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Regioselective synthesis of 4-aryl-3,4-dihydro-1,3,5-triazino[2,1-*a*]-isoindol-2-ones

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Abstract The condensation of binucleophilic 3-amino-1-arylimino-1*H*-isoindoles with bifunctional 1-chlorobenzylisocyanates occurs regioselectively resulting in 3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-one derivatives. The structures of the synthesized compounds were unambiguously established by N*O*E experiments.

Keywords Heterocycles; Cyclizations; NMR Spectroscopy; 3-Amino-1-arylimino-1*H*-isoindoles; 4-Aryl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-ones.

Introduction

In the last few years compounds possessing a broad spectrum of biological activity have been found among derivatives of 1*H*-isoindole [1] and 1,3,5-triazine [2–4]. Therefore, the development of efficient synthesis approaches to the compounds bearing isoindole and triazine units in the same molecule became of considerable interest. A limited number of fused 1,3,5-triazinoisoindoles, that were described to date includes 4-amino-2,6-diimino-2,6-dihydro[1,3,5]-triazino[2,1-*a*]isoindole, which was synthesized by interaction of 3-amino-1-imino-1*H*-isoindole and *N*-cyanoguanidine and was used in the dye synthesis [5, 6]. A few (3*R*)-3,4-dihydro[1,3,5]triazino[2,1-*a*]-isoindol-6-ones are known to be prepared by reaction of 3-imino-1*H*-isoindol-1-one with formaldehyde and amines [7].

A simple approach to fused 1,3,5-triazines which is based on the reaction of 2-aminoazoles and 2-aminoazines with 1-chloroalkylisocyanates has been elaborated earlier [8]. Upon exploring the interaction of 1-aryl-1-chloro-2,2,2-trifluoroethylisocyanates and 3-amino-1-arylimino-1*H*-isoindoles as binucleophilic aminoazole system two isomeric [1,3,5]triazino-isoindolones **A** and **B** have been isolated (Fig. 1). It has been found that the regioselectivity of this reaction depends on both reaction temperature and nature of substituents in *Ar* and *Ar′* [9]. The approach mentioned above seems to be one of the most efficient ways to the fused [1,3,5]triazino[2,1-*a*]-isoindolones.

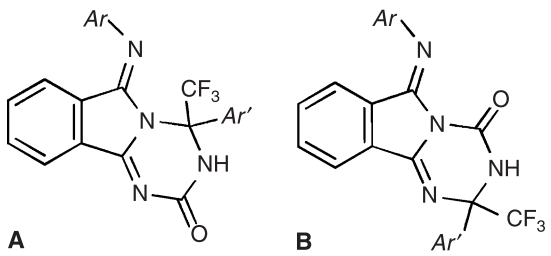

Fig. 1 Isomeric triazinoisoindolones obtained from 1-aryl-1-chloro-2,2,2-trifluoroethylisocyanates and 3-amino-1-arylimino-1*H*-isoindoles

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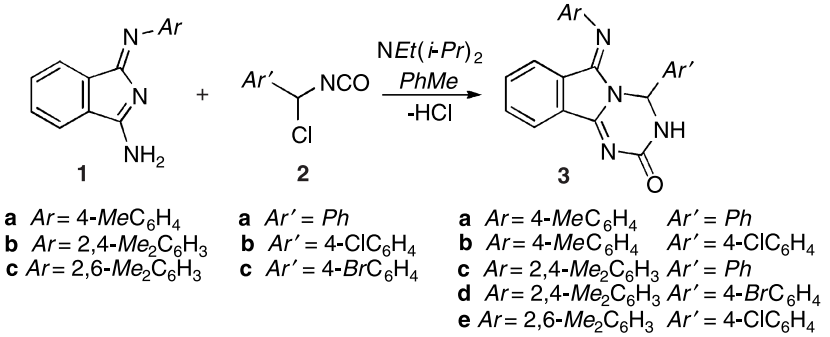


Scheme 1

It should be noticed that bifunctional nucleophiles are reported to react with 1-aryl-1-chloro-2,2,2-trifluoroethylisocyanates and 1-chlorobenzylisocyanates in different manner due to tautomeric equilibria between isocyanate and *N*-arylidenecarbamoyl forms [10–12]. Here we report on our further study of the interaction of 3-amino-1-arylimino-1*H*-isoindoles with 1-chlorobenzylisocyanates and 1-chloro-1-phenylbenzylisocyanate.

