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The Povarov reaction of ethyl (18-carbomethoxyabieta-8,11,13-triene-12-imino)glyoxylate with electron-donating dienophiles

Alexey V. Tarantin,[a] Vladimir A. Glushkov,*[a] Olga A. Mayorova,[a] Irina A. Shcherbinina[b] and Alexander G. Tolstikov[a]

[a] *Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, 614990 Perm, Russian Federation. Fax: +7 342 237 8262; e-mail: glusha@nm.ru*
[b] *Department of Chemistry, Perm State University, 614990 Perm, Russian Federation. Fax: +7 342 237 1611*

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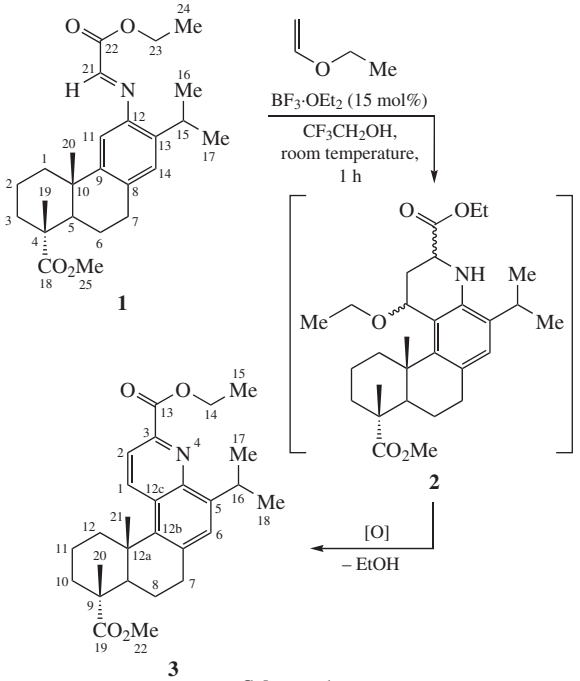
Ethyl (18-carbomethoxyabieta-8,11,13-triene-12-imino)glyoxylate undergoes cyclization with ethyl vinyl ether or *N*-vinylpyrrolidone to 3-ethoxycarbonyl-5-isopropyl-9-methoxycarbonyl-9,12a-dimethyl-7,8,8a,9,10,11,12,12a-octahydronaphtho[1,2-*f*]quinoline under $BF_3{\cdot}OEt_2$ catalysis; the corresponding reaction with cyclopentadiene proceeds with moderate diastereoselectivity at –20 °C.

The synthesis of substituted 1,2,3,4-tetrahydroquinolines by the Povarov reaction is a widespread methodology in heterocyclic chemistry.[1–5] This reaction is suitable for the preparation of quinolines annulated to cyclopentene,[6] cyclohexane,[7] indan,[4] tetrahydrofuran,[8] tetrahydropyran[9] and pyrroline[10] moieties. Quinolines annulated to a terpene skeleton are of special interest. Recently, we have disclosed[11] the way to substituted naphtho-[1,2-*f*]quinolines by the condensation of cyclopentadiene with Schiff bases from methyl 12-aminodehydroabietate. To our regret, diterpene imines from some aromatic aldehydes do not enter into this reaction.[11] Looking for more active 2-azadienes, we turned our attention to the imines from ethyl glyoxylate. Glyoxylates are well-known building blocks in organic synthesis.[12] According to published data, imines from ethyl glyoxylate are excellent 2-azadienes for tetrahydroquinoline synthesis.[13–15] These observations prompted us to explore ethyl (18-carbomethoxyabieta-8,11,13-triene-12-imino)glyoxylate **1**[†] in the Povarov reaction.



