Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2012, **22**, 29–31
Mendeleev Communications

1,3-Dipolar cycloadditions of nonstabilised azomethine ylides at 3-substituted coumarins: synthesis of 1-benzopyrano[3,4-*c*]pyrrolidines

Vladimir S. Moshkin,*[a] Vyacheslav Ya. Sosnovskikh,[a] Pavel A. Slepukhin[b] and Gerd-Volker Röschenthaler[c]

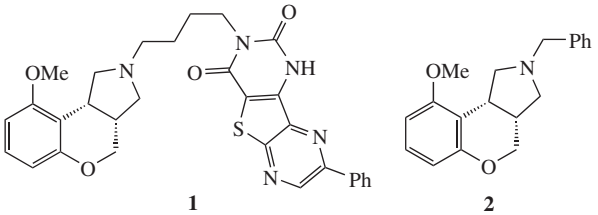
[a] *Department of Chemistry, Ural Federal University, 620083 Ekaterinburg, Russian Federation. Fax: +7 343 261 5978; e-mail: mvslc@mail.ru*
[b] *Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620041 Ekaterinburg, Russian Federation*
[c] *School of Engineering and Science, Jacobs University Bremen, 28759 Bremen, Germany*

DOI: 10.1016/j.mencom.2012.01.011

Reaction of 3-substituted coumarins with *N*-alkyl-α-amino acids and aldehydes proceeds regio- and stereoselectively to give 1-benzopyrano[3,4-*c*]pyrrolidines as a result of 1,3-dipolar cycloaddition of the intermediate azomethine ylides at the Δ^3-bond of the coumarins.

1,3-Dipolar cycloaddition as an approach to five-membered heterocycles proceeds with high regio- and stereoselectivity.[1] In particular, azomethine ylides generated from *N*-alkyl-α-amino acids and carbonyl compounds enable one-step syntheses of substituted pyrrolidines.[2] On the other hand, chromane derivatives are widespread in the plant world and also possess valuable biological and pharmacological properties.[3] In view of this, fusing benzopyran and pyrrolidine moieties in a single molecule seems being of current interest.[4]

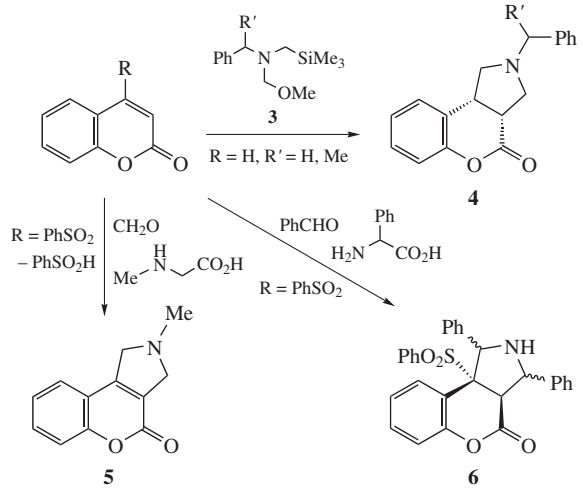
To this, *cis*-benzopyranopyrrolidine **1** (Fiduxosin) is an α_1 adrenoreceptor antagonist and shows an α_{1a}/α_{1b} selectivity for adrenoreceptors;[5] whereas *cis*-benzopyranopyrrolidine **2** is an antagonist of 5-HT_{2C} receptors with respect to 5-HT_{2A}.[4]



1 **2**

The key stage in the synthesis of compounds **1** and **2** is cycloaddition of nonstabilised azomethine ylides to benzopyranones; however, information about such reactions in the coumarin series is quite limited. It is known that coumarin reacts with azomethine ylide generated from *N*-trimethylsilylmethyl-*N*-methoxymethylbenzylamines **3** to give *cis*-2-benzylbenzopyrano[3,4-*c*]pyrrolidines **4** (Scheme 1).[4,5] The reaction of 4-phenylsulfonylcoumarin with the azomethine ylide from sarcosine and formaldehyde with elimination of phenylsulfinic acid affords dihydropyrrole **5**, whereas the reaction of the former with α-phenylglycine leads to a mixture of diastereomers **6**.[6] No data are available concerning the participation of 3-substituted coumarins in 1,3-dipolar cycloaddition with nonstabilised azomethine ylides.