Results and discussion

Unexpectedly, it was found that the reaction of 3-amino-1-arylimino-1*H*-isoindoles **1a**–**1c** with 1-chlorobenzylisocyanates **2** in toluene in the presence of Et_3N did not take place, and only the starting 1*H*-isoindoles were isolated from the reaction mixture. It was reasonable to suggest that concurrent alkylation of Et_3N by **2** takes place instead of the desired carbamoylation of **1**. When the less nucleophilic *Hünig*'s base was used instead of Et_3N the reaction resulted in smooth formation of the desirable 3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-ones **3** of type **A** as the sole isolated products (Scheme 1). It should be noted that the reaction occurred regioselectively irrespective of substituents in *Ar* and *Ar′*, in contrast to the behavior of 1-aryl-1-chloro-2,2,2-trifluoroethylisocyanates [9].

To confirm the structure of the synthesized triazinoisoindoles **3** an N*O*E experiment was performed for the 2,6-dimethylphenylimino compound **3e**. This experiment reveals the presence of an N*O*E between pairs of signals at $\delta = 2.01$, 6.60 ppm and 1.30, 7.42 ppm (Fig. 2). For an alternative structure **B** these effects should not be observed, that unequivocally confirms the proposed structure of compounds **3**.

Notably, in the ^{1}H NMR spectrum of **3e** protons of methyl groups are observed as two sharp singlets at $\delta = 1.30$ and 2.01 ppm due to their non-equivalence,

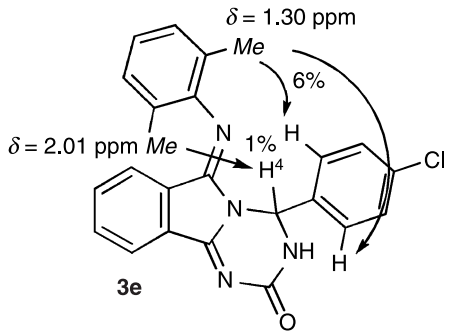
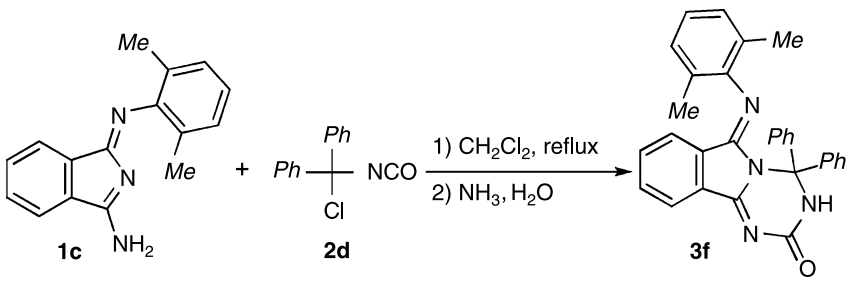


Fig. 2 N*O*E Experiment data for **3e**



Scheme 2

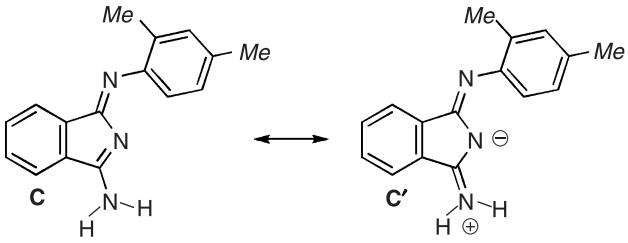
which is caused by restricted rotation about C–N bond of the 2,6-dimethylphenyl residue. The high field shift of one methyl group protons ($\delta = 0.6$ ppm) is caused by influence of Ar' ring currents.

Another similar bielectrophilic reagent, 1-chloro-1-phenylbenzylisocyanate (**2d**), was explored in the reaction with 3-amino-2,6-dimethylphenylimino-1*H*-isoindole (**1c**). As in the previous case, it was demonstrated that the reaction occurs regioselectively on heating the reagents without any base in CH_2Cl_2 and results in formation of one isomeric triazinoisoindole **3f** in high yield (86%) (Scheme 2).