Scheme 1

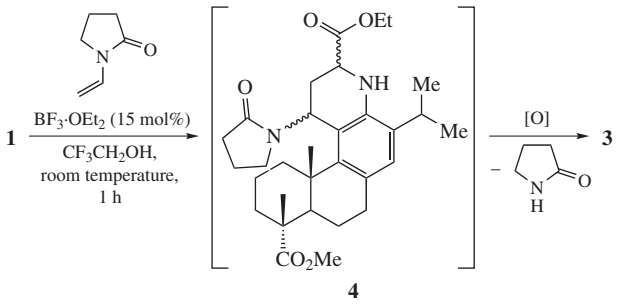
We investigated the following dienophiles: ethyl vinyl ether, *N*-vinylpyrrolidone, cyclopentadiene and indene. All cyclization reactions were conducted in 2,2,2-trifluoroethanol.[‡] This solvent, due to its high dielectric constant and low nucleophilicity, could have a pronounced effect on the cyclization reaction.[16–18]

[†] *Ethyl (18-carbomethoxyabieta-8,11,13-triene-12-imino)glyoxylate* **1**. A mixture of 2 g (6.1 mmol) of methyl 12-aminodehydroabietate,[24] 0.63 ml of ethyl glyoxylate (6.1 mmol, 40% toluene solution), 0.2 g of molecular sieves 4 Å and 15 ml of toluene was stirred under an argon atmosphere at 25 °C for 12 h; toluene was evaporated under reduced pressure. Purification of the residue on a silica gel column (Silicagel 60, Merck, 0.035–0.070 mm, hexane–ethyl acetate, 19:1) gave compound **1** as a greenish yellow semi-solid substance, mp ~ 15 °C, yield 90%; $[\alpha]_D^{18}$ +136.2 (*c* 1.035, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.14 (d, 3H, Me, *J* 6.9 Hz), 1.18 (d, 3H, Me, *J* 6.9 Hz), 1.22 (s, 3H, Me), 1.26 (s, 3H, Me), 1.39 (t, 3H, *Me*CH_2, *J* 7.2 Hz), 1.46–1.86 [m, 7H, $H_aC(1)$, $H_2C(2)$, $H_2C(3)$, $H_2C(6)$], 2.22 [m, 2H, $H_eC(1)$, HC(5)], 2.88 [m, 2H, $H_2C(7)$], 3.40 [m, 1H, HC(15)], 3.65 (s, 3H, OMe), 4.38 (q, 2H, OCH_2, *J* 7.2 Hz), 6.71 [s, 1H, HC(14)], 6.93 [s, 1H, HC(11)], 7.78 (s, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.18 (*Me*CH_2), 16.49 [C(19)], 18.48 [C(2)], 21.60 [C(6)], 23.17 [C(16)], 23.51 [C(17)], 25.04 [C(20)], 27.59 [C(15)], 29.75 [C(7)], 36.61 [C(3)], 37.17 [C(10)], 38.04 [C(1)], 44.76 [C(5)], 47.61 [C(4)], 51.86 [C(25)], 61.72 [C(23)], 112.99 [C(14)], 126.47 [C(11)], 135.45 [C(13)], 140.53 [C(8)], 145.53 [C(12)], 147.77 [C(9)], 149.53 [C(21)], 163.35 [C(22)], 178.86 [C(18)]. IR (Specord M80, Nujol, ν/cm^{-1}): 1752 (O–C=O), 1728 (O–C=O), 1632 (C=N), 1604 (C=C), 1560, 1496 (C=C), 1348, 1288, 1248, 1194, 1134, 1108, 1042, 908, 888. MS, *m*/*z* (%): 413 (84) [M$^+$], 384 (34), 340 (100), 272 (14), 216 (23), 196 (14), 158 (100). Found (%): C, 73.06; H, 8.74; N, 3.02. Calc. for $C_{25}H_{35}NO_4$ (%): C, 72.61; H, 8.53; N, 3.39.

