Monatshefte für Chemie 133, 1165–1175 (2002)
DOI 10.1007/s00706-002-0470-2

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

The Behaviour of Nitrilimines Towards Ethyl Isocyanoacetate

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Received March 5, 2002; accepted March 19, 2002
Published online July 15, 2002

Summary. Interactions between nitrilimines and the title isocyanide afford, through two competing pathways, 2,3-dihydro-1,2,4-triazines and 1,3-oxazoles. *In situ* cycloaddition of unreacted nitrilimine with the triazines gives rise to a third class of products, the bicyclic 1,5,6,8a-tetrahydro[1,2,4]triazolo[4,3-*d*][1,2,4]triazines. Acceptor-free representatives of the latter are prone to triazine ring cleavage, yielding triazolyl ketone hydrazones which served as a structure proof. Substituent effects became apparent upon employment of *N*-(4-methoxyphenyl)- and *N*-(4-nitrophenyl)nitrilimines: whereas the former afforded a quinoxaline as the fourth product, triazine formation was totally blocked with the latter, the corresponding oxazole being the sole product. The constitution of acceptor-substituted bicyclic compounds (which failed to give the structure-revealing hydrazones) was established by an X-ray diffraction analysis.

Keywords. Cyclizations; Heterocycles; Isocyanides; Nitrilimines; X-Ray structure determination.

Introduction

Reactions between nitrilimines and free isocyanides afford, compared to closely related interactions [1, 2], an unrivalled diversity of products [3–5] (Scheme 1). Depending on the substituents of **1**/**2** and **3**, six different classes of compounds (**4**–**6**, **8**–**10**) have been obtained until now, excluding **11** [5a] and the respective dequaternization products of **4** and **5** which occurred in the case of $Z = t$-Bu [5b]. We expected that employment of an isocyanide **3** bearing a strongly activated α-methylene group would give rise to further product classes.

Results and Discussion

When equimolar amounts of **1** ($Q = Ar = \mathrm{Ph}$) and the title isocyanide were heated with an excess of triethylamine in boiling benzene (*i.e.* under the conditions

