under classical heating, yielding 7,7'-bis-indolizines derivatives in the range of 50-60% (5). As an extension of this work we report here a simple and practical method that affords aromatic indolizines in high yield starting from diquaternary salts of 4,4-bipyridine and activated alkynes in the presence of the basic catalyst KF on alumina under microwave irradiation that was in part the subject of a preliminary note (6). Cycloaddition reactions carried out under microwave irradiation seem to be the most promising synthetic sequence for construction of such systems. With the microwave irradiation method the reactions are carried out in neat phase and hence this technique is environmentally benign.

Experimental

4,4'-bipyridyl and phenacyl halides were purchased from Aldrich (Milwaukee) and used as received. Solvent evaporations were always carried out under vacuum using rotary evaporator. The samples for microanalysis were dried *in vacuo* to constant weight

(20°C, *ca* 0.1 Torr). All syntheses were carried out under a nitrogen atmosphere. Hydrocarbon solvents were dried by distillation from sodium-potassium. All solvents were degassed with dry nitrogen prior to use.

Elemental analyses (C,H,N) were performed with a Fisons Instruments 1108 CHNS-O Elemental analyser. IR spectra were recorded from 4000 to 100 cm^{-1} with a Perkin-Elmer System 2000 FT-IR instrument. ^1H and ^{13}C NMR spectra were recorded on a VXR-300 Varian spectrometer operating at room temperature (300 MHz for ^1H and 75 MHz for ^{13}C). The chemical shifts (δ) are reported in parts per million (ppm) from $SiMe_4$ (^1H calibration by internal deuterium solvent lock). Peaks multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; multiplet, m; pseudotriplet, pt; complex multiplet, mc; broad, br. Melting points are uncorrected and were taken on an IA 8100 Electrothermal instrument and on a capillary apparatus.

Experimental procedure for the synthesis of 7,7'-bis-indolizines 1-18 under classical conditions.

4,4'-bipiridinium diquaternary salt (1 mmol) previously obtained by reaction of 4,4'-bipiridyl and phenacyl halide was suspended in N-methyl-pyrrolidone (10 ml) together with acetylene dicarboxylate (2 mmol). Triethylamine (2 mmol) in N-methyl-pyrrolidone (3 ml) was slowly added and the mixture vigorously stirred and heated under inert atmosphere. The suspension was filtered off and the precipitate washed with methanol. All compounds have been recrystallized (methanol:chloroform 1:1).

General Procedure for the synthesis of of 7,7'-bis-indolizines 1-18 under microwave irradiation.

4,4'-bipiridinium diquaternary salt (1 mmol) and acetylene dicarboxylate (2 mmol) were dissolved into 1 ml of acetone and adsorbed on KF-Merck Alumina 70-230 mesh. The solvent was then evaporated and the mixture was irradiated at atmospheric pressure in a focused microwave reactor Prolabo MX350 with measurement and control of power and temperature by infrared detection for the time and at the power indicated in Table 1. After 10 min, the mixture was dissolved in chloroform and filtrated at room temperature. The solvent was evaporated under vacuum. The residue was eluted with methanol and purified from methanol-chloroform.

The compounds 1-18 were purified by chromatography (alumina), in vacuum and eluted with ethylacetate-light petroleum (40-60 °C).

1,2,1',2'-Tetraethoxycarbonyl-3,3'-bis(benzoyl)-7,7'-bis(indolizine) 1. Bright yellow crystals, mp: 220-221°C. Anal. calcd. for $C_{42}H_{36}N_2O_{10}$: C, 69.22; H, 4.98; N, 3.84. Found C, 69.45; H, 4.74; N, 4.10%. ^1H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.65 (d, 2H), 8.86 (d, 2H), 7.78 (q, 2H), 7.45-7.58 (m, 10H), 4.39 (q, 4H), 3.71 (q, 4H), 1.39 (t, 6H); 1,08 (t, 6H). IR (cm^{-1}, nujol): 1734s, 1694s, 1614m (C=O).