[‡] *General procedure for cyclization reactions.* Compound **1** (0.35 g, 0.847 mmol) was dissolved in 15 ml of 2,2,2-trifluoroethanol, $BF_3{\cdot}OEt_2$ (0.018 ml, 0.13 mmol, 15 mol%) was added and stirred for 15 min; next, 2.54 mmol of a dienophile (ethyl vinyl ether, *N*-vinylpyrrolidone, cyclopentadiene or indene) was added. The reaction mixture was stirred for 0.5–1 h at 25 °C (–20 °C in the case of cyclopentadiene and indene). The reaction was monitored by TLC [Sorbfil, hexane–ethyl acetate, 9:1, detection with phosphomolybdic acid (ethanolic solution) with heating at 100–120 °C]. After 0.5–1 h, the solvent was evaporated under a reduced pressure, the residue was dissolved in 50 ml of ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Purification on a silica gel column (hexane–ethyl acetate, 19:1) gave compound **3** or a mixture of diastereomers **5a**,**b** and **6a**–**d**. Three recrystallizations from hexanes gave diastereomer **5a** with 90.5% *ee*.

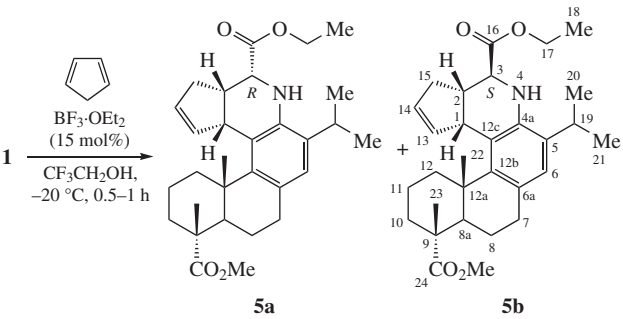
The reaction of iminoglyoxylate **1** with ethyl vinyl ether in the presence of 15 mol% $BF_3{\cdot}OEt_2$ after work-up and purification by silica gel column chromatography afforded 3-ethoxycarbonyl-5-isopropyl-9-methoxycarbonyl-9,12a-dimethyl-7,8,8a, 9,10,11,12,12a-octahydronaphtho[1,2-*f*]quinoline **3** in 32% yield (Scheme 1). Ethanol elimination from the intermediate of the Povarov reaction and subsequent spontaneous oxidation of 1,2-dihydroquinolines is well documented.[1] In the ^{1}H NMR spectrum of compound **3**,[§] the H-1 and H-2 proton signals appear as two doublets at δ 8.65 and 7.93 ppm, respectively (J 9 Hz), which is consistent with the structure of **3**.

Surprisingly, the reaction of imine **1** with *N*-vinylpyrrolidone afforded compound **3** in 27% yield (Scheme 2).



Scheme 2

Pyrrolidone elimination from intermediate **4** is also known, although it is uncommon.[19–21] The driving force of such an elimination is aromatization of the quinoline.



Scheme 3

The structures and stereochemistry of compounds **5a**,**b**, obtained by interaction of **1** with cyclopentadiene (Scheme 3), were assigned by coupling constants and NOE experiments.[¶] We noticed NOE contacts between protons C(22)H_3 and HC(1) [4% in $(CD_3)_2CO$ and 2.8% in $CDCl_3$], as well as for protons HC(1) and β-HC(12). Previously,[11] the *endo-cis*-annulation of a cyclopentene ring in an analogous reaction was unambiguously determined by NMR spectroscopy. The above *endo*-type annulation was observed for compounds **5a**,**b**. Compounds **5a**,**b** could be clearly distinguished by NMR spectra. The signals of HC(13) and HC(14) protons of *trans*-isomer (*S*)-**5b** are relatively downfield and appear at δ 5.34 and 5.77 ppm while corresponding protons in the *cis*-isomer (*R*)-**5a** are relatively upfield and resonate at δ 4.99 and 5.62 ppm, respectively.

