An Approach to the Synthesis of Spiro[indene-pyridoisoquinoline] Derivatives *via* 1,4-Dipolar Cycloaddition of Isoquinoline and Acetylene Esters, and (1,3-Dihydro-1,3-dioxo-2*H*-inden-2-ylidene)malononitrile

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A concise and efficient approach to the spiro-tetrahydroisoquinoline derivatives has been developed by 1,4-dipolar cycloaddition of zwitterions resulting from isoquinoline and acetylene esters and (1,3-dihydro-1,3-dioxo-2*H*-inden-2-ylidene)malononitrile in MeCN at room temperature. The significance of this method lies in good yields and ease of product purification, and no inert atmosphere is required. The structures of the products were confirmed spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this reaction is proposed (*Scheme*).

Introduction. – Since the first preparation of the zwitterionic intermediate resulted from pyridine and dimethyl acetylenedicarboxylate (DMAD) in 1932 by *Diels* and *Alder* [1], and pioneering work of *Huisgen*, who recognized this reaction as the 1,4-dipolar cycloaddition [2], impressive advances have been made in the synthesis of six membered heterocycles. The zwitterion generated *in situ* from the reaction of nucleophiles, like N-containing heterocyclic compounds, with activated acetylenes or allenoate could be trapped by various dipolarophiles such as alkenes [3], ketones [4], and imines [5] to form six-membered heterocyclic compounds. *Nair et al.* envisaged that 1,4-zwitterionic intermediates generated *in situ* from quinoline or isoquinoline, and DMAD could be trapped by arylidenemalononitrile to form tetrahydrobenzoquinolizines [6].

Results and Discussion. – As part of our ongoing work on heterocyclic synthesis by developing zwitterions in multicomponent reactions [7], we investigated herein, an efficient synthesis of spiro[indene-pyridoisoquinolines *via* the three-component reaction of isoquinoline, acetylene ester, and the *Knoevenagel* adduct of ninhydrin and malononitrile. Initially, the reaction of isoquinoline, DMAD, and (1,3-dihydro-1,3-dioxo-2*H*-inden-2-ylidene)malononitrile was carried out in different solvents, whereby MeCN turned out to be the best choice (*Table 1*).

Having established the optimal conditions, we next examined the scope of acetylene esters in the said reaction for the construction of spiro[indene-pyridoisoquinolines]. The results are compiled in *Table 2*.

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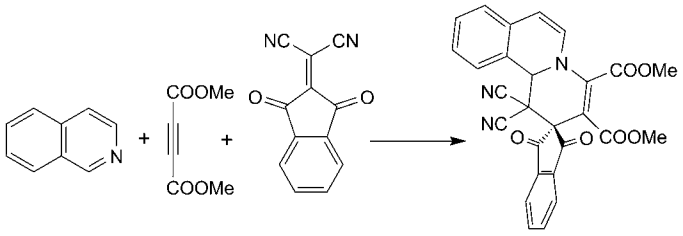
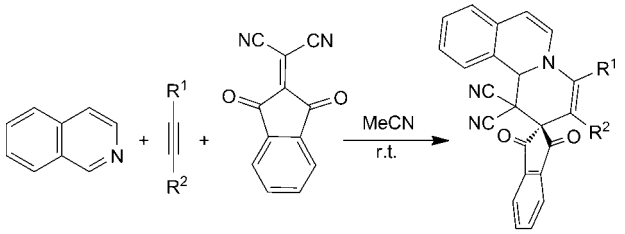
Table 1. *Synthesis of* **4a** *under Different Reaction Conditions*



1 **2a** **3** **4a**

Entry	Solvent	Time [h]	Yield [%]
1	**MeCN**	12	**78**
2	EtOH	12	0
3	MeOH	12	0
4	Et_2O	12	45
5	CH_2Cl_2	12	54
6	THF	12	71

Table 2. *Synthesis of Spiro[indene-pyridoisoquinoline] Derivatives* **4a**–**4e**



1 **2** **3** **4**

Entry	R^1	R^2	Product	Yield [%]
1	MeOOC	MeOOC	**4a**	83
2	EtOOC	EtOOC	**4b**	79
3	^{t}BuOOC	^{t}BuOOC	**4c**	73
4	H	MeOOC	**4d**	75
5	H	EtOOC	**4e**	70

The structures of all products **4a**–**4e** were elucidated from their mass spectrometric analyses, and IR, and ^{1}H- and ^{13}C-NMR spectra. The structure of product **4b** was further confirmed by X-ray crystallographic analysis (*Fig.*).

