FULL PAPER

A Diastereoselective Synthesis of Functionalized Tetrahydroindeno[2′,1′,3,4]pyrido[2,1-*a*]isoquinolines

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An effective route to alkyl 9a-(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)-9a,14,14a,14b-tetrahydro-14-oxoindeno[2′,1′:3,4]pyrido-[2,1-*a*]isoquinoline-9-carboxylates *via* a diastereoselective one-pot four-component reaction of isoquinoline and alkyl prop-2-ynoates with two equivalents of indane-1,3-dione, in aqueous MeOH at room temperature, is described.

Introduction. – Multicomponent reactions (MCRs) are an elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks. MCRs show high atom-economy, high selectivity, and procedural simplicity [1 – 3]. The rich and fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. *N*-Heterocycles are known to form zwitterions with activated acetylene compounds such as dimethyl acetylenedicarboxylate [4 – 6]. These zwitterions can be trapped by a variety of electrophiles and proton donors, which is a novel protocol for the synthesis of heterocyclic compounds [4 – 6].

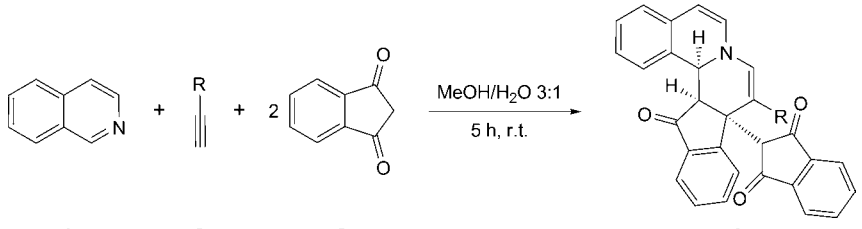
Recently, the formation of novel polycyclic compounds containing a spiro C-atom by the reaction of indane-1,3-dione with *Huisgen*'s zwitterions, formed *in situ* from quinoline or isoquinoline and activated acetylenes, were reported [7 – 9]. As part of our continuing interest in the construction of novel heterocycles [10 – 12], we now report the results of our studies involving the reactions of zwitterions derived from isoquinoline (**1**) and alkyl prop-2-ynoates **2** in the presence of two equivalents of indane-1,3-dione (**3**), which constitutes a synthesis of alkyl 9a-(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)-9a,14,14a,14b-tetrahydro-14-oxoindeno[2′,1′:3,4]pyrido[2,1-*a*]isoquinoline-9-carboxylates **4** (*Table*).

Results and Discussion. – The structures of products **4a** – **4c**, as 1 : 1 : 2 adducts of **1**, **2**, and **3**, were deduced from their ^{1}H- and ^{13}C-NMR spectroscopic data and a single-crystal X-ray analysis. The ^{1}H-decoupled ^{13}C-NMR spectra of products **4a** – **4c** exhibited four resonances above 165 ppm that are attributed to the four C=O groups. The IR spectra of **4a** – **4c** displayed characteristic ketone and ester C=O bands.

Unambiguous evidence for the structure and the relative configuration of **4a** was obtained from a single-crystal X-ray analysis. An ORTEP [13] diagram of **4a** is shown in the *Figure*. There are four molecules of **4a** in the unit cell. The configuration deduced from the crystallographic experiment, by analogy can be applied to the other products **4b** and **4c** on account of their NMR-spectroscopic similarities.

A plausible mechanism may be advanced to explain the product formation (*Scheme*). Presumably, the zwitterionic

Table. *Diastereoselective Synthesis of Functionalized Tetrahydroindeno[2′,1′,3,4]pyrido[2,1-a]isoquinolines* **4**