The structure of **3f** was also confirmed by an N*O*E experiment. In contrast to **3e**, in the ^{1}H NMR spectrum of triazinoisoindole **3f** the protons of the methyl groups of the 2,6-dimethylphenyl moiety are observed as only one 6-proton singlet at $\delta = 1.55$ ppm. The N*O*E between these protons and 2,6- ($\delta = 7.59$ ppm) and 3,5-protons ($\delta = 7.37$ ppm) of the phenyl moieties of the triazine ring (12 and 5% enhancement) allows us to assign the structure of the synthesized compound to 6-(2,6-dimethylphenyl)imino-4,4-diphenyl-3,4-dihydro-[1,3,5]triazino[2,1-*a*]isoindol-2-one (**3f**) with type **A** skeleton.

To the contrary to starting isoindole derivatives **1** the synthesized 4-aryl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-ones **3** have the *Ar* moiety in an (*E*)-configuration at the exocyclic C=N bond. This conclusion comes from the ^{1}H NMR spectra of all studied compounds **3a**–**3f** where the doublet at $\delta =$ 6.40–6.70 ppm was observed assigned to 7-H of triazinoisoindole moiety. Its high field shift at $\delta = 2$ ppm in comparison with starting compounds **1a**–**1c** can be explained by the shielding influence of ring currents of the *Ar* moiety [13].

For one of the starting isoindoles **1b** we examined its structure in the solid state by X-ray diffraction. It was demonstrated that compound **1b** exists in the tautomeric form of 3-amino-1-arylimino-1*H*-isoindole with (*Z*)-configuration of 2,4-xylidine residue at the exocyclic C=N bond. The aryl substituent at the N(2) atom is oriented almost orthogonally relatively the isoindole bicycle (the C(14)–C(9)–N(2)–C(6) torsion angle is 87.4(3)°). This leads to disruption of conjugation between π-systems of these fragments manifested itself in elongation of the C(9)–N(2) bond (1.436(4) Å) which is close to the mean value for non-conjugated systems (1.43 Å) [14]. The analysis of the bond lengths within the N(1)=C(7)–N(3) fragment shows that the N(3)–



Scheme 3

C(7) single bond (1.314(3) Å) is considerably shorter than the C(7)=N(1) double bond (1.346(3) Å). For comparison, the average values of C(sp^2)–NH_2 single and N=C(sp^2) double bonds are 1.34 and 1.28 Å [14]. Therefore, it is possible to conclude a considerable contribution of the bipolar zwitter ionic resonance form **C′** into the total structure of the molecule **1b** similar to the related compound [15, 16] (Scheme 3). In the crystal phase the molecules **1b** form centrosymmetrical dimers due to the intermolecular hydrogen bond N(3)–H(3NA)···N(1)′ ($-x$, $1-y$, $1-z$) N···H′2.05 Å, N–H···N′ 173°.

Taking into account the equilibrium between amino-imino and diimino forms of the starting aryliminoisoindoles **1a**–**1c** [17] on one hand, and isocyanate and *N*-arylidenecarbamoyl forms of isocyanates **2a**–**2d** [10] on the other hand, two alternative routes of compounds **3a**–**3f** formation could be suggested (Scheme 4). According to literature data for the interaction of 1-chlorobensylisocyanates with C,N–, C,O–, and C,S– binucleophiles [11, 12, 18] the first most probable step of the reaction seems to be alkylation of isoindole at endocyclic nitrogen atom leading to intermediates **D**. They undergo further intramolecular carbamoylation at the exocyclic nitrogen atom of the imino group giving rise compounds **3a**–**3f**.

To conclude, the interaction of 3-amino-1-arylimino-1*H*-isoindoles and 1-chlorobenzylisocyanates occurs regioselectively and results in formation of 4-

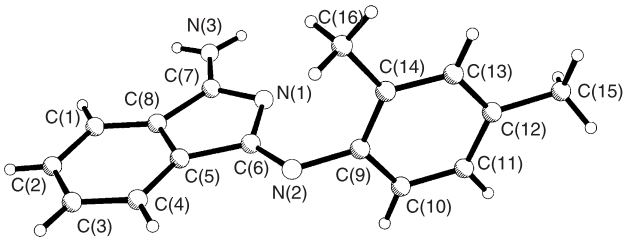
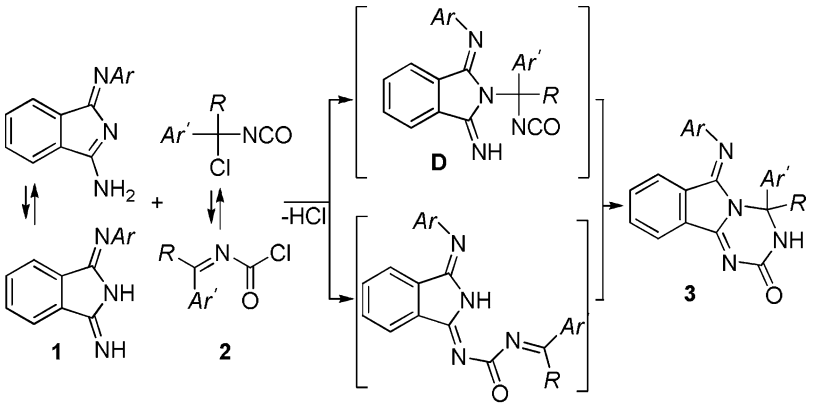