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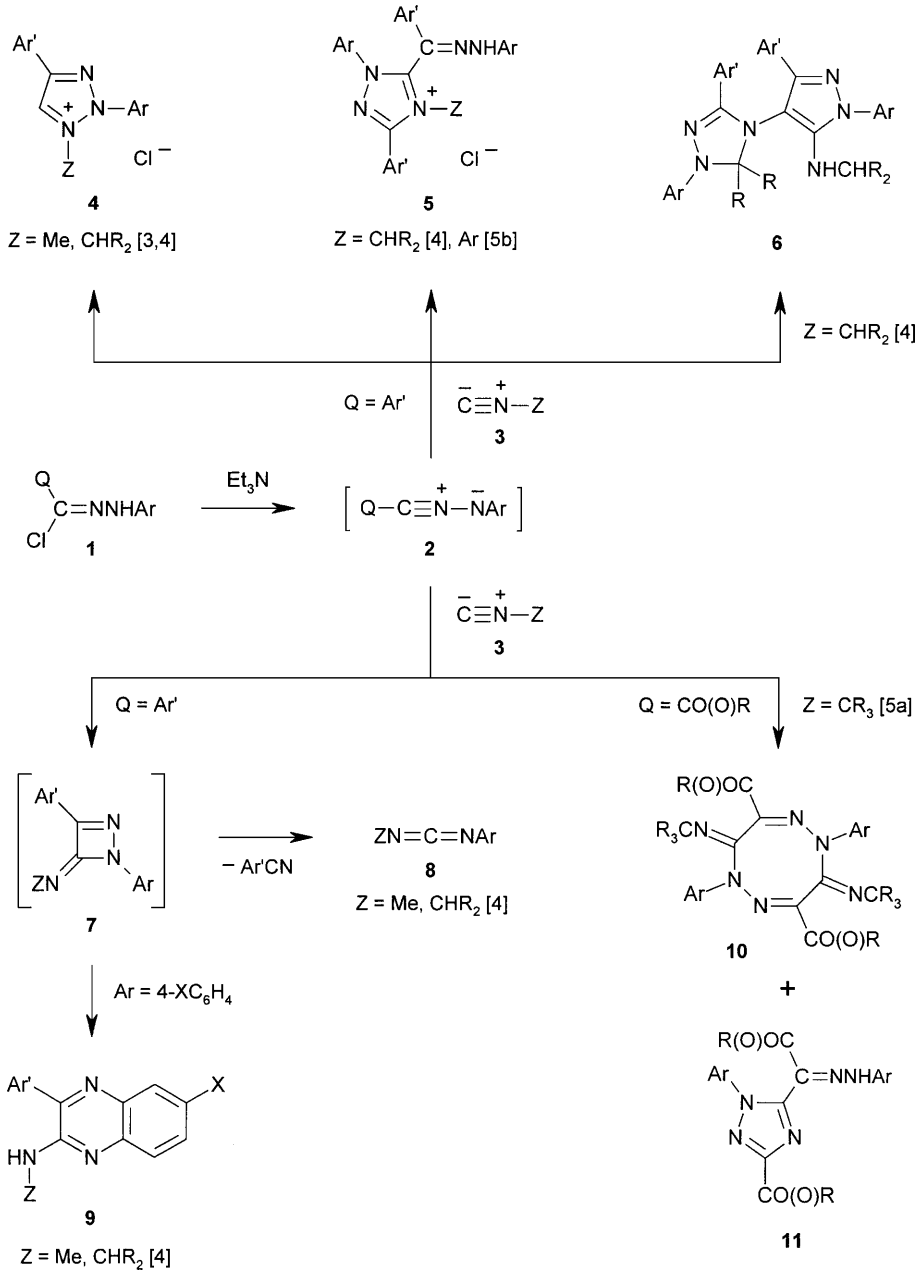
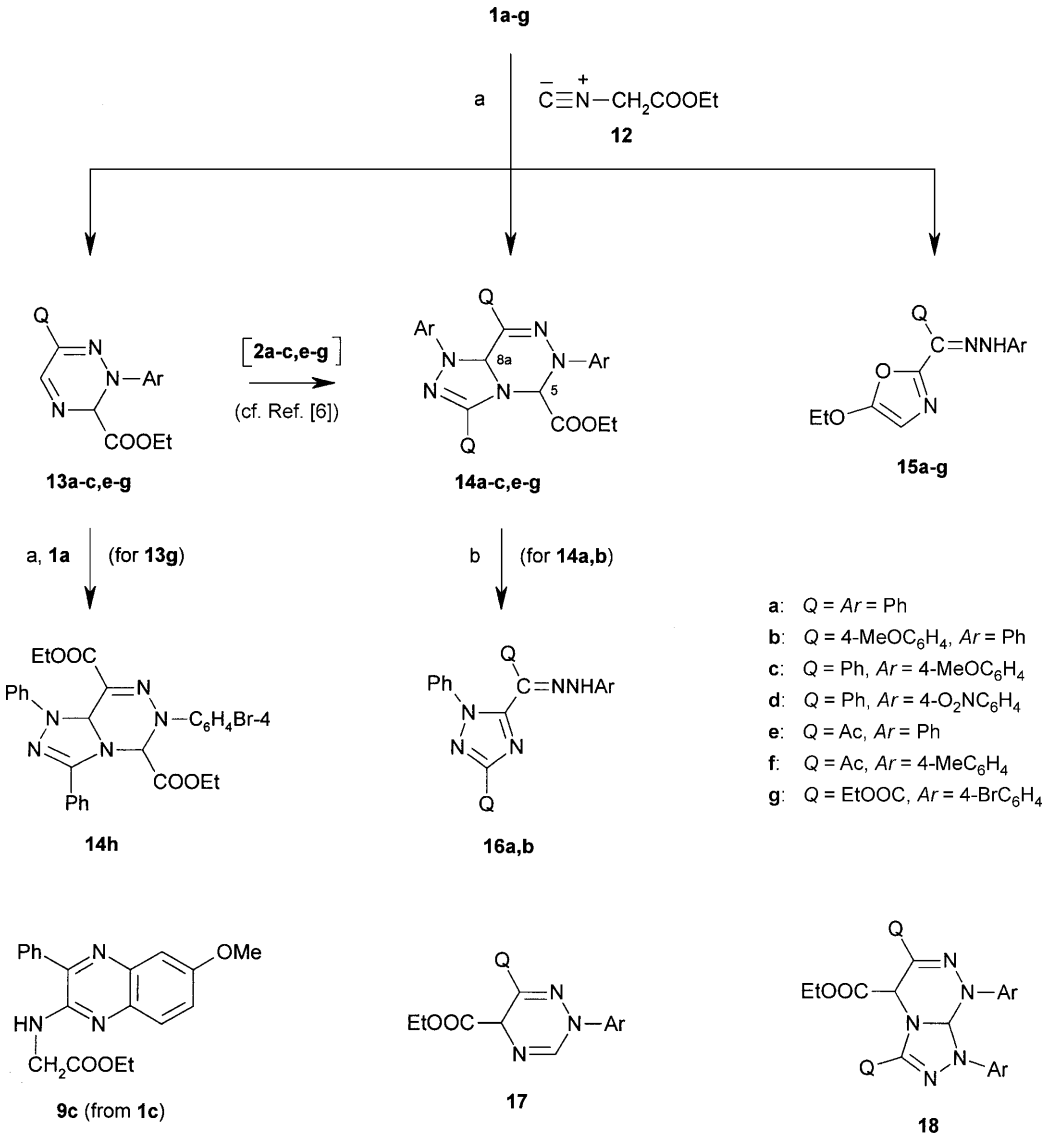


