ISSN 1070-4280, Russian Journal of Organic Chemistry, 2012, Vol. 48, No. 7, pp. 953–956. © Pleiades Publishing, Ltd., 2012.
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Unusual Michael Reaction of 3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one with 3-Amino-*N*-phenyl-3-thioxopropanamide

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Received October 31, 2011

Abstract—3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one reacted with 3-amino-*N*-phenyl-3-thioxopropanamide under basic conditions in ethanol to give a mixture of 3-(4-chlorophenyl)-2-cyano-5-oxo-*N*,5-diphenylpentanamide and 3-(4-chlorophenyl)-1,5-diphenylpentane-1,5-dione. The structure of the former was determined by X-ray analysis. The reaction of the same compounds in DMSO in the presence of sodium hydroxide produced 4-(4-chlorophenyl)-*N*,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamide.

DOI: 10.1134/S1070428012070111

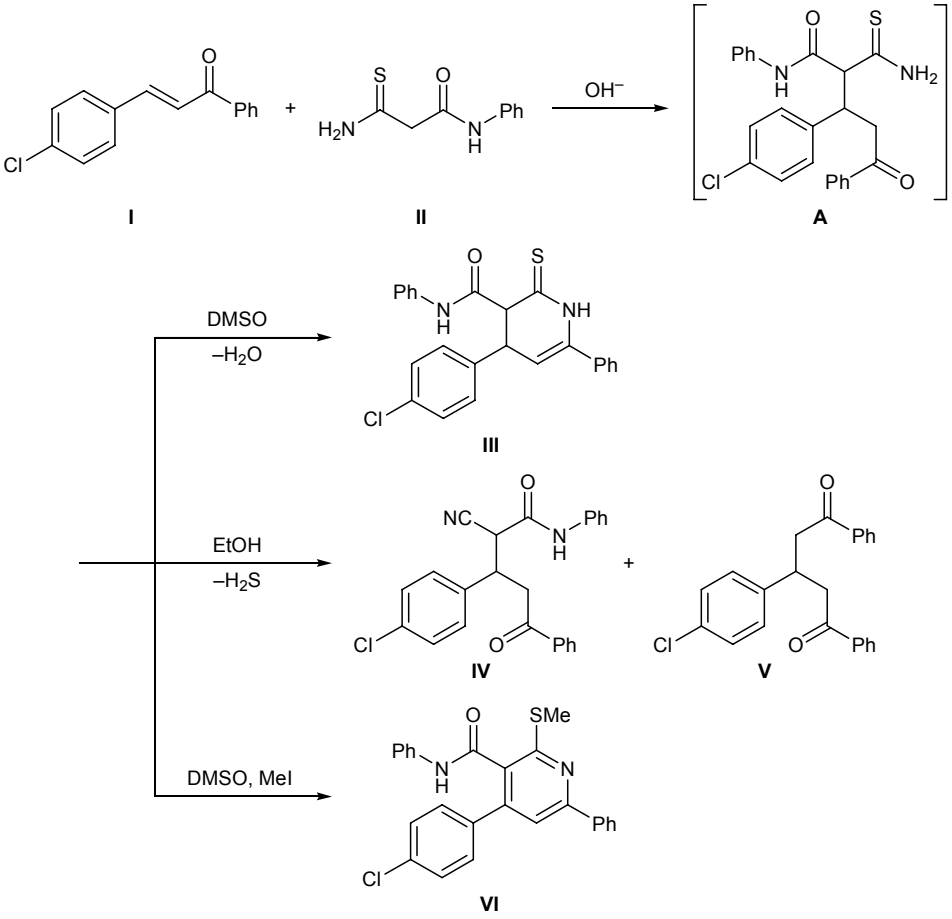
We previously reported on the synthesis of *N*-phenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamides from chalcones and 3-amino-*N*-phenyl-3-thioxopropanamide (**II**) [1]. In the present communication we describe the reaction of 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**I**) with compound **II**. The reaction in ethanol in the presence of sodium hydroxide did not produce the expected product, 4-(4-chlorophenyl)-*N*,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamide (**III**) [1], but afforded 3-(4-chlorophenyl)-2-cyano-5-oxo-*N*,5-diphenyl-pentanamide (**IV**) (presumably as a result of elimination of hydrogen sulfide from hypothetical primary Michael adduct **A**) and 3-(4-chlorophenyl)-1,5-diphenylpentane-1,5-dione (**V**) (Scheme 1). The latter is likely to be formed via exchange of methylene components, which is known for analogous reactions (see also [2]).