Fig. 3 X-Ray molecular structure of **1b** with the atom numbering used in crystallographic analysis



Scheme 4

aryl-3,4-dihydro-1,3,5-triazino[2,1-*a*]isoindol-2-ones **3** with high yields. The structure of the synthesized compounds **3** was established by N*O*E experiments.

Experimental

3-Amino-1-arylimino-1*H*-isoindoles **1a**–**1c** were prepared starting from phthalonitrile and corresponding amines [17]. The amines are commercially available; they were used without additional purification. Isocyanates **2** were prepared as it has been reported [18, 19]. Toluene and CH_2Cl_2 were dried over P_2O_5. Melting points were measured on a *Boetius* microscope hot plate apparatus. ^{1}H and ^{13}C NMR spectra were measured on Mercury (Varian) 400 spectrometer (400 MHz ^{1}H and 100 MHz ^{13}C) in *DMSO*-d_6 solutions with *TMS* as internal standard. Elemental analyses for C, H, and N were conducted using *Perkin-Elmer* C, H, and N Analyzer, their results were found to be in good agreement (±0.2%) with the calculated values. Mass spectra were recorded on Agilent 1100 LC/MSD instrument with chemical ionization (CI).

General procedure for the synthesis of 4-aryl-3,4-dihydro-1,3,5-triazino[2,1-a]isoindol-2-ones (**3a**–**3e**)

1-Chlorobenzylisocyanate (**2a**–**2c**) (0.2 mmol) dissolved in 5 cm^3 toluene was added dropwise to the mixture of appropriate 3-amino-1-arylimino-1*H*-isoindole (**1a**–**1c**) (0.2 mmol) and 0.43 cm^3 *N*-ethyl-*N*,*N*-diisopropylamine (0.25 mmol) in toluene. The resulting suspension was stirred for 2 h at ambient temperature and then the solid was filtered, thoroughly washed with *n*-hexane. The yellow powder of product was purified by recrystallization from 60% aqueous ethanol and dried on air.

rac-6-[(4-Methylphenyl)imino]-4-phenyl-3,4-dihydro[1,3,5]-triazino[2,1-a]isoindol-2(6H)-one (**3a**, $C_{23}H_{18}N_4O$)

From **1a** (0.47 g, 2 mmol) and **2a** (0.34 g, 2 mmol). Yield 0.59 g (81%); mp 207–208°C; ^{1}H NMR: $\delta = 2.34$ (s, CH_3), 6.49 (d, 1H, $J = 2$ Hz), 6.64 (d, 2H, $J = 7.6$ Hz), 6.75 (d, 1H, $J = 7.2$ Hz), 7.14 (d, 2H, $J = 7.6$ Hz), 7.38 (br, s, *Ph*), 7.49 (t, 1H, $J = 7.2$ Hz), 7.70 (t, 1H, $J = 7.2$ Hz), 8.00 (d, 1H, $J = 7.2$ Hz), 8.45 (d, 1H, $J = 2$ Hz, NH) ppm; ^{13}C NMR: $\delta = 20.65$ (CH_3), 65.74, 123.10, 123.75, 126.22, 127.21, 128.43, 128.62, 129.40, 130.19, 131.20, 131.56, 131.76, 136.17, 136.72, 149.82, 153.71, 156.19, 158.82 ppm; MS: $m/z = 467.2$ $[MH]^+$.

rac-4-(4-Chlorophenyl)-6-[(4-methylphenyl)imino]-3,4-dihydro[1,3,5]triazino[2,1-a]isoindol-2(6H)-one

(**3b**, $C_{23}H_{17}ClN_4O$)