Herein, we have found that refluxing of sarcosine, paraformaldehyde and coumarin **7a** (Scheme 2)† in benzene for 6 h with azeotropic removal of water results in 1-benzopyrano[3,4-*c*]pyrrolidines derivative **8a** (yield 78%).‡ This reaction is an alternative to the previously known addition of azomethine ylides generated from compounds **3** to coumarins (see Scheme 1). 3-Cyano-, 3-ethoxycarbonyl- and *N*,*N*-dimethyl-3-carbamoylcoumarins **7b–d** react

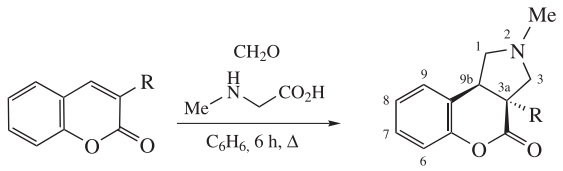


Scheme 1

† *General procedure.* A mixture of the corresponding coumarin **7** (1.0 mmol), paraformaldehyde (0.03 g, 1.0 mmol) and adust sarcosine (0.11 g, 1.2 mmol) or proline (0.14 g, 1.2 mmol) was refluxed in dry benzene (8 ml) with magnetic stirring and removal of the water formed *via* a Dean–Stark trap. After 3 h, a second portion of paraformaldehyde (0.02 g, 0.5 mmol) was added, and the refluxing was continued for additional 3–5 h. The resulting yellow mixture was cooled to room temperature and slowly filtered through a thin layer of silica gel, then washed with benzene. The colourless solution was evaporated *in vacuo* to give a viscous oil. Anhydrous oxalic acid (0.10 g, 1.1 mmol) dissolved in hot acetone (1.5 ml) was added with stirring to the crude product in hot acetone (1.5 ml). A dispersion was refluxed for additional 5 min with partial evaporation of acetone (to 2 ml). After cooling to 5 °C, precipitate was filtered off and washed with dry acetone. The colourless powder was dried to a constant weight.

‡ *(3a*S*,9b*S*)-2-Methyl-1,3,3a,9b-tetrahydrochromeno[3,4-*c*]pyrrol-4(2*H*)-one* **8a** *adduct with oxalic acid*. Yield 78%, colourless powder, mp 191–193 °C. ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ: 2.66 (s, 3H, MeN), 2.98 (t, 1H, H-1′, *J* 10.0 Hz), 3.45 (dd, 1H, H-3′, *J* 10.8 and 4.2 Hz), 3.56 (t, 1H, H-1″, *J* 9.0 Hz), 3.64 (t, 1H, H-3″, *J* 10.0 Hz), 3.72 (td, 1H, H-3a, *J* 8.8 and 4.2 Hz), 3.88 (q, 1H, H-9b, *J* 9.0 Hz), 7.03 (d, 1H, H-6, *J* 8.1 Hz), 7.14 (t, 1H, H-8, *J* 7.5 Hz), 7.30 (t, 1H, H-7, *J* 8.1 Hz), 7.32 (d, 1H, H-9, *J* 7.5 Hz). IR (ATR, ν/cm^{-1}): 2486, 1759, 1716, 1649, 1456, 1221, 1185, 1165, 763, 698. Found (%): C, 57.06; H, 4.98; N, 4.81. Calc. for $C_{12}H_{13}NO_2 \cdot (CO_2H)_2$ (%): C, 57.34; H, 5.16; N, 4.78.

For characteristics of compound **8c**, see Online Supplementary Materials.



a R = H **c** R = CO_2Et
b R = CN **d** R = $CONMe_2$

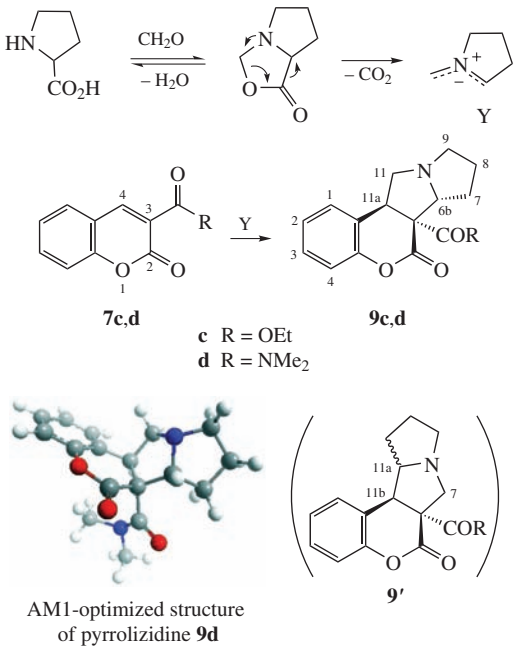
Scheme 2

with sarcosine and paraformaldehyde similarly to give products **8b**–**d** in 51%, 84% and 87% yields, respectively.