In the reaction of chalcone **I** with amide **II** in DMSO in the presence of sodium hydroxide at room temperature we isolated only expected 4-(4-chlorophenyl)-*N*,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamide (**III**). Addition of methyl iodide to the reaction mixture, other conditions being equal, resulted in the formation of substituted pyridine **VI**.

In the ^{1}H NMR spectrum of **IV** all proton signals were doubled. No appreciable change of the spectral pattern was observed on heating to 70°C (DMSO-d_6); only the amide proton signal was displaced upfield by 0.3 ppm. These findings indicated free rotation of the amide fragment. The structure of **IV** was determined by X-ray analysis (see figure).

The phenacyl group on C^1 occupies +*sc*-position with respect to the chlorophenyl ring plane [the torsion angle $C^2C^1C^{19}C^{24}$ is 40.9(3)°], despite repulsion between the methylene group and aromatic ring (shortened intramolecular contacts $H^{2A}\cdots C^{24}$ 2.86 and $H^{24}\cdots C^2$ 2.72 Å were detected, the sum of the corresponding van der Waals radii being 2.87 Å [3]). As a result, the $C^{19}C^1C^2$ bond angle at the tetrahedral C^2 carbon atom increases to 113.6(2)°. The benzoyl group has *antiperiplanar* orientation with respect to the C^{19}–C^1 bond [the trosion angle $C^{19}C^1C^2C^3$ is 156.8(2)°] and is turned in such a way that orientation of the carbonyl group is intermediate between *sp* and –*sc* with respect to the C^1–C^2 bond [the torsion angle $C^1C^2C^3O^1$ is 29.2(3)°]. Appreciable repulsion between the methylene group and benzoyl fragment [shortened intramolecular contacts $H^{2B}\cdots C^5$ 2.70 (2.87), $H^{2B}\cdots H^5$ 2.18 (2.34), $H^5\cdots C^2$ 2.67 (2.87) Å] makes the carbonyl noncoplanar to the aromatic ring [torsion angle $O^1C^3C^4C^9$ 10.0(4)°]. The phenylcarbamoyl(cyano)-methyl fragment is oriented almost orthogonally to the plane of the chlorophenyl ring [torsion angle $C^{10}C^1C^{19}C^{24}$ 82.1(3)°]. The cyano group appears in –*sc*-conformation with respect to the C^{19}–C^1 bond [torsion angle $C^{19}C^1C^{10}C^{11}$ 47.8(3)°]. The phenylcarbamoyl group occupies *ap*-position relative to the C^{19}–C^1 bond, and the carbamoyl group is almost orthogonal to the C^1–C^{10} bond [torsion angles $C^{19}C^1C^{10}C^{12}$ 170.9(2)° and $C^1C^{10}C^{12}O^2$ 75.7(3)°], so that shortened contacts $H^{2B}\cdots H^{10}$ 2.32 (2.34) and $H^{10}\cdots H(N^1)$ 2.11 (2.34) Å are observed. The N-phenyl ring is noncoplanar to the carbamoyl group [torsion angle $C^{12}N^1C^{13}C^{18}$

Scheme 1.