The mass spectrum of **4a** displayed the molecular ion peak at *m*/*z* 479, which was in agreement with the proposed structure. The IR spectrum of **4a** showed absorption bands due to the CN groups at 2325, the COOMe groups at 1745 and 1705, and the aromatic moieties at 1593 and 1498 cm^{-1}. The ^{1}H-NMR spectrum of **4a** showed three

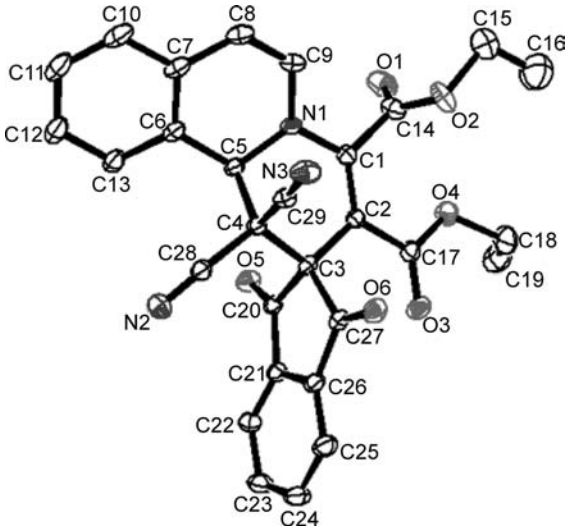


Figure. *ORTEP Diagram of the crystal structure of* **4b**

sharp *singlet*s for two MeO groups, and the signal of one CH group at δ(H) 3.48, 3.98, and 6.09, respectively. Signals of two =CH groups were observed at δ(H) 6.04 and 6.69 with ^3J(H,H) = 6.4 Hz, and the aromatic moieties gave rise to *multiplet*s in the aromatic region of the spectrum at δ(H) 7.33 – 8.21. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 26 distinct resonances in agreement with the suggested structure.

It should be mentioned that, in the reaction of quinoline or isoquinoline, and DMAD with arylidenemalononitrile, which have been reported by *Nair et al.*, high temperature (refluxing toluene) or an inert atmosphere is needed, whereby two diastereoisomeric tetrahydrobenzoquinolizines are obtained [6]. The present reaction of isoquinoline, acetylene esters, and (1,3-dihydro-1,3-dioxo-2*H*-inden-2-ylidene)malononitrile results in one diastereoisomeric spirotetrahydroisoquinoline due to the symmetry of the ninhydrin–malononitrile product. The 1,4-dipolar addition takes place at room temperature and no inert atmosphere was necessary.

Mechanistically, it is conceivable that the reaction involves the cycloaddition of a zwitterionic intermediate, generated from isoquinoline and acetylene ester, and (1,3-dihydro-1,3-dioxo-2*H*-inden-2-ylidene)malononitrile (**3**) to produce the products **4** (*Scheme*).

In conclusion, we have developed a novel multicomponent synthesis of spiro[indene-pyridoisoquinoline] from simple materials such as isoquinoline, acetylene esters, and (1,3-dihydro-1,3-dioxo-2*H*-inden-2-ylidene)malononitrile. The high yields, mild reaction conditions (no metal catalyst, no high temperature, no inert atmosphere), the ease of purification, and the economic availability of the synthons are the advantages of the described procedure.