We noticed the enhancement of stereoselectivity at –20 °C. At 25 °C, the reaction of imine **1** with cyclopentadiene afforded a mixture of *cis*/*trans* isomers **5a**:**5b** in a ratio of 1:1 (total yield, 82%), but at –20 °C the ratio **5a**:**5b** was 1:2, (33% *de* for **5b**; total yield, 91%). The predominance of the *cis* isomer was noted in an analogous reaction of methyl 12-arylydeneaminodehydroabietate.[11] Pure *trans* isomer **5b** can be obtained after repeated recrystallizations of a mixture of **5a** + **5b** from hexanes. In our hands, after a first crystallization the ratio of **5b**:**5a** (3*S*:3*R*) was enhanced to 4:1 (**5b** 60% *de*), after second reached 20:1 (**5b** *de* 90.5%) and showed no more changes after next recrystallizations from hexanes.

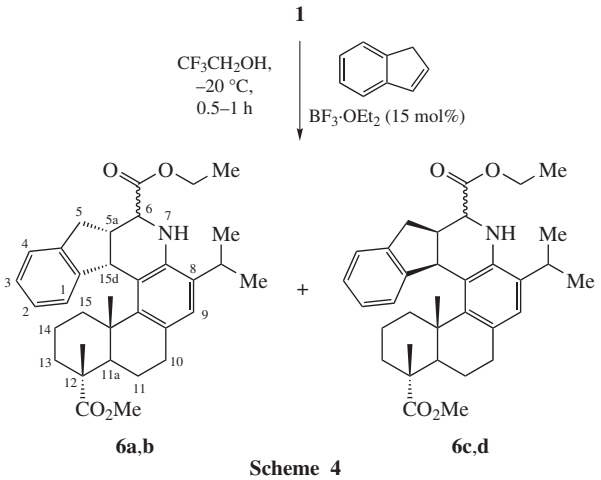
In the case of indene the reaction loses diastereoselectivity. After usual work-up, four products were obtained, which could not be separated by column chromatography (Scheme 4). A mixture of compounds **6a–d** was analysed on an Agilent 6890N chromatograph with a 5975B mass spectrometer.[††] Four diastereomers with (*m*/*z*) M^+ 529 were detected (retention times, 23.74, 24.46, 24.92 and 25.12 min; yields, 22, 18, 16 and 23%, respectively). It is obvious that in the case of indene diastereomers differ not only by orientation at C(6) atom but also by the type of indene annulation. The ^{1}H NMR spectrum of **6a–d** also indicates the formation of four diastereomers.

To our opinion, such results are due to the reversibility of the Povarov reaction in the presence of Lewis acids.[22] In the case of