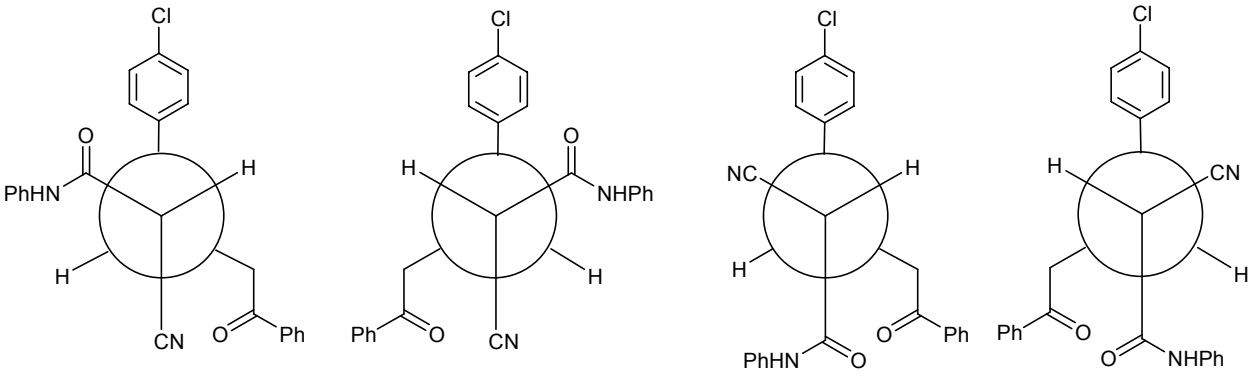
32.1(4)°], presumably due to repulsion between the carbonyl group and aromatic ring (shortened contact $H^{18}\cdots C^{12}$ 2.79 Å). The presence of fairly bulky substituents at one carbon atom is likely to be responsible for extension of the C^1–C^{10} bond to 1.565(3) Å against standard value 1.542 Å [4].

Molecules **IV** in crystal are linked through intermolecular hydrogen bonds N^1–$H(N^1)\cdots O^{2'}$ [(x, 0.5 – y, z – 0.5), H···O 2.04 Å, ∠NHO 165°] and C^{10}–$H^{10}\cdots O^{2'}$ [(x, 0.5 – y, z – 0.5), H···O 2.37 Å, ∠CHO 152°] to form infinite chains along the [001] crystallographic axis. Weak hydrogen bonds C–H···π [C^{20}–$H^{20}\cdots C^{23'}$ (x, 0.5 – y, z + 0.5), H···π 2.85 Å, ∠CHπ 132°] were also found inside the chains. Neighboring chains are linked through hydrogen bond C^{16}–$H^{16}\cdots Cl^{1'}$ (1 + x, 0.5 – y, 0.5 + z), H···Cl 2.80 Å, ∠CHCl 144°. Hydrogen bonding N–H···O also leads to extension of the O–C^{12} bond to 1.237(3) Å (against standard value 1.210 Å).

Compound **IV** was also synthesized previously by Girgis et al. [5] from chalcone **I** and cyanoacetanilide in the presence of morpholine. However, the authors did not note doubling of signals in the ^{1}H NMR spectrum of **IV** recorded in $CDCl_3$ displayed, whereas proton chemical shifts of homologous compound in DMSO-d_6 coincided with those of one set of signals found by us for compound **IV**. Taking into account that molecule **IV** possesses two neighboring asymmetric carbon atoms, it is reasonable to presume that two sets of signals belong to different diastereoisomers present in equal amounts. They may be represented as two enantiomer couples **IVa** and **IVb** in the most favorable conformations. Protons in **IVa** and **IVb** are characterized by different environments which exert different shielding effects. The X-ray analysis was performed for a single crystal of only one diastereoisomer **IVb**.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance II spectrometer at 400 MHz from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were



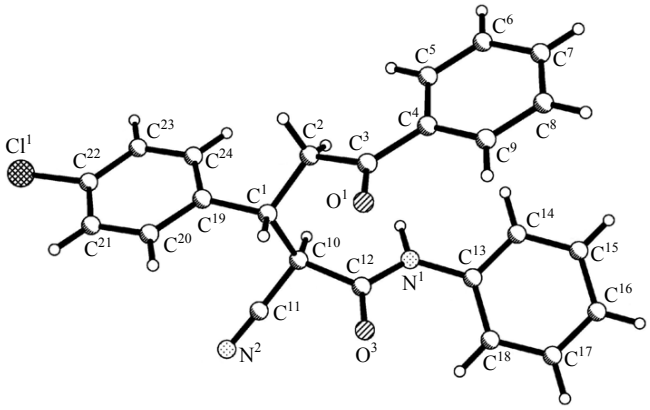
IVa IVb

obtained on a Hewlett–Packard 5890/5972 GC–MS system using an HP-5MS column; samples were injected in methylene chloride. The melting points were determined on a Kofler hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; spots were visualized by treatment with iodine vapor or by UV irradiation.