From **1a** (0.47 g, 2 mmol) and **2b** (0.40 g, 2 mmol). Yield 0.61 g (76%); mp 246–247°C; ^{1}H NMR: $\delta = 2.35$ (s, CH_3), 6.48 (d, 1H, $J = 2$ Hz), 6.67 (d, 2H, $J = 7.2$ Hz), 6.74 (d, 1H, $J = 7.2$ Hz), 7.16 (d, 2H, $J = 7.2$ Hz), 7.34 (d, 2H, $J = 7.6$ Hz), 7.49 (t, 1H, $J = 7.2$ Hz), 7.55 (d, 2H, $J = 7.6$ Hz), 7.69 (t, 1H, $J = 7.2$ Hz), 7.99 (d, 1H, $J = 7.2$ Hz), 8.45 (d, $J = 2$ Hz, NH) ppm; ^{13}C NMR: $\delta = 20.80$ (CH_3), 65.21, 123.74, 124.55, 126.40, 127.51, 128.39, 128.92, 129.57, 130.01, 131.51, 131.69, 135.92, 136.21, 136.90, 150.02, 153.68, 156.39, 157.92 ppm; MS: $m/z = 401.1$ $[MH]^+$.

rac-6-[(2,4-Dimethylphenyl)imino]-4-phenyl-3,4-dihydro-[1,3,5]triazino[2,1-a]isoindol-2(6H)-one (**3c**, $C_{24}H_{20}N_4O$)

From **1b** (0.50 g, 2 mmol) and **2a** (0.34 g, 2 mmol). Yield 0.55 g (73%); mp 221–222°C; ^{1}H NMR: $\delta = 1.56$ (s, CH_3), 2.29 (s, CH_3), 6.49 (d, 1H, $J = 2.2$ Hz), 6.57 (d, 1H, $J = 7.6$ Hz), 6.64 (d, 1H, $J = 7.6$ Hz), 6.95 (d, 1H, $J = 7.6$ Hz), 6.98 (s, 1H), 7.36 (br, s, *Ph*), 7.49 (t, 1H, $J = 7.6$ Hz), 7.70 (t, 1H, $J = 7.6$ Hz), 8.02 (d, 1H, $J = 7.6$ Hz), 8.45 (d, $J = 2.2$ Hz, NH) ppm; ^{13}C NMR: $\delta = 17.49$ (CH_3), 20.24 (CH_3), 65.31, 123.39, 125.97, 126.37, 127.09, 127.43, 128.41, 128.78, 129.13, 130.75, 131.31, 131.59, 132.01, 132.29, 136.53, 137.08, 152.22, 152.35, 157.17, 158.82 ppm; MS: $m/z = 381.2$ $[MH]^+$.

rac-4-(4-Bromophenyl)-6-[(2,4-dimethylphenyl)imino]-3,4-dihydro[1,3,5]triazino[2,1-a]isoindol-2(6H)-one

(**3d**, $C_{24}H_{19}BrN_4O$)

From **1b** (0.50 g, 2 mmol) and **2c** (0.49 g, 2 mmol). Yield 0.72 g (78%); mp 210–211°C; ^{1}H NMR: $\delta = 1.62$ (s, CH_3), 2.30 (s, CH_3), 6.50 (d, 1H, $J = 1.8$ Hz), 6.57 (d, 1H, $J = 7.2$ Hz), 6.64 (d, 1H, $J = 7.2$ Hz), 6.95 (d, 1H, $J = 7.2$ Hz), 7.00 (s, 1H), 7.34 (d, 2H, $J = 7.6$ Hz), 7.49 (t, 1H, $J =$

7.2 Hz), 7.52 (d, 2H, $J = 7.6$ Hz), 7.70 (t, 1H, $J = 7.2$ Hz), 8.02 (d, 1H, $J = 7.2$ Hz), 8.45 (d, $J = 1.8$ Hz, NH) ppm; ^{13}C NMR: $\delta = 17.81$ (CH_3), 20.32 (CH_3), 65.28, 123.84, 125.13, 125.47, 126.52, 127.54, 128.47, 128.91, 129.15, 130.32, 130.75, 131.39, 131.63, 132.37, 136.39, 137.17, 152.31, 152.43, 156.39, 159.15 ppm; MS: $m/z = 459.0$ $[MH]^+$.

rac-4-(4-Chlorophenyl)-6-[(2,6-dimethylphenyl)imino]-3,4-dihydro[1,3,5]triazino[2,1-a]isoindol-2(6H)-one (**3e**, $C_{24}H_{19}ClN_4O$)