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

Entry	R	Product	Yield [%]
1	COOMe	**4a**	87
2	COOEt	**4b**	82
3	COO′Bu	**4c**	83

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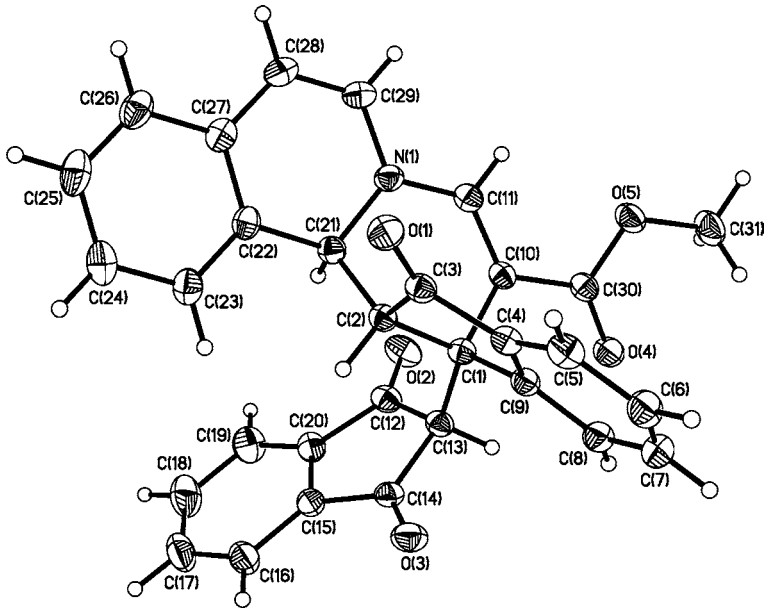
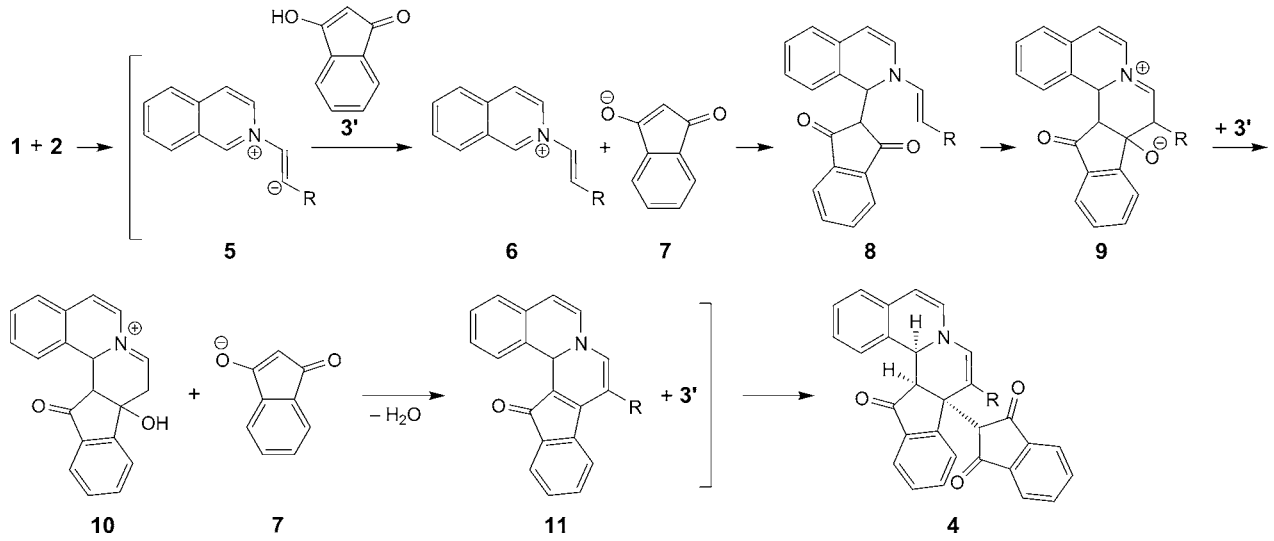


Figure. *X-Ray crystal structure of* **4a** (*ORTEP-III* plot [13]; arbitrary atom numbering)

Scheme



intermediate **5** (*cf.* [4 – 6]) formed from isoquinoline and the alkyl prop-2-ynoate, is protonated by **3** to furnish intermediate **6**, which is attacked by enolate ion **7** to produce **8**. The enamine moiety of intermediate **8** attacks one of the C=O groups to generate **9**, which is protonated by **3** to afford **10**. The latter is converted to **11** by elimination of H_2O and deprotonation. Then, *Michael* addition of the enol form of **3** (**3′**) to **11**, followed by proton transfer, leads to products **4**.

In summary, we have reported a transformation involving *Huisgen*'s zwitterions formed *in situ* from isoquinoline and alkyl prop-2-ynoates, and indane-1,3-dione, which affords a new route to the stereoselective synthesis of alkyl 9a-(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)-9a,14,14a,14b-tetrahydro-14-oxoindeno[2′,1′:3,4]pyrido[2,1-*a*]isoquinoline-9-carboxylates. This protocol offers a convenient route for the diastereoselective synthesis of complex polycyclic compounds. The significance of this method lies in good yields and ease of product purification, and no inert atmosphere is required.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-500 Avance* instrument at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430* EI-MS mass spectrometer; at 70 eV; in m/z (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer.