1,2,1',2'-Tetraethoxycarbonyl-3,3'-bis(p-chlorobenzoyl)-7,7'-bis(indolizine) 2. Bright yellow crystals, mp: 223-224°C. Anal. calcd. for $C_{42}H_{34}Cl_2N_2O_{10}$: C, 63.24; H, 4.30; N, 3.51. Found C, 63.63; H, 4.41; N, 3.63%. ^1H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.68 (d, 2H), 8.80 (d, 2H), 7.78 (q, 2H), 7.75 (d, 2H), 7.42 (d, 2H), 4.40 (q, 4H), 3.70 (q, 4H), 1.37 (t, 6H), 1.08 (t, 6H). IR (cm^{-1}, nujol): 1735s, 1693s, 1639m (C=O).

1,2,1',2'-Tetraethoxycarbonyl-3,3'-bis(p-bromobenzoyl)-7,7'-bis(indolizine) 3. Bright yellow crystals, mp: 254-255°C. Anal. calcd. for $C_{42}H_{34}Br_2N_2O_{10}$: C, 56.90; H, 3.87; N, 3.16. Found C, 56.68; H, 3.94; N, 3.24%. ^1H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.72 (d, 2H), 8.85 (d, 2H), 7.95 (q, 2H); 7.71 (d, 2H), 6.98 (d, 2H) 4.40 (q, 4H), 3.72 (q, 4H), 1.40 (t, 6H), 1.10 (t, 6H). IR (cm^{-1}, nujol): 1737s, 1692s, 1621m (C=O).

1,2,1',2'-Tetraethoxycarbonyl-3,3'-bis(p-nitrobenzoyl)-7,7'-bis(indolizine) 4. Bright yellow crystals, mp = 273-274°C. Anal. calcd. for. $C_{42}H_{34}N_4O_{14}$: C, 61.61; H, 4.19; N, 6.84. Found. C, 61.61; H, 4.41; N, 6.85%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.85 (d, 2H), 8.88 (d, 2H), 8.33 (q, 2H), 7.88 (d, 2H), 7.61 (d, 2H) 4.40 (q, 4H), 3.71 (q, 4H), 1.39 (t, 6H), 1.08 (t, 6H). IR (cm^{-1}, nujol): 1732s, 1691s, 1623m (C=O).

1,2,1',2'-Tetraethoxycarbonyl-3,3'-bis(p-methoxybenzoyl)-7,7'-bis(indolizine) 5. Bright yellow crystals, mp = 176-177°C. Anal. calcd. for $C_{44}H_{40}N_2O_{12}$: C, 67.00; H, 5.11; N, 3.55. Found C, 66.79; H, 5.47; N, 3.78%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.49 (d, 2H), 8.81 (d, 2H), 7.78 (q, 2H), 7.47 (d, 2H) 6.98 (d, 2H) 4.40 (q, 4H), 3.92 (s, 6H), 3.79 (q, 4H) 1.40 (t, 6H), 1.09 (t, 6H). ^{13}C-NMR ($CDCl_3$, 20°C, δ, ppm): 14.1 (C_{17}), 14.7 (C_{18}), 56.0 (C_{14}), 61.1 (C_{19}), 62.3 (C_{16}), 113.0 (C_7), 114.0 (C_2), 114.0 (C_8), 117.7 (C_5), 122.0 (C_{10}), 122.2 (C_{12}), 129.0 (C_{11}), 131.8 (C_6), 132.4 (C_3), 136.6 (C_4), 138.5 (C_1), 163.5 (C_{13}), 163.7 (C_{15}), 165.3 (C_{20}), 186. (C_9). IR (cm^{-1}, nujol): 1733s, 1684s, 1595m (C=O).

1,2,1',2'-Tetraethoxycarbonyl-3,3'-bis(m-methoxybenzoyl)-7,7'-bis(indolizine) 6. Bright yellow crystals, mp = 153-154°C. Anal. calcd. for $C_{44}H_{40}N_2O_{12}$: C, 67.00; H, 5.11; N, 3.55. Found C, 66.86; H, 5.37; N, 3.70%. ^{1}H-NMR (DMF-d_7, 20°C, δ, ppm): 9.65 (d, 2H), 8.82 (d, 2H), 7,51 (q, 2H); 7.49 (d, 2H), 7.37(d, 2H), 4.38 (q, 4H), 3.91 (s, 6H), 3.75 (q, 4H), 1.39 (t, 6H), 1.09 (t, 6H). IR (cm^{-1}, nujol): 1733s, 1694s, 1640m (C=O).