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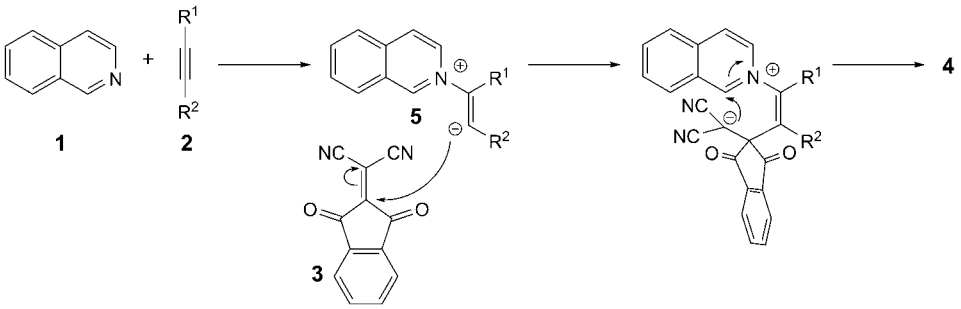
Scheme. *Proposed Mechanism for the Synthesis of* **4**



Experimental Part

General. Ninhydrin, isoquinoline, acetylene esters, and malononitrile were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. IR Spectra: as KBr pellets on a *NICOLET FT-IR 100* spectrometer, absorbances in cm^{-1}. ^1H- and ^{13}C-NMR spectra: at 400 and 100 MHz, resp., *Bruker DRX-400 AVANCE* and *Bruker DRX-500 AVANCE* spectrometers. MS: *Finnigan-Mat 8430* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses: *Heraeus CHN–O–Rapid* analyzer.

General Procedure (exemplified for **4a**). To a mixture of *isoquinoline* (**1**; 0.129 g, 1 mmol) and *dimethyl acetylenedicarboxylate* (dimethyl but-2-ynedioate; **2a**; 0.142 g, 1 mmol) in MeCN (5 ml) was added (*1,3-dihydro-1,3-dioxo-2*H-*inden-2-ylidene)malononitrile* (**3**; 0.208 g, 1 mmol), and the resulting mixture was stirred at r.t. for 12 h (monitoring by TLC). Upon completion, the mixture was filtered, and the precipitate was washed with MeCN (5 ml) to afford the pure product **4a**. All products gave satisfactory spectroscopic data in accordance with the assigned structures. The structures of **4d** and **4e** were documented by the expected intermediates **5d** and **5e**, resp.

*Dimethyl 1′,1′-Dicyano-1,1′,3,11b′-tetrahydro-1,3-dioxospiro[indene-2,2′-pyrido[2,1-*a*]isoquinoline]-3′,4′-dicarboxylate* (**4a**). Yield: 0.248 g (83%). Light-green powder. M.p. 250°. IR: 2325 (CN), 1745 and 1705 (COOMe), 1630 (C=O), 1593 and 1498 (Ar), 1296 and 1158 (C–O). ^1H-NMR: 3.48 (*s*, 3 H); 3.98 (*s*, 3 H); 6.04 (*d*, $^3J = 6.4$, 1 H); 6.09 (*s*, 1 H); 6.69 (*d*, $^3J = 6.4$, 1 H); 7.33 (*d*, $^3J = 6.8$, 3 H); 7.47 (*t*, $^3J = 6.8$, 1 H); 8.19–8.23 (*m*, 4 H). ^{13}C-NMR: 52.9; 54.1; 58.78; 62.3; 101.4; 107.2; 109.1; 110.60; 121.1; 124.1; 124.7; 126.0; 126.3; 127.5; 128.8; 130.9; 138.1; 138.4; 129.8; 138.7; 140.8; 147.6; 162.4; 163.7; 194.0; 196.2. EI-MS: 479 (50, M^+), 420 (10), 350 (71), 319 (12), 163 (23), 129 (100), 102 (17), 57 (16). Anal. calc. for $C_{27}H_{17}N_3O_6$ (479.44): C 67.64, H 3.57, N 8.76; found: C 67.56, H 3.62, N 8.81.