X-Ray duffraction data for compound **IV**. Monoclinic crystals; $C_{24}H_{19}ClN_2O_2$, M_r 402.86. Unit cell parameters (at –173°C): a = 15.761(1), b = 13.907(1), c = 9.001(1) Å; β = 92.28(1)°; V = 1971.4(3) Å^3; Z = 4; space group $P2_1/c$; d_{calc} = 1.357 g/cm^3; μ(MoK_α) = 0.217 mm^{-1}; F(000) = 840. The unit cell parameters and intensities of 11247 reflections (3462 independent reflections, R_{int} = 0.106) were measured on an Xcalibur-3 diffractometer (MoK_α irradiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 50°). The structure was solved by the direct method using SHELXTL software package [6]. The positions of hydrogen atoms were determined by difference synthesis of electron density and were refined according to the riding model (U_{iso} = 1.2U_{eq} for a non-hydrogen atom linked to a given hydrogen atom). The NH hydrogen atom involved in N–H···O hydrogen bond was refined in isotropic approximation. The structure was refined against F^2 by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms; wR_2 = 0.064 for 3400 reflections; R_1 = 0.045 for 1453 reflections with $F > 4\sigma(F)$; goodness of fit 0.667.

4-(4-Chlorophenyl)-*N*,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamide (III). Sodium hydroxide, 0.20 g (5 mmol), was dissolved in 20 ml of DMSO, 0.97 g (5 mmol) of 3-amino-*N*-phenyl-3-thioxopropanamide (**II**) and 1.21 g (5 mmol) of chalcone **I** were added, and the mixture was stirred for 4 h at room temperature, diluted with 20 ml of water, and kept for 16 h on cooling. The precipitate was filtered off, washed with ethanol, and recrystallized from glacial acetic acid. Yield 1.49 g (71%), mp 198–200°C. ^{1}H NMR spectrum, δ, ppm: 4.11–4.15 m (2H, 3-H, 4-H), 5.84 d (1H, 5-H, J = 3.8 Hz), 7.02 t (1H, H$_{arom}$, J = 7.4 Hz), 7.25–7.43 m (9H, H$_{arom}$), 7.51 d (2H, H$_{arom}$, J = 7.9 Hz), 7.55 d (2H, H$_{arom}$, J = 7.9 Hz), 10.15 s (1H, CONH), 11.93 s (1H, N^{1}H). Mass spectrum, m/z (I_{rel}, %): 383 (3) [M – Cl]$^+$, 264 (100), 230 (20), 104 (10), 77 (45). Found, %: C 68.77; H 4.49; N 6.88. $C_{24}H_{19}ClN_2OS$. Calculated, %: C 68.81; H 4.57; N 6.69. M 418.95.

3-(4-Chlorophenyl)-2-cyano-5-oxo-*N*,5-diphenylpentanamide (IV). Sodium hydroxide, 0.20 g (5 mmol), was dissolved in 20 ml of ethanol, 0.97 g (5 mmol) of compound **II** and 1.21 g (5 mmol) of



Structure of the molecule of 3-(4-chlorophenyl)-2-cyano-5-oxo-*N*,5-diphenylpentanamide (**IV**) according to the X-ray diffraction data. Principal bond lengths and bond angles: C^1–C^2 1.522(3), C^1–C^{10} 1.565(3), C^1–C^{19} 1.517(3), C^{10}–C^{12} 1.547(4), N^1–C^{12} 1.346(3), N^1–C^{13} 1.419(3), C^2–C^3 1.520(3), C^3–C^4 1.478(3), O^1–C^3 1.230(3) Å; C^{12}N^{1}C^{13} 126.3(3), C^{3}C^{2}C^1 114.0(2), C^{19}C^{1}C^2 113.6(2), C^{4}C^{3}C^2 120.9(2), C^{19}C^{1}C^{10} 109.3(2), C^{9}C^{4}C^3 119.4(2), C^{2}C^{1}C^{10} 109.8(2), C^{12}C^{10}C^1 112.5(2), O^{2}C^{12}N^1 124.8(3), O^{2}C^{12}C^{10} 120.6(2), N^{1}C^{12}C^{10} 114.5(2), C^{14}C^{13}N^1 118.4(3)°.