[§] *(8a*R,*9*R,*12a*S*)-3-Ethoxycarbonyl-5-isopropyl-9-methoxycarbonyl-9,12a-dimethyl-7,8,8a,9,10,11,12,12a-octahydronaphtho[1,2-*f*]quinoline* **3**: yield 33%, mp 154–157 °C (hexanes); $[\alpha]_D^{27}$ +39.2 (*c* 0.53, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (d, 3H, Me, *J* 6.9 Hz), 1.29 (s, 3H, Me), 1.30 (d, 3H, Me, *J* 6.9 Hz), 1.41 (t, 3H, CH_2*Me*, *J* 7.5 Hz), 1.62 (s, 3H, Me), 1.64–1.90 [m, 7H, $H_2C(8)$, $H_2C(10)$, $H_2C(11)$, $H_{ax}C(12)$], 2.16 [m, 1H, HC(8a)], 2.83 [m, 2H, $H_{ax}C(7)$, $H_{eq}C(12)$], 3.08 [m, 1H, $H_{eq}C(7)$], 3.61 (s, 3H, OMe), 4.25 (m, 1H, HCAr), 4.44 (q, 2H, OCH_2, *J* 7.5 Hz), 7.23 [s, 1H, HC(6)], 7.93 [d, 1H, HC(2), *J* 9 Hz], 8.65 [d, 1H, HC(1), *J* 9 Hz]. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3 (*Me*CH_2), 17.23 [C(20)], 18.92 [C(11)], 21.56 [C(8)], 21.60 [C(21)], 23.36 (*C*HMe), 23.41 (*C*HMe), 27.24 [C(9)], 27.80 [C(12a)], 33.50 [C(7)], 36.29 [C(10)], 39.24 [C(12)], 48.39 [C(8a)], 51.96 [OMe], 61.44 (OCH_2), 118.14 [C(2)], 127.25 [C(12c)], 128.38 [C(6)], 134.83 [C(1)], 136.86 [C(6a)], 140.66 [C(5)], 144.39 [C(12b)], 146.15 [C(3)], 146.35 [C(4a)], 165.79 (*C*O_2Et), 178.87 (*C*O_2Me). IR (Nujol, ν/cm^{-1}): 1730 (O–C=O), 1710 (O–C=O), 1608 (C=C), 1318, 1292, 1244, 1158, 1130, 1080, 1048, 1024, 998, 908, 852. MS, *m*/*z* (%): 437 (84) [M^+], 422 (66), 408 (100), 363 (41), 348 (15). Found (%): C, 73.44; H, 8.22; N, 2.91. Calc. for $C_{27}H_{35}NO_4$ (%): C, 74.11; H, 8.06; N, 3.20.

[¶] *(1*R,*2*S,*3*R,*8a*R,*9*R,*12a*S*)-3-Ethoxycarbonyl-5-isopropyl-9-methoxycarbonyl-9,12a-dimethyl-1,2-(1-propenylene)-1,2,3,4,7,8,8a,9,10,11,12,12a-dodecahydronaphtho[1,2-f]quinoline* **5a** and its 3*S* isomer **5b**. Total yield (**5a** + **5b**) 91%. After three crystallizations from hexanes, compound **5b** was obtained with yield 27%, mp 153–155 °C; $[\alpha]_D^{18}$ +231.0 (*c* 0.09, $CHCl_3$, 90% *de*). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (d, 3H, Me, *J* 6.6 Hz), 1.18 (d, 3H, Me, *J* 6.6 Hz), 1.26 (s, 3H, Me), 1.30 (t, 3H, Me, *J* 7.2 Hz), 1.44 (s, 3H, Me), 1.55–1.82 [m, 7H, $H_2C(8)$, $H_2C(10)$, $H_2C(11)$, $H_\alpha C(12)$], 2.26 [m, 2H, H(8a), HC(15)], 2.68 [m, 3H, $H_2C(7)$, HC(15)], 2,84 [m, 2H, $H_\beta C(12)$, *H*CAr], 3.34 [m, 1H, HC(2)], 3.40 [d, 1H, HC(3), *J* 4.5 Hz], 3.67 (s, 3H, OMe), 4.11–4.31 (m, 3H, OCH_2, NH), 4.76 [m, 1H, HC(1)], 5.34 [m, 1H, HC(13)], 5.77 [m, 1H, HC(14)], 6.69 [s, 1H, HC(6)]. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.98 (*Me*CH_2), 17.19 [C(23)], 18.40 [C(11)], 20.87 [C(8)], 21.47 [C(22)], 22.00 [C(21)], 22.39 [C(20)], 26.06 [C(19)], 31.68 [C(7)], 35.64 [C(15)], 35.84 [C(10)], 38.25 [C(12a)], 38.62 [C(12)], 42.17 [C(2)], 47.20 [C(1)], 47.81 [C(9)], 47.97 [C(8a)], 51.70 (OMe), 60.60 [C(3)], 61.86 [C(17)], 123.31 [C(6)], 125.69 [C(6a)], 125.93 [C(12c)], 129.20 [C(14)], 130.19 [C(5)], 133.27 [C(13)], 144.05 [C(12b)], 144.67 [C(4a)], 171.43 [CO_2Et], 178.09 [*C*O_2Me]. IR (Nujol, ν/cm^{-1}): 3404 (NH), 1736 (O–C=O), 1722 (O–C=O), 1668 (C=C), 1636, 1562, 1288, 1244, 1220, 1154, 1132, 1108, 1080, 1048, 1020, 988, 940, 876, 840. MS, *m*/*z* (%): 479 (100) [M^+], 406 (73), 224 (14). Found (%): C, 75.09; H, 8.41; N, 2.89. Calc. for $C_{30}H_{41}NO_4$ (%): C, 75.12; H, 8.62; N, 2.92.