*Diethyl 1′,1′-Dicyano-1,1′,3,11b′-tetrahydro-1,3-dioxospiro[indene-2,2′-pyrido[2,1-*a*]isoquinoline]-3′,4′-dicarboxylate* (**4b**). Yield: 0.247 g (79%). Light-green powder. M.p. 246°. IR: 2250 (CN), 1735, 1703 (COOEt), 1654 (C=O), 1592, 1490 (Ar), 1294, 1238, 1155 (C–O). ^1H-NMR: 0.74 (*t*, $^3J = 6.0$, 3 H); 1.34 (*t*, $^3J = 6.0$, 3 H); 3.88 (*d*, $^3J = 6.0$, 2 H); 4.43 (*d*, $^3J = 6.0$, 2 H); 6.04 (*d*, $^3J = 6.4$, 1 H); 6.10 (*s*, 1 H); 6.65 (*d*, $^3J = 6.4$, 1 H); 7.33 (*d*, $^3J = 7.2$, 3 H); 7.46 (*t*, $^3J = 7.2$, 1 H); 8.18–8.22 (*m*, 4 H). ^{13}C-NMR: 12.9; 13.6; 55.9; 58.7; 61.9; 63.4; 101.8; 107.2; 109.1; 110.6; 121.1; 124.2; 124.7; 125.9; 126.0; 127.5; 128.9; 130.9; 138.2; 138.4; 129.9; 138.9;140.8; 147.9; 161.9; 162.8; 194.1; 196.2. EI-MS: 507 (9, M^+), 378 (18), 311 (46), 239 (24), 196 (29), 167 (34), 129 (100), 104 (19), 76 (19). Anal. calc. for $C_{29}H_{21}N_3O_6$ (507.49): C 68.63, H 4.17, N 8.28; found: C 68.56, H 4.23, N 8.25. *Crystallographic data* for **4b** were deposited with the *Cambridge Crystallographic Data Center* with No. CCDC-956310. These data can be obtained free of charge from the *Cambridge Crystallographic Data Center via* www.ccdc.cam.ac.uk/data_request/cif. Formula, $C_{29}H_{21}N_3O_6$; M_r 507.49, triclinic, unit cell parameters, $a = 10.6857(6)$ Å, $b = 11.0230(7)$ Å, $c = 11.7369(7)$ Å, $\alpha = 78.651(5)$, $\beta = 69.537(6)$, $\gamma = 73.366(6)$, $V = 1233.82(13)$ Å^3, $Z = 2$, $D_{calc} = 1.363$ g·cm^{-3}; space group, $P\bar{1}$; $F(000) = 526$, crystal dimension $0.38 \times 0.36 \times 0.32$ mm, radiation, MoK_α ($\lambda = 0.71073$Å), $4.04 \leq 2\theta \leq 67.40$; intensity data were collected at 295(2) K with a *Bruker APEX-II CCD*

area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-9 \le h \le 12$, $-12 \le k \le 13$, $-13 \le l \le 14$; the structure was solved by a direct method, all non-H-atoms were positioned, and anisotropic thermal parameters were refined from 4322 observed reflections with R(into) of 0.0739 by a full-matrix least-squares technique converged to $R = 0.0630$ and $R_w = 0.1844$ [$I > 2\sigma(I)$].

*Di-(*tert*-butyl) 1′,1′-Dicyano-1,1′,3,11b′-tetrahydro-1,3-dioxospiro[indene-2,2′-pyrido[2,1-*a*]isoquinoline]-3′,4′-dicarboxylate* (**4c**). Yield: 0.250 g (73%). Light-green powder. M.p. 251°. IR: 2227 (CN), 1703 (COO), 1668 (C=O), 1576 (Ar), 1351, 1296, 1251 (C–O). ^{1}H-NMR: 1.48 (*s*, 18 H); 7.34 (*d*, ^3J = 7.2, 1 H); 7.41 (*s*, 1 H); 7.47 (*d*, ^3J = 7.2, 1 H); 8.12 (*t*, ^4J = 1.2, 1 H); 8.16 (*d*, ^4J = 1.2, 3 H); 8.33–8.36 (*m*, 4 H). ^{13}C-NMR: 23.9; 57.9; 62.1; 83.6; 85.4; 91.8; 115.4; 116.8; 119.2; 122.7; 123.7, 123.8; 127.9; 130.1; 134.0; 134.6; 137.7; 138.2; 138.7; 131.8; 139.1; 153.2; 161.4; 169.1; 189.4; 198.5. EI-MS: 563 (8, M^+), 451 (9), 433 (23), 368 (17), 210 (100), 155 (25), 129 (100), 104 (33), 76 (36). Anal. calc. for $C_{33}H_{29}N_3O_6$ (563.60): C 70.33, H 5.19, N 7.46; found: C 70.36, H 5.14, N 7.39.