Scheme 1

applied previously [4, 5]), a mixture of products was obtained that did not show any of the types obtained before (Scheme 1). Instead, we isolated three new components provisionally denoted as **A**, **B**, and **C**. Mass spectra revealed that **A** and **C** each contained one molecule of nitrilimine and isocyanide, whereas with **B** the proportion was 2:1. According to NMR data (one-proton signals at 6.49 and 8.31 ppm; carbon doublets at 69.8 and 150.2 ppm), component **A** could represent a dihydrotriazine such as **13a** or **17** ($Q = Ar =$ Ph), with an enhanced likelihood for



a: Et_3N (3-4 equivs.), benzene, reflux, 1 h; b: chloroform, daylight, reflux, 12 h

Scheme 2

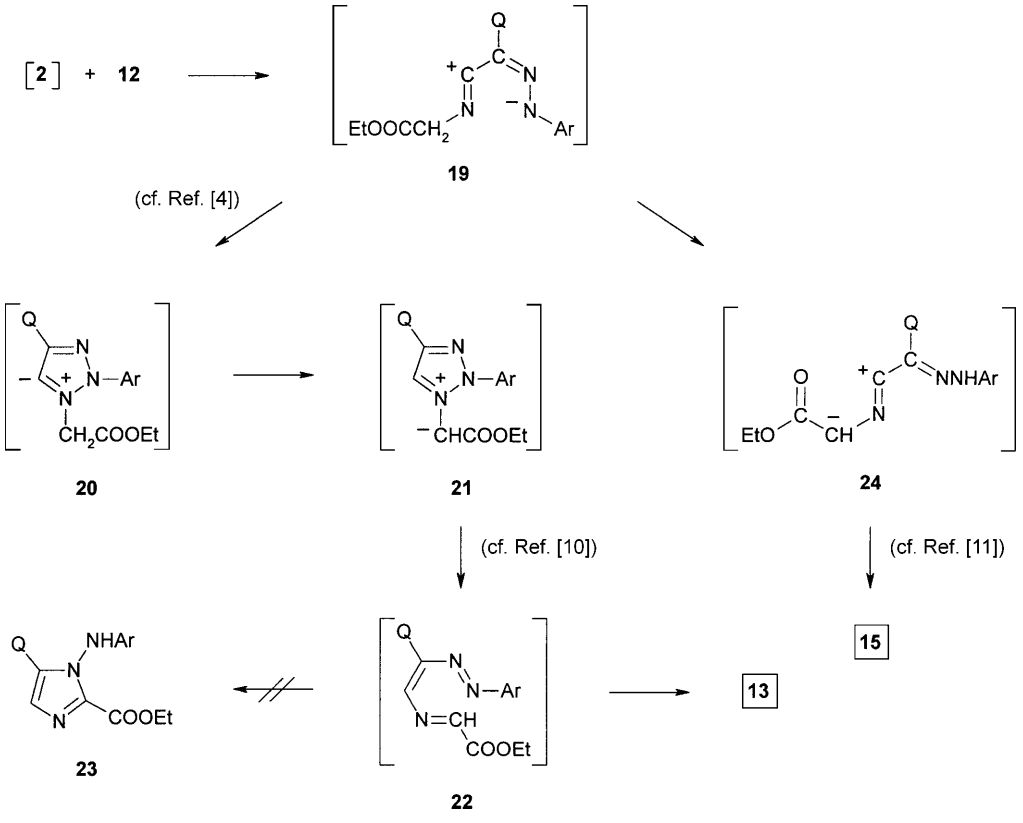
the first of these constitutions (Scheme 2). Treatment of this material with additional nitrilimine **2a** gave a derivative that was identical to **B** and therefore assigned structure **14a** (cf. Ref. [6]) or **18** ($Q = Ar = Ph$). Whereas spectroscopic differentiation between these isomers seemed ambiguous, the key evidence came from chemical transformation: we observed that, on keeping the $CDCl_3$ solution for several hours, a one-proton singlet developed at 10.59 ppm which obviously originated from a phenylhydrazono group. We thereupon heated a fresh sample of **B** in chloroform for 12 h and indeed obtained in high yield the known triazolyl ketone hydrazone **16a** [7] (the CHCOOEt fragment of the triazine half-ring eluded