1,1'-Dimethyldicarboxylate-3,3'-benzoyl-7,7'-bis(indolizine) 7. Dark yellow crystals, mp = 274-275°C. Anal. calcd. for $C_{34}H_{24}N_2O_6$: C, 73.37; H, 4.35; N, 5.03. Found C, 73.17; H, 4.18; N, 4.86%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.98 (d, 2H, J_{H-H} = 7.5Hz), 8.77 (d, 2H, J_{H-H} = 1.2 Hz), 7.78-7.88 (m, 6H), 7.42-7.73 (m, 8H, J_{H-H} = 1.2 Hz), 4.08 (s, 6H) IR (cm^{-1}, nujol): 1700s, 1656s (C=O).

1,1'*-Dimethyldicarboxylate-3,3'-bis(p-chlorobenzoyl)-7,7'-bis(indolizine)* 8. Light yellow crystals, mp = 263-264°C. Anal. calcd. for $C_{34}H_{22}Cl_2N_2O_6$: C, 65.29, H, 3.55; N, 4.48. Found C, 65.10; H, 3.54; N, 4.26%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 10.05 (d, 2H, J_{H-H} = 7.5 Hz), 8.78 (d, 2H, J_{H-H} = 1.2 Hz), 7.85 (d, 4H), 7.59 (m, 6H), 7.41 (d, 2H), 3.89 (s, 6H). IR (cm^{-1}, nujol): 1700s, 1656s (C=O).

1,1'-Dimethyldicarboxylate-3,3'-bis(p-bromobenzoyl)-7,7'-bis(indolizine) 9. Dark yellow crystals, mp = 235-236°C. Anal. calcd. for $C_{36}H_{22}Br_2N_2O_6$: C, 57.17; H, 3.10; N, 3.92. Found C, 57.01; H, 2.93; N, 3.75%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 10.05 (d, 2H, J_{H-H} = 7.5 Hz), 8.78 (d, 2H, J_{H-H} = 1.2 Hz), 7.85 (d, 4H), 7.59 (m, 6H), 7.41 (d, 2H), 3.89 (s, 6H). IR (cm^{-1}, nujol): 1704s, 1623s (C=O).

1,1'-Dimethyldicarboxylate-3,3'-bis(p-nitrobenzoyl)-7,7'-bis(indolizine) 10. Yellow crystals, mp = 224-225°C. 58% yield. Anal. calcd. for $C_{34}H_{22}N_4O_{10}$: C, 63.16; H, 3.43; N, 8.67. Found C, 63.00; H, 3.29; N, 8.51%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 10.08 (d, 2H, J_{H-H} = 7,5), 8.85 (d, 2H, J_{H-H} = 1.2), 8.45 (d, 4H), 8.01 (d, 4H), 7.80 (s, 2H), 7.61 (d, 2H), 3.95 (s, 6H). IR (cm^{-1}, nujol): 1700s, 1656s (C=O).

1,1'-Dimethyldicarboxylate-3,3'-bis(p-methoxybenzoyl)-7,7'-bis(indolizine) 11. Yellow crystals, mp = 251-252°C. Anal. calcd. for $C_{36}H_{28}N_2O_8$ C, 70.12; H, 4.58; N, 4.54. Found C, 69.97; H, 4.43; N, 4.39%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.98 (d, 2H, J_{H-H} = 7.5 Hz), 8.77(d, 2H, J_{H-H} = 1.2 Hz), 7.85 (m, 4H) 7.35 (d, 4H), 7.05 (d, 4H), 3.95 (s, 6H), 3,93 (s, 6H). IR (cm^{-1}, nujol): 1694s, 1638s (C=O).

1,1'-Dimethyldicarboxylate-3,3'-bis(m-methoxybenzoyl)-7,7'-bis(indolizine) 12. Yellow crystals, mp =257-258°C. Anal. calcd. for $C_{36}H_{28}N_2O_8$: C, 70.12; H, 4.58; N, 4.54. Found C, 69.96; H, 4.39; N, 4.41%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 10.01 (d, 2H, J_{H-H} = 7.5 Hz), 8.84 (d, 2H, J_{H-H} = 1.2 Hz), 7.89 (s, 2H), 7.25-7.54 (m, 8H), 3.95 (s, 6H), 3.87 (s, 6H). IR (cm^{-1}, nujol): 1701s 1620s (C=O).