chalcone **I** were added, and the mixture was stirred at 50°C until it turned homogeneous, stirred for 2 h at room temperature, and kept for 16 h at 7°C. The precipitate was filtered off and recrystallized from methanol. Yield 0.93 g (46%), mp 161–163°C. ^{1}H NMR spectrum, δ, ppm: first set of signals: 3.45 d.d (1H, C**H**$_2$CH, J = 4.0, 17.6 Hz), 3.81 d.d (1H, C**H**$_2$CH, J = 9.8, 17.6 Hz), 4.04–4.13 m (1H, CH$_2$C**H**), 4.36 d (1H, CH$_2$CHC**H**, J = 8.5 Hz), 7.07–7.12 m (1H, H$_{arom}$), 7.28–7.51 m (10H, H$_{arom}$), 7.59–7.64 m (1H, H$_{arom}$), 7.93 d (2H, H$_{arom}$, J = 7.3 Hz), 10.40 s (1H, CONH); seond set of signals: 3.62 d.d (1H, C**H**$_2$CH, J = 4.0, 17.6 Hz), 3.87 d.d (1H, C**H**$_2$CH, J = 9.6, 17.6 Hz), 4.04–4.13 m (1H, CH$_2$C**H**), 4.25 d (1H, CH$_2$CHC**H**, J = 7.8 Hz), 7.07–7.12 m (1H, H$_{arom}$), 7.28–7.51 m (10H, H$_{arom}$), 7.59–7.64 m (1H, H$_{arom}$), 7.88 d (2H, H$_{arom}$, J = 7.3 Hz), 10.49 s (1H, CONH). Mass spectrum: m/z 401 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 71.61; H 4.79; N 7.19. $C_{24}H_{19}ClN_2O_2$. Calculated, %: C 71.55; H 4.75; N 6.95. M 402.88.

3-(4-Chlorophenyl)-1,5-diphenylpentane-1,5-dione (V). The filtrate obtained after separation of compound **IV** was diluted with an equal volume of water and was left to stand for 24 h on cooling. The precipitate was filtered off and recrystallized from methanol. Yield 0.2 g (11%), mp 104–106°C. ^{1}H NMR spectrum, δ, ppm: 3.47 d (4H, CH$_2$, J = 7.1 Hz), 3.86–3.93 m (1H, CH), 7.27 d (2H, H$_{arom}$, J = 8.3 Hz), 7.35 d (2H, H$_{arom}$, J = 8.3 Hz), 7.49 t (4H, H$_{arom}$, J = 7.6 Hz), 7.61 t (2H, H$_{arom}$, J = 7.3 Hz), 7.93 d (4H, H$_{arom}$, J = 7.9 Hz). Mass spectrum: m/z 361 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 76.26; H 5.06. $C_{23}H_{19}ClO_2$. Calculated, %: C 76.13; H 5.28. M 362.86.

4-(4-Chlorophenyl)-2-methylsulfanyl-*N*,6-diphenylpyridine-3-carboxamide (VI). Sodium hydroxide, 0.20 g (5 mmol), was dissolved in 20 ml of DMSO, 0.97 g (5 mmol) of 3-amino-*N*-phenyl-3-thioxopropanamide (**II**) and 1.21 g (5 mmol) of chalcone **I** were added, the mixture was stirred at room temperature until it turned homogeneous, 0.31 ml (5 mmol) of methyl iodide was added, and the mixture was left to stand for 24 h. The mixture was then diluted with an equal volume of water and was kept for 24 h on cooling. The precipitate was filtered off and recrystallized from glacial acetic acid. Yield 0.2 g (9%), mp 197–199°C. ^{1}H NMR spectrum, δ, ppm: 3.34 s (3H, CH$_3$), 7.11 t (1H, H$_{arom}$, J = 7.4 Hz), 7.29–7.63 m (11H, H$_{arom}$), 7.90 s (1H, 5-H), 8.13 d (2H, H$_{arom}$, J = 7.3 Hz), 10.70 s (1H, CONH). Mass spectrum: m/z 429 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 69.55; H 4.46; N 6.57. $C_{25}H_{19}ClN_2OS$. Calculated, %: C 69.68; H 4.44; N 6.50. M 430.96.

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