isolation). This finding clearly pointed to structure **14a** (and thereby to **13a**). The remaining 1:1 product (**C**) did not show an ester group; it was easily recognized as **15a** by means of the carbon doublet at 99.8 ppm which is typical of 4-unsubstituted 5-alkoxy-1,3-oxazoles [8].

In order to discover to what extent these reactions are susceptible to nitrilimine substituents, we studied the behaviour of the hydrazonoyl chlorides **1b–g**. It was found that replacing the *C*-phenyl group of **1a** with a donor or acceptor group had no major effect (examples **1b**,**e–g**); using the *N*-(4-methoxyphenyl) and *N*-(4-nitrophenyl) representatives **1c** and **1d**, however, resulted in conspicuous deviations. Thus, employment of **1c** led to a fourth component: the quinoxaline **9c** (formed through the respective cycloadduct **7**). This derivative, in contrast to the congeners of Scheme 1 where *X* equals H or Me [4], was obtained in substantial amounts. In fact, an earlier study of the behaviour of **2c** towards cyclohexyl isocyanide had demonstrated that quinoxaline formation is generally favoured by this particular nitrilimine. Thus, a derivative **9** ($X = \mathrm{MeO}$, $Z = c\text{-}C_6H_{11}$, $Ar' = \mathrm{Ph}$) had been isolated in 25% yield (along with 10% of the appropriate salt **5** and 6% of the pyrazole **6**) [5b], whereas from **2a** there had been a mere 2% of **9** (besides 34% of **5** and 29% of **6**) [4]. A carbodiimide of type **8**, however, which in addition to the 6-methoxyquinoxaline **9** had then been obtained in more than 40% yield (**8**: $Z = c\text{-}C_6H_{11}$, $Ar = 4\text{-}MeOC_6H_4$) [5b], was not found in the present case ($Z = CH_2COOEt$, $Ar = 4\text{-}MeOC_6H_4$), evidently because of instability (cf. Ref. [9]). In complete contrast to the foregoing experiment, the reaction with the acceptor-substituted analogue **1d** failed to give the triazine **13d** (and, consequently, the cycloadduct **14d**); the only compound detectable was the oxazole **15d** which could be isolated in almost 90% yield. This finding is rationalized as follows (Scheme 3).