From **1c** (0.50 g, 2 mmol) and **2b** (0.40 g, 2 mmol). Yield 0.68 g (82%); mp 240–241°C; ^{1}H NMR: $\delta = 1.30$ (s, CH_3), 2.01 (s, CH_3), 6.44 (d, 1H, $J = 7.6$ Hz), 6.60 (d, 1H, $J = 2$ Hz), 6.95–7.01 (m, 2H), 7.05 (d, 1H, $J = 7.2$ Hz), 7.40 (d, 2H, $J = 8$ Hz), 7.42 (d, 2H, $J = 8$ Hz), 7.48 (t, 1H, $J = 7.2$ Hz), 7.72 (t, 1H, $J = 7.2$ Hz), 8.02 (d, 1H, $J = 7.6$ Hz), 8.48 (d, $J = 2$ Hz, NH) ppm; ^{13}C NMR: $\delta = 17.23$ (CH_3), 18.04 (CH_3), 65.98, 123.97, 124.05, 124.07, 126.20, 126.41, 128.49, 128.80, 128.86, 129.11, 129.76, 131.58, 133.07, 133.39, 133.76, 134.74, 140.21, 145.37, 148.37, 155.10, 159.98 ppm; MS: $m/z = 415.0$ $[MH]^+$.

6-[(2,6-Dimethylphenyl)imino]-4,4-diphenyl-3,4-dihydro-[1,3,5]triazino[2,1-a]isoindol-2(6H)-one (**3f**, $C_{30}H_{24}N_4O$)

The mixture of 0.50 g **1c** (2 mmol) and 0.49 g **2d** (2 mmol) in 10 cm^3 CH_2Cl_2 was refluxed for 3 h. After cooling the formed solid was filtered and thoroughly washed with aqueous ammonia solution. The yellow powder was recrystallized from 60% aqueous ethanol and dried on air. Yield 0.79 g (86%); mp 235–236°C; ^{1}H NMR: $\delta = 1.55$ (s, $2 \times CH_3$), 6.35 (d, 1H, $J = 7.6$ Hz), 6.86–6.93 (m, 3H), 7.37 (br, s, 6H, *m-*, and *p-Ph*), 7.44 (t, 1H, $J = 7.6$ Hz), 7.59 (d, 4H, $J = 7.2$ Hz, *o-Ph*), 7.71 (t, 1H, $J = 7.6$ Hz), 8.04 (d, 1H, $J = 7.6$ Hz), 8.80 (s, NH) ppm; ^{13}C NMR: $\delta = 18.04$ ($2 \times CH_3$), 78.43, 123.98, 124.01, 125.83, 128.19, 128.50, 128.54, 128.82, 132.60, 133.46, 134.90, 140.84, 145.49, 149.11, 154.95, 159.85 ppm; MS: $m/z = 457.2$ $[MH]^+$.

X-Ray crystal structure determination

The crystals of $C_{16}H_{15}N_3$ are monoclinic. At 293 K $a =$ 9.073(3), $b = 11.193(4)$, $c = 13.631(4)$ Å, $\beta = 130.71(3)°$, $V = 1344.8(8)$ Å^3, $M_r = 249.3$, $Z = 4$, *space group* $P2_1/n$, $d_{calc} = 1.231$ g/cm^3, $\mu(MoK_\alpha) = 0.08$ mm^{-1}, $F(000) = 528$. Intensity of 2473 reflections (2319 independent, $R_{int} = 0.04$) was measured on a *Siemens* P3/PC diffractometer with graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å) 2θ-scans, $2\theta_{max} = 50°$. The structure was solved by direct method and refined by full-matrix least-squares techniques on all F^2 data using the SHELX-97 package [20]. All non-hydrogen atoms were refined with anisotropic thermal parameters. Positions of hydrogen atoms were located from difference maps of the electron density and included in the refinement as a riding-model approximation with $U_{iso} = nU_{eq}$ of the carrier atom ($n = 1.5$ for methyl and $n = 1.2$ for the remaining hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 2319 reflections was converged to $wR_2 = 0.204$ ($R_1 = 0.069$ for 1442 reflections with $F > 4\sigma(F)$, $S = 1.008$). Atomic coordinates and crystallographic parameters have been deposited to the Cambridge Crystallographic Data Centre (CCDC 658687). These data can be obtained from the CCDC *via* www.ccdc.cam.ac.uk/data_request/cif.

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