Treatment of products **8a**,**c** with oxalic acid provided conversion of these liquid pyrrolidines to analytically pure crystalline oxalates escaping chromatographic purification. On the other hand, oxalate of **8d** was found to be a highly hygroscopic compound. Judging by ^{1}H NMR data, it undergoes partial hydrolysis in a DMSO-d_6 solution with opening of the dihydrocoumarin ring (a set of aromatic protons typical of phenols is observed at δ 6.7–7.1 ppm).[7] In another experiment, compound **8d** was obtained as a free base by crystallization from diethyl ether. 3-Cyanocoumarin derivative **8b** was isolated as an oily base after extraction of non-basic admixtures from the aqueous solution of its hydrochloride followed by neutralization with sodium hydrocarbonate.

The structures of products **8a–d** were determined by elemental analyses and by comparison of their IR, ^{1}H and ^{13}C NMR spectra with data for related benzopyrano[3,4-*c*]pyrrolidines.[5,8] The synchronism of reactions of nonstabilised azomethine ylides with alkenes results in the *cis*-fusion in the new pyrrolidine ring.[2,4,5] In the case of the symmetric 1,3-dipole formed from sarcosine and paraformaldehyde, the *endo*- and *exo*-transition states become degenerate owing to the simplicity of its structure. The ^{1}H NMR spectra of oxalates of **8a**,**c**,**d** in DMSO-d_6 contain the following characteristic signals: a triplet or a doublet of doublets of the H-1′ proton at δ 2.7–3.0 ppm, which is subject to the shielding effect of the benzene moiety in the *cis*-position; a triplet of H-1″ at δ 3.2–3.6 ppm (this proton manifests itself at δ 3.20–3.27 ppm in the presence of an ethoxycarbonyl or dimethylamide group at the 1,3-*cis* position that show a shielding effect[9]); a doublet of doublets and a triplet or two doublets of H-3′ and H-3″ geminal protons at δ 3.3–3.8 ppm (J_{gem} = 10–11 Hz); a quartet or a triplet of the H-9b benzyl proton at δ 3.88–3.94 ppm (J = 7–9 Hz). The signals of the H-6 and H-8 aromatic protons are observed at δ 7.03–7.06 and 7.14–7.17 ppm, respectively, whereas the partially overlapping signals of H-7 and H-9 are observed at δ 7.25–7.35 ppm.

The literature contains no data on reactions of coumarins with unsymmetrical nonstabilised azomethine ylides, which may be due to the expected formation of a complex mixture of regio- and stereoisomers. In fact, we have found that refluxing of coumarin **7a**, proline and paraformaldehyde in benzene led to a hardly separable mixture of isomers. However, the same reaction with *N*,*N*-dimethyl-3-carbamoylcoumarin **7d** gave only one diastereomer **9d** (Scheme 3)[§] isolated as an oxalate in 60% yield (we failed to isolate the oxalate of the minor isomer, which was formed in an amount of about 10%, by crystallization). The observed regio- and *exo*-selectivity are, first, due to a difference in the atomic contributions of HOMO in active centers of the azomethine ylide in favor of the terminal carbon atom and its orientation near the highly-polarised double bond of coumarin **7d** with the highest contribution of LUMO at C-4; second, due to secondary orbital interactions between the *N*,*N*-dimethylcarboxamide group and the dipole molecule; third, due to the absence of unfavourable *cis* steric interactions between the cycloalkyl moiety and the benzopyranone ring, in contrast to the *endo*-process. Note that