We assume that the products **13** and **15** arise from a joint precursor, the linear adduct **19**. To form the triazine (**13**) as a final product, this intermediate cyclizes to the triazolium ylide **20** (cf. Ref. [4]); the latter is not protonated to yield the respective salt **4** (by the triethylammonium chloride present in the reaction mixture) but, as a consequence of the acidic side chain, tautomerizes to the triazolium *N*-methanide **21**. Species of this kind have been reported to ring-open rapidly to give a triazahexatriene (akin to **22**), which in turn reverts to the triazine in question (and to a 1-aminoimidazole corresponding to the non-observed material **23**) [10]. We sought to prove the sequence **21** → **22** → **13** using authentic **21** ($Q = Ar = \mathrm{Ph}$), but efforts to prepare the necessary salt **4** ($Z = CH_2COOEt$) under the conditions suitable for this class of compounds [3] remained unrewarded. To afford the oxazole (**15**), the intermediate **19** undergoes deprotonation to give the conjugated nitrile ylide **24** which then cyclizes in the usual way (cf. Ref. [11]). The first of these steps competes with the kinetically controlled ring closure to **20** so as to impede triazine formation if the *N–Ar* moiety of **19** is insufficiently nucleophilic. This is apparently the case with $Ar = 4\text{-}O_2NC_6H_4$.

Regarding an alternate pathway to **13**, one might consider an attack of the carbanion of **12** at the terminal N atom of the nitrilimine (allenic structure); however, this mode appears less plausible since involvement of anionized **12** should preferentially give the isomeric triazine **17**, in particular with the nitrilimine **2d** whose allenic structure is disfavoured (cf. Ref. [12]).



Scheme 3

As mentioned above, structural proof for the triazolotriazine **14a** was provided by its conversion to the triazolyl ketone hydrazone **16a**, simply achieved through heating the bicyclic compound in chloroform. Hence, we were tempted to check the remaining derivatives for this noteworthy behaviour and treated **14b**,**c**,**e**–**g** accordingly. But whereas **14b** gave the expected hydrazone **16b** very readily and also **14c** ring-opened easily, the acceptor-substituted derivatives **14e**–**g** could not be induced to react in this manner and decomposed under more stringent conditions. Since the failure to give **16e**–**g** (*i.e.* the former products **11** [5a]) aroused our suspicion that these cycloadducts might belong to the type **18**, we performed an X-ray analysis of the representative **14e** (see below). This, however, established the originally proposed constitution **14e**. The inertness of **14e**–**g** towards triazine ring opening obviously originates in the presence of an acceptor group at C(8): we found that the model compound **14h** (prepared from the triazine **13g** and **1a**) also failed to yield a hydrazone of type **16**.

Crystal structure of **14e** *(Fig. 1)*

The dimensions of the ring system are rather similar to those measured for a congener, *i.e.* 1-(4-nitrophenyl)-3,6,8,8a-tetraphenyl-1,5,6,8a-tetrahydro[1,2,4]-triazolo[4,3-*d*][1,2,4]triazine [6]; the angle N(4)–C(8a)–N(1) is narrow, whereas

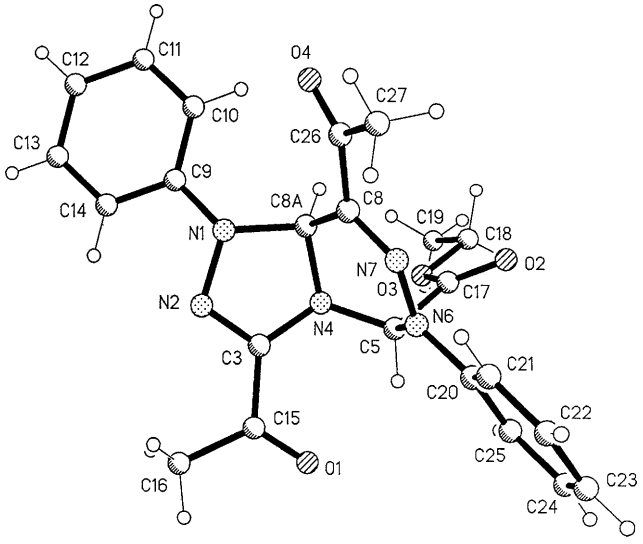


Fig. 1. X-Ray crystal structure of **14e**

N(7)–C(8)–C(8a) is wide (100.21(7) and 124.65(8)°, respectively), and the bond C(8)–C(8a) (1.5295(14) Å) is long for a $C(sp^2)$–$C(sp^3)$ bond. The bridgehead angles are 122.00(8)° (C(3)–N(4)–C(5)) and 112.11(8)° (C(8)–C(8a)–N(1)), with torsion angles of 99.65(8)° (C(3)–N(4)–C(8a)–C(8)) and −155.08(8)° (C(5)–N(4)–C(8a)–N(1)). The crystal packing involves a number of short C–H···O contacts that could be classified as hydrogen bonds, notably C(8a)–H(8a)···O(4) and C(23)–H(23)···O(2) with H···O distances and C–H···O angles of 2.36, 2.48 Å and 147, 146°, respectively.