Diastereomer (*R*)-**5a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (d, 3H, Me, *J* 6.6 Hz), 1.16 (d, 3H, Me, *J* 6.6 Hz), 1.28 (s, 3H, Me), 1.29 (t, 3H, Me, *J* 7.2 Hz), 1.44 (s, 3H, Me), 1.55–1.75 [m, 7H, $H_2C(8)$, $H_2C(10)$, $H_2C(11)$, $H_\alpha C(12)$], 1.96 [m, 1H, HC(15)], 2.23 [m, 2H, H(8a), HC(15)], 2.54 [m, 2H, $H_2C(7)$], 2.79 [m, 2H, $H_\beta C(12)$, HCAr], 3.41 [m, 1H, HC(2)], 3.47 [d, 1H, HC(3), *J* 4.5 Hz], 3.64 (s, 3H, OMe), 4.18–4.32 (m, 2H, OCH_2), 4.82 [m, 1H, HC(1)], 4.99 [m, 1H, HC(13)], 5.62 [m, 1H, HC(14)], 6.61 [s, 1H, HC(6)]. Group NH is not detected in the ^{1}H NMR spectrum due to proton exchange.



Scheme 4

cyclopentadiene stereoisomers obtained are reversibly converted into more stable *endo-trans* isomer **5b**, meanwhile inden is not subjected to such conversion.

The structures of compounds **1**, **3**, **5**, **6** were confirmed by elemental analysis, ^{1}H NMR and IR spectroscopy and mass spectrometry. Interpretation of ^{1}H NMR spectra was made according to the published data.[23]

We are grateful to Alexey Gorbunov for recording the mass spectra.

†† *(5a*S*,6*R*,11a*R,12*R,15a*S,15d*S*)-6-Ethoxycarbonyl-8-isopropyl-12-methoxycarbonyl-12,15a-dimethyl-5,5a,6,10,11,11a,12,13,14,15,15a,15d-7*H*-dodecahydronaphtho[1,2-*f*]indeno[2,1-*c*]quinoline* (a mixture of diastereomers **6a**–**d**): yield 80%, mp 141–157 °C (hexanes). **6a** (major isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90–1.83 (m, 23H), 2.12 [m, 1H, HC(11a)], 2.54–3.00 [m, 6H, H_2C(5), HC(5a), H_2C(10), HCAr], 3.63 (s, 3H, OMe), 4.16–4.33 (m, 3H, OCH_2 + NH), 5.09 [d, H, HC(6), *J* 7.2 Hz], 6.16 [d, H, HC(15d), *J* 7.5 Hz], 6.60 [s, 1H, HC(9)], 6.80–7.12 (m, 4H, $H_{arom.}$). IR (Nujol, ν/cm^{-1}): 3460 (NH), 1736 (O–C=O), 1720 (O–C=O), 1594 (C=C), 1568, 1288, 1246, 1208, 1174, 1138, 1128, 1050, 1012, 988, 876. MS, *m*/*z* (%): 529 (100) [M$^+$], 456 (91), 274 (13), 207 (19). Found (%): C, 76.52; H, 8.29; N, 2.43. Calc. for $C_{34}H_{43}NO_4$ (%): C, 77.09; H, 8.18; N, 2.64.

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