General Procedure for the Syntheses of Compounds **4**. A soln. of 0.13 g isoquinoline (**1**; 1 mmol) in 4 ml of MeOH/H_2O 3 : 1 was added to a stirred soln. of the alkyl prop-2-ynoate **2** (1 mmol) and 0.30 g of

indane-1,3-dione (**3**; 2 mmol) in 6 ml of MeOH/H_2O 3 : 1 at r.t. The mixture was then allowed to stir for 5 h. The precipitate was washed with Et_2O and recrystallized from EtOH to afford pure products.

Methyl rel-*(9a*S*,14a*R*,14b*S*)-9a-(2,3-Dihydro-1,3-dioxo-1*H*-inden-2-yl)-9a,14,14a,14b-tetrahydro-14-oxoindeno[2′,1′:3,4]pyrido[2,1-*a*]isoquinoline-9-carboxylate* (**4a**). Yield: 0.42 g (87%). Colorless crystals. M.p. 180 – 182°. IR (KBr): 1720, 1718, 1605, 1601, 1546, 1249, 1217. ^{1}H-NMR: 3.45 (*d*, ^3J = 2.5, CH); 3.72 (*s*, MeO); 4.94 (*d*, ^3J = 2.5, CH); 5.33 (*s*, CH); 5.50 (*d*, ^3J = 7.7, CH); 6.02 (*d*, ^3J = 7.6, CH); 6.11 (*d*, ^3J = 7.7, CH); 6.83 (*t*, ^3J = 7.5, CH); 6.92 (*d*, ^3J = 7.7, CH); 7.05 (*t*, ^3J = 7.5, CH); 7.30 (*s*, CH); 7.40 – 7.43 (*m*, 2 CH); 7.57 (*d*, ^3J = 7.5, CH); 7.66 (*dd*, ^3J = 7.4, 7.2, CH); 7.86 – 7.91 (*m*, 2 CH); 7.92 – 7.99 (*m*, 2 CH); 8.23 (*d*, ^3J = 7.5, CH). ^{13}C-NMR: 48.9 (C); 51.0 (CH); 53.8 (CH); 55.9 (CH); 60.4 (MeO); 104.5 (CH); 104.9 (C); 123.1 (CH); 123.2 (CH); 123.3 (CH); 123.5 (CH); 125.6 (CH); 126.6 (CH); 127.6 (CH); 127.7 (CH); 128.4 (CH); 129.0 (CH); 129.4 (C); 131.1 (C); 132.8 (C); 134.3 (CH); 136.0 (CH); 136.2 (CH); 142.1 (CH); 142.2 (C); 142.3 (C); 155.1 (CH); 166.6 (C=O); 198.4 (C=O); 199.1 (C=O); 200.7 (C=O). MS: 487 (7, M^+), 456 (1), 341 (58), 340 (60), 326 (54), 298 (100), 246 (70), 189 (50), 146 (90), 129 (70), 104 (60), 76 (70). Anal. calc. for $C_{31}H_{21}NO_5$ (487.50): C 76.38 H, 4.34, N 2.87; found: C 76.87, H 4.37, N 2.90.

Ethyl rel-*(9a*S*,14a*R*,14b*S*)-9a-(2,3-Dihydro-1,3-dioxo-1*H*-inden-2-yl)-9a,14,14a,14b-tetrahydro-14-oxoindeno[2′,1′:3,4]pyrido[2,1-*a*]isoquinoline-9-carboxylate* (**4b**). Yield: 0.41 g (82%). Colorless crystals. M.p. 176 – 178°. IR (KBr): 1733, 1705, 1702, 1678, 1605, 1568, 1455, 1252, 1249, 1092, 1228. ^{1}H-NMR: 1.29 (*t*, ^3J = 7.1, Me); 3.44 (*d*, ^3J = 2.6, CH); 4.10 (*dq*, ^3J = 10.7, 7.1, CH_2O); 4.20 (*dq*, ^3J = 10.9, 7.1, CH_2O); 4.93 (*d*, ^3J = 2.6, CH); 5.32 (s, CH); 5.50 (*d*, ^3J = 7.7, CH); 6.02 (*d*, ^3J = 7.5, CH); 6.11 (*d*, ^3J = 7.6, CH); 6.83 (*t*, ^3J = 7.5, CH); 6.94 (*d*, ^3J = 7.7, CH); 7.05 (*t*, ^3J = 7.5, CH); 7.29 (*s*, CH); 7.41 (*d*, ^3J = 6.5, CH); 7.57 (*d*, ^3J = 7.4, CH); 7.65 (*t*, ^3J = 7.5, CH); 7.87 (*t*, ^3J = 7.4, CH); 7.90 (*t*, ^3J = 7.3, CH); 7.98 – 8.0 (*m*, 2 CH); 8.22 (*d*, ^3J = 8.0, CH). ^{13}C-NMR: 14.4 (Me); 48.9 (C); 53.8 (CH); 55.9 (CH); 60.5 (CH); 60.6 (CH_2O); 104.3 (CH); 105.2 (C); 123.1 (CH); 123.2 (CH); 123.3 (CH); 123.5 (CH); 125.6 (CH); 126.5 (CH); 127.6 (CH); 127.7 (CH); 128.3 (CH); 129.1 (CH); 129.5 (C); 130.2 (C); 132.9 (C); 134.3 (CH); 135.9 (CH); 136.2 (CH); 141.9 (CH); 142.9 (C); 143.0 (C); 155.2 (CH); 166.2 (C=O); 198.5 (C=O); 199.2 (C=O); 200.7 (C=O). MS: 501 (6, M^+), 456 (2), 355 (62), 357 (59), 326 (58), 298 (100), 189 (55), 146 (85), 129 (73), 104 (55), 76 (71). Anal. calc. for $C_{32}H_{23}NO_5$ (501.53): C 76.63, H 4.62, N 2.79; found: C 76.27, H 4.59, N 2.81.