Experimental

M.p.: Kofler microscope; elemental analysis: CHN Analyzer 1106 Carlo Erba (the data were in accordance with the calculated values); IR: PU-9800 FTIR; NMR: Bruker DRX-400 (400.1 and 100.6 MHz for ^1H and ^{13}C); UV/Vis: Philips PU-8730; fluorescence: Kontron SFM 25; MS (EI, 70 eV): Finnigan MAT 90.

Hydrazonoyl chlorides **1a–d** [13], **1e**, **f** [14], and **1g** [15] and the isocyanide **12** [16] were prepared according to (or by adopting) literature procedures.

Reaction of the hydrazonoyl chlorides **1a–g** *with ethyl isocyanoacetate* (**12**); *general procedure*

To a stirred solution of the appropriate hydrazonoyl chloride **1** (5 mmol) and 0.57 g **12** (5 mmol) in 25 cm^3 of anhydrous benzene, 2.5 cm^3 of triethylamine (*ca.* 18 mmol) were added. The mixture was heated under reflux for 1 h, cooled to room temperature, and diluted with 25 cm^3 of light petroleum followed by work-up as detailed below.

a) Runs with **1a–c**: After standing for 2–3 h, the triethylammonium chloride was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (CH_2Cl_2 as eluent) to yield, successively, the 1,3-oxazoles **15a–c**, the tetrahydro[1,2,4]triazolo[4,3-*d*]-[1,2,4]triazines **14a–c**, the dihydro-1,2,4-triazines **13a–c** and, in the case of **1c**, the quinoxaline **9c** which was accompanied by some **13c**.

b) Runs with **1e–g**: The residue was chromatographed as above to afford, successively, the derivatives **14e–g**, **15e–g** (inverse order!), and **13e–g**; this procedure was followed by fractional crystallization in order to achieve complete separation of **14** from **15**.
c) Run with **1d**: After standing for 2–3 h, the solid was filtered off and washed with light petroleum and H_2O to give the derivative **15d**; the organic filtrate was concentrated to dryness, and the residue was chromatographed as above to yield a second crop of **15d**.

Recrystallization of the products was effected as indicated below. The intermediary dihydro-1,2,4-triazines **13b**,**c**,**e–g** (*ca.* 0.1–0.2 g; coloured oils) could not be obtained analytically pure; they were identified by the following pairs of one-proton ^{1}H NMR signals ($CDCl_3$) which match those of **13a** (see below): $\delta = 6.47$ (s)/8.27 (s) ppm (**13b**), 6.26 (s)/8.26 (d, $J = 0.7$ Hz) ppm (**13c**), 6.42 (d, $J = 1.1$ Hz)/8.39 (d, $J = 1.1$ Hz) ppm (**13e**), 6.39 (s)/8.38 (d, $J = 0.9$ Hz) ppm (**13f**), 6.39 (d, $J = 0.9$ Hz)/8.32 (d, $J = 0.9$ Hz) ppm (**13g**; further signals of this compound: 1.28 (t, $J = 7$ Hz, 3H), 1.39 (t, $J = 7$ Hz, 3H), 4.25 (q, $J = 7$ Hz, 2H), 4.38 (q, $J = 7$ Hz, 2H), 7.33/7.52 (AA′BB′, $N = 9$ Hz, 4H) ppm).