1,1'-Diethyldicarboxylate-3,3'-bis(benzoyl)-7,7'-bis(indolizine) 13. Light yellow crystals, mp = 272-275°C. Anal. calcd for $C_{36}H_{32}N_2O_6$: C, 73.45; H, 5.48; N, 4.76. Found C, 73.31; H, 5.26; N, 4.63%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.98 (d, 2H, J_{H-H} = 7.5), 8.77 (d, 2H, J_{H-H} =

1.2 Hz); 7.78-7.88 (m, 6H), 7.42-7.73 (m, 8H, J_{H-H} = 7.5 Hz, J_{H-H} = 1.2 Hz) 4.4 (q, 4H, J_{H-H} = 7.2 Hz), 1.43 (t, 6H, J_{H-H} = 7.2 Hz). IR (KBr,cm^{-1}):1700s, 1656s (C=O).

1,1'-Diethyldicarboxylate-3,3'-bis(p-chlorobenzoyl)-7,7'-bis(indolizine) 14. Light yellow crystals, mp = 263-264°C. Anal. calcd. for $C_{36}H_{30}Cl_2N_2O_6$: C, 65.76; H, 4.58; N, 4.26. Found C, 65.57; H, 4.40; N, 4.13%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.98 (d, 2H, J_{H-H} =7.5 Hz), 8.80 (d, 2H, J_{H-H} = 1.2 Hz), 7.79 (d, 2H), 7.76 (d, 2H), 7.33 (d, 4H), 7.03 (d, 4H), 4.43 (q, 4H, J= J_{H-H} = 7.2 Hz), 1.43 (t, 6H, J_{H-H} = 7.2 Hz). IR (cm^{-1}, nujol): 1700s, 1656s (C=O).

1,1'-Diethyldicarboxylate-3,3'-bis(p-bromobenzoyl)-7,7'-bis(indolizine) 15. Light yellow crystals, mp = 282-284°C. Anal. calcd. for $C_{36}H_{30}Br_2N_2O_6$: C, 57.93; H, 4.05; N, 3.75. Found C, 57.76; H, 3.85; N, 3.59%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.98 (d, 2H, J_{H-H} = 7.5 Hz); 8.80 (d, 2H, J_{H-H} = 1.2 Hz), 7.79 (d, 2H), 7.76 (d, 2H), 7.33 (d, 4H), 7.03 (d, 4H), 4.43 (q, 4H, J_{H-H} = 7.2 Hz), 1.43 (t, 6H, J_{H-H} = 7.2 Hz). IR (cm^{-1}, nujol): 1700s, 1656s (C=O).

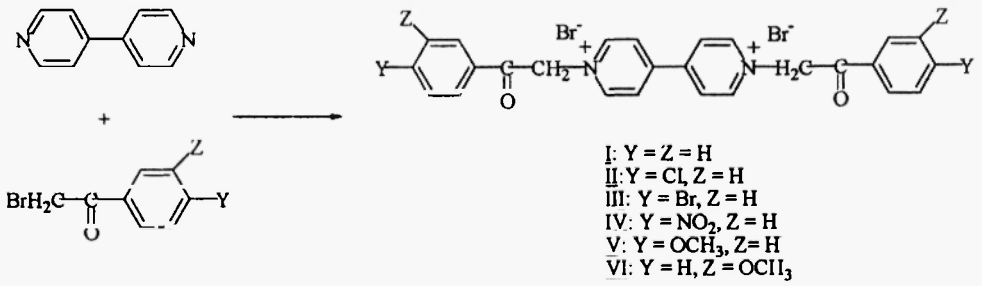
1,1'-Diethyldicarboxylate-3,3'-bis(p-nitrobenzoyl)-7,7'-bis(indolizine) 16. Dark yellow crystals, mp = 310-312°C. Anal. calcd. for $C_{36}H_{30}N_4O_{10}$: C, 63.71; H, 4.46; N, 8.26. Found C, 63.59; H, 4.37; N, 8.16%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 10.13 (d, 2H, J_{H-H} = 7.5 Hz), 8.99 (d, 2H, J_{H-H} = 1.2 Hz), 7.42 (s, 2H), 8.03 (d, 4H), 7.8 (d, 4H), 7.48 (d, 4H), 4.4 (q, 4H, J_{H-H} = 7.2), 1.43 (t, 6H, J_{H-H} = 7.2 Hz). IR (cm^{-1}, nujol): 1700s, 1656s (C=O).