*Methyl 1′,1′-Dicyano-1,1′,3,11b′-tetrahydro-1,3-dioxospiro[indene-2,2′-pyrido[2,1-*a*]isoquinoline]-3′-carboxylate* (**4d**). Yield: 0.256 g (75%). Light-green powder. M.p. 271°. IR: 2248 (CN), 1699 (COOMe), 1622 (C=O), 1560 (Ar), 1257, 1219, 1153 (C–O). ^{1}H-NMR: 3.55 (*s*, 3 H); 5.88 (*d*, ^3J = 6.8, 1 H); 6.29 (*s*, 1 H); 7.08 (*d*, ^3J = 6.8, 1 H); 7.24 (*t*, ^3J = 8.0, 1 H); 7.29 (*d*, ^3J = 8.0, 1 H); 7.40 (*t*, ^3J = 8.0, 2 H); 8.17–8.19 (*m*, 4 H); 8.49 (*s*, 1 H). ^{13}C-NMR: 52.0; 57.9; 63.7; 99.4; 104.6; 109.5; 111.3; 121.5; 123.8; 124.4; 126.0; 127.0; 128.2; 129.7; 137.9; 138.3; 130.6; 130.9; 138.9; 141.1, 145.5; 164.9; 195.4; 197.1. EI-MS: 421 (49, M^+), 404 (39), 362 (40), 292 (42), 266 (43), 189 (59), 129 (100), 102 (77), 76 (60). Anal. calc. for $C_{25}H_{15}N_3O_4$ (421.40): C 71.25, H 3.59, N 9.97; found: C 71.28, H 3.51, N 10.03.

*Ethyl 1′,1′-Dicyano-1,1′,3,11b′-tetrahydro-1,3-dioxospiro[indene-2,2′-pyrido[2,1-*a*]isoquinoline]-3′-carboxylate* (**4e**): Yield: 0.230 g (70%). Light-green powder. M.p. 240°. IR: 2250 (CN), 1712 (COOEt), 1679 (C=O), 1620, 1496 (Ar), 1260, 1214, 1154 (C–O). ^{1}H-NMR: 0.98 (*t*, ^3J = 6.0, 3 H); 3.96 (*q*, ^3J = 6.0, 2 H); 5.88 (*d*, ^3J = 5.2, 1 H); 6.29 (*s*, 1 H); 7.10 (*d*, ^3J = 5.2, 1 H); 7.26 (*d*, ^3J = 7.2, 2 H); 7.40 (*d*, ^3J = 7.2, 2 H); 8.18–8.21 (*m*, 4 H); 8.47 (*s*, 1 H). ^{13}C-NMR: 13.7; 58.0; 60.8; 70.8; 99.6; 104.4; 109.6; 111.3; 121.5; 123.8; 124.4; 126.0; 127.0; 128.2; 129.7; 137.9; 138.3; 130.6; 131.0; 139.0; 141.1; 145.4; 164.1; 195.5; 197.1. EI-MS: 435 (15, M^+), 362 (12), 306 (12), 184 (18), 129 (100), 85 (87), 69 (29). Anal. calc. for $C_{26}H_{17}N_3O_4$ (435.43): C 71.72, H 3.94, N, 9.65; found: C 71.76, H 3.88, N 9.63.

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