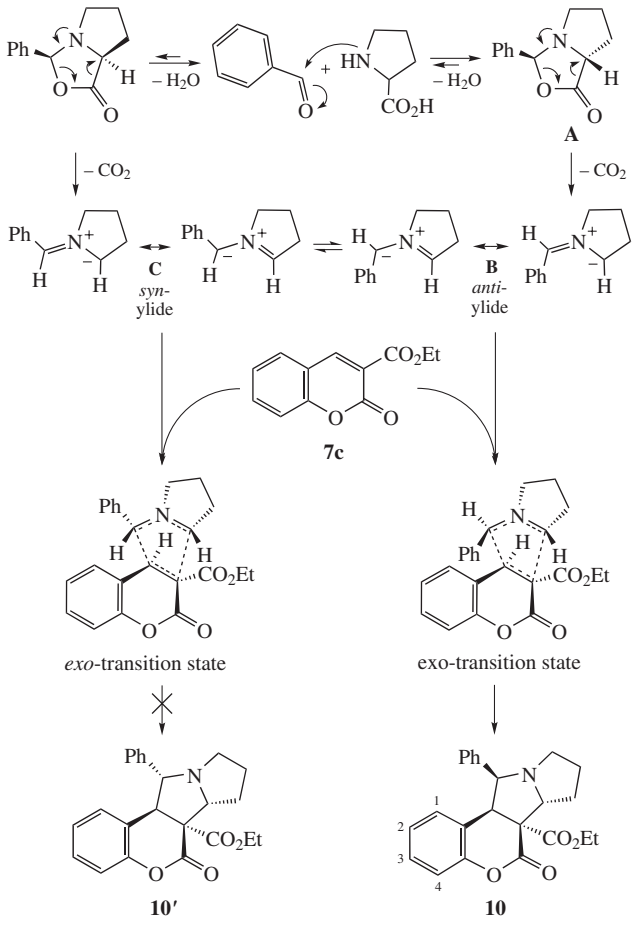
Scheme 3

the *exo*-selectivity in azomethine ylide addition to cyclic dipolarophiles is known from the literature.[5,10]

The reaction of the azomethine ylide formed from proline and paraformaldehyde with 3-ethoxycarbonylcoumarin **7c** occurred in a similar way to give product **9c** in 47% yield (isolated as an oxalate). The signals of pyrrolizidines **9c**,**d** in the ^{1}H NMR spectra are similar to the corresponding signals of pyrrolidines **8a–d**, except for the signals of the new fused pyrrolidine ring such as a characteristic H-6b methine proton at δ 4.6–5.0 ppm that is subject to 1,2- and 1,3-*cis*-deshielding effects of carbonyl and benzene ring of the dihydrocoumarin system.[9] The doublet of doublets of the H-11a benzyl proton in compounds **9c**,**d** allows us to rule out the alternative regioisomeric structure **9′**, in which the H-11b proton should interact with only one vicinal proton, H-11a.

Treatment of coumarin **7c** with proline and benzaldehyde afforded diastereomer **10** isolated as a hydrochloride in 26% yield (Scheme 4).[¶] It follows from structure **10** that the observed 1,3-dipolar cycloaddition occurs *via* an *exo*-transition state (as in the case of **9c**,**d**) involving *anti*-azomethine ylide **B**. The formation of the latter can be explained by the higher stability of *trans*-azalactone **A** that is initially formed in the reaction of proline with benzaldehyde. Concerted cycloreversion of the azalactone ring in **A** with extrusion of carbon dioxide follows a disrotatory pathway to give *anti*-ylide **B**. Apparently, isomerisation of dipoles **B** and **C** has small rate constants and the reaction of **B** with coumarin **7c** becomes the main reaction.[6] Secondary orbital inter-

§ *(6a*S**,6b*R**,11a*R**)*-N,N-*Dimethyl-6-oxo-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4*-a*]pyrrolizine-6a-carboxamide* **9d** *adduct with oxalic acid*. Yield 60%, pale yellow powder, mp 147–152 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4) δ: 1.47–1.58 (m, 1H, H-7′), 1.81–1.93 (m, 1H, H-8′), 2.00–2.09 (m, 1H, H-7″), 2.13–2.21 (m, 1H, H-8″), 2.81 (s, 3H, MeN), 2.95 (t, 1H, H-11′, J 13.0 Hz), 3.09 (s, 3H, MeN), 3.09–3.15 (m, 1H, H-9′), 3.45 (dd, 1H, H-11″, J 12.4 and 7.0 Hz), 3.63 (dd, 1H, H-9″, J 9.7 and 7.0 Hz), 4.38 (dd, 1H, H-11a, J 13.4 and 7.0 Hz), 4.94 (dd, 1H, H-6b, J 10.4 and 7.5 Hz), 7.01 (d, 1H, H-4, J 8.2 Hz), 7.15 (t, 1H, H-2, J 7.5 Hz), 7.28 (td, 1H, H-3, J 7.8 and 1.3 Hz), 7.43 (d, 1H, H-1, J 7.5 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 25.3 (C-8), 27.8 (C-7), 37.0 (MeN), 37.1 (MeN), 41.3 (C-11a), 54.1 (C-9), 55.8 (C-11), 60.4 (C-6a), 68.0 (C-6b), 116.1 (C-4), 119.7 (C-11b), 125.0 (C-2), 129.2 (C-3), 129.4 (C-1), 150.2 (C-4a), 161.1 (CO), 163.6 (CO_2H), 164.4 (C-6). IR (ATR, ν/cm^{-1}): 3017, 2529, 1755, 1712, 1646, 1177, 1150, 762, 712, 687. Found (%): C, 58.50; H, 6.04; N, 6.87. Calc. for $C_{17}H_{20}N_2O_3 \cdot (CO_2H)_2$ (%): C, 58.46; H, 5.68; N, 7.18.