1,1'-Diethyldicarboxylate-3,3'-bis(p-methoxybenzoyl)-7,7'-bis(indolizine) 17. Light yellow crystals, mp = 280-282°C. Anal. calcd. for $C_{38}H_{36}N_2O_8$: C, 70.36; H, 5.59; N, 4.32. Found C, 70.50; H, 5.44; N, 4.19%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 9.98 (d, 2H, J_{H-H} = 7.5 Hz); 8,80(d, 2H, J_{H-H} = 1.2 Hz), 7.79 (d, 2H), 7.76 (d, 2H), 7.33 (d, 4H); 7.03 (d, 4H), 4.43 (q, 4H, J_{H-H} = 7.2 Hz), 3.93 (s, 6H) 1.43 (t, 6H, J_{H-H} = 7.2 Hz). IR (cm^{-1}, nujol): 1698s, 1696s (C=O).

1,1'-Diethyldicarboxylate-3,3'-bis(m-methoxybenzoyl)-7,7'-bis(indolizine) 18. Light yellow crystals, mp = 244-246°C. Anal. calcd. for $C_{38}H_{36}N_2O_8$: C, 70.36; H, 5.59; N, 4.32. Found C, 70.54; H, 5.34; N, 4.09%. ^{1}H-NMR ($CDCl_3$, 20°C, δ, ppm): 10.03 (d, 2H, J_{H-H} = 7.5 Hz), 8.83 (d, 2H, J_{H-H} = 1.2 Hz), 7.90 (d, 2H), 7.55-7.13 (m, 10H), 4.45 (q, 4H, J_{H-H} = 7.2 Hz), 3.92 (s, 6H), 1.43 (t, 6H, J_{H-H} = 7.2 Hz). IR (cm^{-1}, nujol): 1712s, 1667s (C=O).

Results and Discussion

The 4,4'-bipyridinium diquaternary I-VI have been obtained from 4,4'-bipyridyl and the corresponding phenacyl halides (scheme 1) following literature procedures (7).



Scheme 1

Derivatives I-VI react with dipolarophile reagents (diethylacetylene dicarboxylate, methyl propiolate or ethyl propiolate) on basic catalyst potassium fluoride, on alumina, without solvent under microwave irradiation yielding the non-stabilized 4,4'-bipyridinium ylides Ia-VIa, which subsequently underwent cyclo-addition with activated carbon-carbon multiple bonds to afford the 7,7'-bis-indolizines 1-18 (scheme 2).

All reactions were carried out at atmospheric pressure in a focused microwave reactor with measurement and control of power and temperature. The cycloaddition reaction conditions have been optimised to obtain the best yields. As previously pointed out, formation of 7,7'-bis-indolizines likely proceeds via an unisolable intermediate which undergo a dehydrogenation process (Scheme 2). As indicated in Table 1, this procedure allowed 7,7'-bis-indolizines to be obtained in 7-10 min with very high yields.

In order to compare the efficiency of microwave irradiation to carry out [3+2] cycloaddition of 4,4-bipyridinium ylides with activated alkynes, we also performed some reactions in refluxing benzene (or *N*-methylpirrolidone) in presence of triethylamine. The results are summarized in Table 1.

All the structures of compounds 1-18 were consistent with their elemental analyses and spectral data (IR and ^{1}H NMR reported in the experimental section).

The IR spectra of 1-18 show one absorption band between 1680-1700 cm^{-1} typical of ketonic carbonyl groups whereas the ester CO stretching vibrations appears at *ca.* 1730 cm^{-1}.

In the ^{1}H NMR spectra of 1-18 a signal at ca 9.7 ppm appeared which can be assigned to aromatic protons nearest to nitrogen of the indolizine ring. When strong electron-withdrawing substituents are on phenyl rings, the indolizine ring signals are shifted to lower fields. In the ^{13}C-NMR spectrum of 5 the carbonyl resonances are at 163.5, 163.7, 165.3 and 186 ppm suggesting the non equivalence of the esteric groups.