tert-*Butyl* rel-*(9a*S*,14a*R*,14b*S*)-9a-(2,3-Dihydro-1,3-dioxo-1*H*-inden-2-yl)-9a,14,14a,14b-tetrahydro-14-oxoindeno[2′,1′:3,4]pyrido[2,1-*a*]isoquinoline-9-carboxylate* (**4c**). Yield: 0.44 g (83%). Colorless crystals. M.p. 185 – 187°. IR (KBr): 1724, 1715, 1708, 1675, 1609, 1563, 1451, 1259, 1246, 1091, 1224. ^{1}H-NMR: 1.36 (*s*, Me_3C); 3.47 (*d*, ^3J = 2.5, CH); 4.90 (*d*, ^3J = 2.5, CH); 5.31 (*s*, CH); 5.54 (*d*, ^3J = 7.7, CH); 6.08 (*d*, ^3J = 7.5, CH); 6.14 (*d*, ^3J = 7.6, CH); 6.80 (*t*, ^3J = 7.7, CH); 6.95 (*d*, ^3J = 7.5, CH); 7.09 (*t*, ^3J = 7.5, CH); 7.31 (*s*, CH); 7.44 (*d*, ^3J = 6.5, CH); 7.61 (*d*, ^3J = 7.4, CH); 7.68 (*t*, ^3J = 7.5, CH); 7.84 (*t*, ^3J = 7.4, CH); 7.93 (*t*, ^3J = 7.4, CH); 7.97 – 8.01 (*m*, 2 CH); 8.27 (*d*, ^3J = 8.0, CH). ^{13}C-NMR: 26.3 (Me_3C); 48.6 (C); 53.5 (CH); 55.4 (CH); 60.9 (CH); 83.6 (Me_3C); 104.5 (CH); 105.4 (C); 123.5 (CH); 123.4 (CH); 123.7 (CH); 123.9 (CH); 125.3 (CH); 126.2 (CH); 127.1 (CH); 127.7 (CH); 128.8 (CH); 129.3 (CH); 129.7 (C); 130.4 (C); 132.4 (C); 134.6 (CH); 135.9 (CH); 136.5 (CH); 141.8 (CH); 142.7 (C); 143.2 (C); 155.9 (CH); 166.7 (C=O); 198.2 (C=O); 199.7 (C=O); 200.8 (C=O). MS: 501 (7, M^+), 456 (2), 355 (62), 357 (59), 326 (58), 298 (100), 189 (55), 146 (85), 129 (73), 104 (55), 76 (71). Anal. calc. for $C_{34}H_{27}NO_5$ (529.58): C 77.11, H 5.14, N 2.64; found: C 77.57, H 5.18, N 2.66.

X-Ray Crystal-Structure Determination of **4a**. Structure-determination and refinement data: $C_{31}H_{21}NO_5$, M_r 487.50; crystal system, monoclinic, a = 10.6522(5) Å, b = 24.2712(10) Å, c = 10.5183(4) Å, α = 90°, β = 119.2220(10)°, γ = 90°, space group $P2_1/c$; Z = 4, V = 2373.33(17) Å^3, $D_{calc.}$ = 1.364 g cm^{-3}, crystal size 0.44 × 0.34 × 0.20 mm^3, R = 0.0476 (for 5130 reflections), R_w = 0.1167; $-14 \le h \le 14$; $-33 \le k \le 33$; $-14 \le l \le 14$°; MoK_α radiation (λ = 0.71073 Å); T = 120(2) K. The crystallographic data of **4a** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC-737928. Copies of the data can be obtained, free of charge, *via* the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44-1223-336033).

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