Scheme 4

actions of the *syn*-arranged cycloalkenyl moiety of the azomethine ylide and the ethoxycarbonyl group of coumarin, as well as smaller steric hindrance in comparison with the *endo*-process (for this particular pair of *syn*-substituents), stabilise the *exo*-transition state and make the process regio- and stereoselective. Judging by the product yield, the formation of other diastereomers may not be ruled out; however, we failed to isolate them.

An interesting feature of the ^{1}H NMR spectrum of pyrrolizidine **10** is that it contains signals of the H-1 proton (δ 6.67 ppm) shielded by 0.5–0.6 ppm by the phenyl substituent, and of the H-4 proton (δ 7.61 ppm) deshielded by the same substituent. The regio- and stereochemistry of hydrochloride **10** has been ultimately estimated by X-ray diffraction data (Figure 1).††

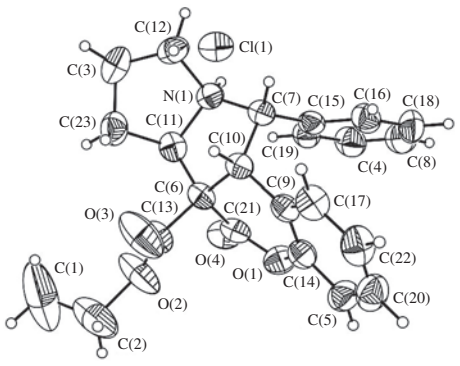


Figure 1 Molecular structure of compound **10** (thermal ellipsoids at 50% probability level).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.01.011.

References

1 A. Padwa, *Synthetic Applications of Dipolar Cycloaddition Chemistry Towards Heterocyclic and Natural Product Chemistry*, Wiley, 2002.

2 (*a*) O. Tsuge and S. Kanemasa, *Adv. Heterocycl. Chem*., 1989, **45**, 231; (*b*) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev*., 2006, **106**, 4484; (*c*) C. Nájera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105; (*d*) I. Coldham and R. Hufton, *Chem. Rev*., 2005, **105**, 2765.

3 (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev*., 2003, **103**, 893; (*b*) R. K. Razdan and J. F. Howes, *Med. Res. Rev*., 1983, **3**, 119.

4 (*a*) T. Dubuffet, O. Muller, S. S. Simonet, J.-J. Descombes, M. Laubie, T. J. Verbeuren and G. Lavielle, *Bioorg. Med. Chem. Lett*., 1996, **6**, 349; (*b*) T. Dubuffet, A. Newman-Tancredi, D. Cussac, V. Audinot, A. Loutz, M. J. Millan and G. Lavielle, *Bioorg. Med. Chem. Lett*., 1999, **9**, 2059; (*c*) G. Lavielle, T. Dubuffet, M. J. Millan and A. Newman-Tancredi, *US Patent 5663191*, 1997; (*d*) M. D. Meyer, R. J. Altenbach, F. Z. Basha, W. A. Carroll, I. Drizin, J. F. Kerwin, M. D. Wendt, A. R. Haight and W. Zhang, *US Patent 6046207*, 2000; (*e*) T. Kiyoi, M. Reid, S. Francis, K. Davies, S. Laats, D. McArthur, A.-M. Easson, Y. Kiyoi, G. Tarver, W. Caulfield, K. Gibson, G. Wishart, A. J. Morrison, J. M. Adam and P. Ray, *Tetrahedron Lett*., 2011, **52**, 3413; (*f*) M. Ghandi, A. Taheri and A. Abbasi, *Tetrahedron*, 2010, **66**, 6744; (*g*) H. G. Pars, F. E. Granchelli, R. K. Razdan, J. K. Keller, D. G. Teiger, F. J. Rosenberg and L. S. Harris, *J. Med. Chem.*, 1976, **19**, 445.