Reinvestigation of the previously described cycloaddition reactions led to the following conclusions: 1) the yields of the reactions under microwave irradiation were higher than those carried out under classical heating and shorter reaction times were required; 2) the reaction conditions on mineral solid support are more efficient because KF/Al_2O_3 is known as a strong base. Alumina is a Lewis-type complexing agent acting on carbonyl function and provoking an increased polarisation of triple bond; 3) the solid support permit increase of temperature over the boiling point of the solvent; 4) the reaction products obtained in solid state are identical with the compounds obtained by classical method. Our results constitute the first example of such a reaction observed on 4,4'-bipyridine derivatives. The reaction here described represents a facile and convenient route for preparation of bis-indolizines derivatives.

In conclusion we have described the first 1,3-dipolar cycloaddition of pyridinium heteroaromatic ylides with acetylenes in the presence of the basic catalyst KF on alumina under microwave irradiation. The absence of solvent coupled with high yields and very short reaction times make this procedure for the preparation of bis-indolizines very attractive.

Table 1

Compound	Classical Heating		Microwave irradiation		
	Time (min)	Yield (%)	Time (min)	Power (W), Temp	Yield (%)
6a	360	50	10	280W, 140°C	86
6b	360	54	10	280W, 140°C	86
6c	180	59	7	240W, 130°C	88
6d	180	59	7	240W, 130°C	90
6e	240	55	9	240W, 130°C	87
6f	240	56	9	240W, 130°C	86

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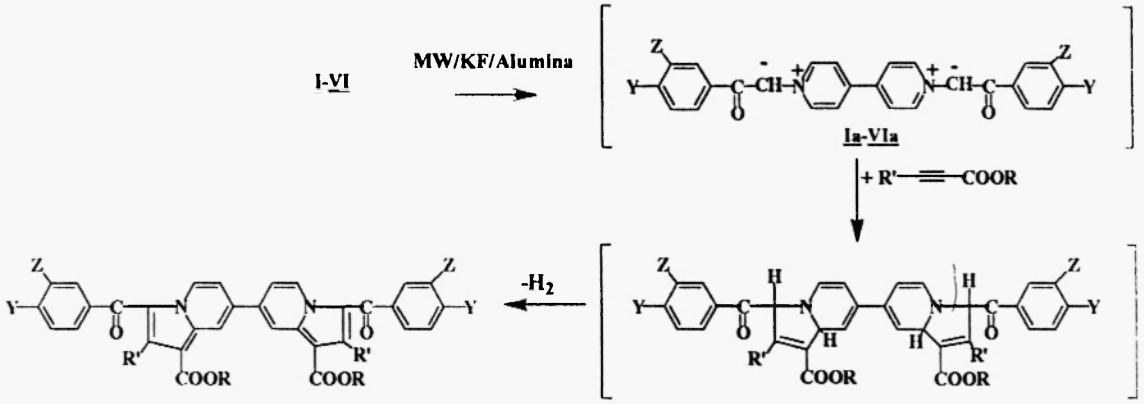

1: Y = Z = H, R = Et, R' = COOEt
2: Y = Cl, Z = H, R = Et, R' = COOEt
3: Y = Br, Z = H, R = Et, R' = COOEt
4: Y = NO_2, Z = H, R = Et, R' = COOEt
5: Y = OCH_3, Z = H, R = Et, R' = COOEt
6: Y = H, Z = OCH_3, R = Et, R' = COOEt
7: Y = Z = R' = H, R = Me
8: Y = Cl, Z = R' = H, R = Me
9: Y = Br, Z = R' = H, R = Me
10: Y = NO_2, Z = R' = H, R = Me
11: Y = OCH_3, Z = R' = H, R = Me
12: Y = R' = H, Z = OCH_3, R = Me
13: Y = Z = R' = H, R = Et
14: Y = Cl, Z = R' = H, R = Et
15: Y = Br, Z = R' = H, R = Et
16: Y = NO_2, Z = R' = H, R = Et
17: Y = OCH_3, Z = R' = H, R = Et
18: Y = R' = H, Z = OCH_3, R = Et

Scheme 2

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