5 A. R. Haight, A. E. Bailey, W. S. Baker, M. H. Cain, R. R. Copp, J. A. DeMattei, K. L. Ford, R. F. Henry, M. C. Hsu, R. F. Keyes, S. A. King, M. A. McLaughlin, L. M. Melcher, W. R. Nadler, P. A. Oliver, Sh. I. Parekh, H. H. Patel, L. S. Seif, M. A. Staeger, G. S. Wayne, S. J. Wittenberger and W. Zhang, *Org. Process Res. Dev*., 2004, **8**, 897.

6 (*a*) R. Grigg and D. Vipond, *Tetrahedron*, 1989, **45**, 7587; (*b*) R. Grigg, J. Idle, P. McMeekin, S. Surendrakumar and D. Vipond, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2703.

7 (*a*) V. Ya. Sosnovskikh, V. S. Moshkin and M. I. Kodess, *Tetrahedron Lett.*, 2009, **50**, 6515; (*b*) V. Ya. Sosnovskikh, V. S. Moshkin and M. I. Kodess, *Tetrahedron Lett*., 2008, **49**, 6859.

8 J. E. Baldwin, S. C. MacKenzie Turner and M. G. Moloney, *Synlett*, 1994, 925.

9 F. Orsini, F. Pelizzoni, M. Forte, M. Sisti, F. Merati and P. Gariboldi, *J. Heterocycl. Chem.*, 1988, **25**, 1665.

10 (*a*) A. Padwa, Y. Y. Chen, U. Chiacchio and W. Dent, *Tetrahedron*, 1985, **41**, 3529; (*b*) I. F. Cottrell, D. Hands, D. J. Kennedy, K. J. Paul, S. H. B. Wright and K. J. Hoogsteen, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1091.

11 G. M. Sheldrick, *Acta Crystallogr*., 2008, **A64**, 112.

Received: 26th July 2011; Com. 11/3770

¶ *Ethyl (6a*S**,6b*R**,11*S**,11a*R**)-6-oxo-11-phenyl-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-*a*]pyrrolizine-6a-carboxylate* **10** *adduct with HCl.* A mixture of ethyl 3-coumarincarboxylate **7c** (0.22 g, 1.0 mmol), benzaldehyde (0.04 g, 0.4 mmol) and adust proline (0.12 g, 1.0 mmol) was refluxed in dry toluene (8 ml) with magnetic stirring and removal of the water formed *via* a Dean–Stark trap. After 3 h, a second part of benzaldehyde (0.04 g, 0.4 mmol) was added; after another 2 h, a third part of benzaldehyde (0.04 g, 0.4 mmol) was added. Refluxing was continued for additional 4 h. The resulting yellow mixture was cooled to room temperature and slowly filtered through a thin layer of silica gel, then washed with toluene. Isopropanol (0.07 g, 1.2 mmol) and acetyl chloride (0.09 g, 1.1 mmol) were added with stirring to the resulting solution, the mixture was allowed to stand overnight at room temperature. The dark-magenta precipitate that formed was dissolved in hot acetone, diluted with EtOAc, and then kept for 2 days in a refrigerator. The colourless crystals of the product were filtered and washed with an acetone–ethyl acetate mixture. The product was dried to a constant weight. Yield 0.49 g (26%), mp 162–167 °C.

For characteristics of compound **10**, see Online Supplementary Materials.

†† *Crystal data for* **10**: $C_{23}H_{24}ClNO_4$, M = 413.89, monoclinic, space group $P2_1/n$, a = 11.4363(6), b = 12.0021(10) and c = 15.9506(15) Å, β = = 108.543(7)°, V = 2075.7(3) Å^3, Z = 4, d_{calc} = 1.324 g cm^{-3}, μ = 0.213 mm^{-1}, $F(000)$ = 872. Diffraction data were collected on an Xcalibur 3 automatic single-crystal diffractometer (graphite-monochromated MoKα radiation, ω-scans). The structures were solved by direct methods and refined by the full matrix least-squares method with respect to F^2 using the SHELX-97 software package.[11] Non-H atoms were refined anisotropically, H-atoms were placed in calculated positions and refined isotropically.

CCDC 858698 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.