Ethyl ((6-methoxy-3-phenylquinoxalin-2-yl)amino)acetate (**9c**; $C_{19}H_{19}N_3O_3$)

Yield: 0.31 g (18%); m.p.: 125–127°C (EtOH); pale yellow prisms; IR (KBr): $\nu_{max} = 3336$, 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (t, $J = 7$ Hz, 3H), 3.90 (s, 3H), 4.22 (q, $J = 7$ Hz, 2H), 4.31 (d, $J = 5.3$ Hz, 2H), 5.56 (t, $J = 5.3$ Hz, 1H), 7.26 (dd, $J = 2.8$ and 9 Hz, 1H), 7.33 (d, $J = 2.8$ Hz, 1H), 7.48–7.57 (m, 3H), 7.65 (d, $J = 9$ Hz, 1H), 7.77–7.79 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.2$ (q), 43.3 (t), 55.6 (q), 61.3 (t), 107.7 (d), 121.7 (d), 127.0 (d), 128.4 (d, 2C), 129.3 (d, 2C), 129.6 (d), 136.5 (s), 136.7 (s), 138.2 (s), 146.2 (s), 148.3 (s), 157.2 (s), 171.0 (s) ppm; UV/Vis (EtOH): λ_{max} (logε) = 261 (4.14), 392 (3.81) nm; fluorescence (EtOH): $\lambda_{max} = 461$ nm (excitation wavelength: 365 nm); MS: m/z (%) = 337 (M^+), 264 (100).

Ethyl 2,6-diphenyl-2,3-dihydro-1,2,4-triazine-3-carboxylate (**13a**; $C_{18}H_{17}N_3O_2$)

Yield: 0.36 g (23%); sticky oil; IR (neat): $\nu_{max} = 1741$ cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.24$ (t, $J = 7$ Hz, 3H), 4.21 (q, $J = 7$ Hz, 2H), 6.49 (s, 1H), 7.13–7.17 (m, 1H), 7.34–7.44 (m, 7H), 7.78–7.80 (m, 2H), 8.31 (d, $J = 0.7$ Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (q), 62.1 (t), 69.8 (d), 117.2 (d, 2C), 123.9 (d), 124.4 (d, 2C), 128.6 (d), 128.8 (d, 2C), 129.1 (d, 2C), 133.7 (s), 139.0 (s), 143.9 (s), 150.2 (d), 167.7 (s) ppm; MS: m/z (%) = 307 (M^+, 10), 234 (100).

Ethyl 1,3,6,8-tetraphenyl-1,5,6,8a-tetrahydro[1,2,4]triazolo[4,3-d][1,2,4]triazine-5-carboxylate (**14a**; $C_{31}H_{27}N_5O_2$)

Yield: 0.64 g (51%); m.p.: 110–113°C (MeOH); prisms; IR (KBr): $\nu_{max} = 1733$ cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.16$ (t, $J = 7$ Hz, 3H), 4.12–4.27 (m, 2H), 5.85 (s, 1H), 6.37 (s, 1H), 6.86–6.98 (m, 6H), 7.12–7.18 (m, 4H), 7.33–7.37 (m, 3H), 7.44–7.48 (m, 3H), 7.63–7.68 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (q), 62.3 (t), 67.1 (d), 73.4 (d), 115.2 (d, 2C), 116.8 (d, 2C), 121.9 (d), 122.0 (d), 126.4 (s), 127.8 (d, 2C), 128.0 (d, 2C), 128.3 (d, 2C), 128.7 (d, 2C), 128.8 (d), 128.9 (d, 2C), 129.1 (d, 2C), 130.7 (d), 136.1 (s), 144.9 (s), 148.1 (s), 155.2 (s), 166.6 (s) ppm; MS: m/z (%) = 501 (M^+, 2), 222 (100).

Ethyl 3,8-bis-(4-methoxyphenyl)-1,6-diphenyl-1,5,6,8a-tetrahydro[1,2,4]triazolo[4,3-d][1,2,4]triazine-5-carboxylate (**14b**; $C_{33}H_{31}N_5O_4$)

Yield: 0.61 g (43%); m.p.: 167–170°C (MeOH); needles; IR (KBr): $\nu_{max} = 1736$ cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.17$ (t, $J = 7$ Hz, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 4.12–4.27 (m, 2H), 5.83 (s, 1H), 6.27 (d, $J = 0.8$ Hz, 1H), 6.84–7.03 (m, 10H), 7.15–7.20 (m, 4H), 7.58 (part of AA′BB′, $N = 9$ Hz, 2H), 7.62 (part of AA′BB′, $N = 9$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (q), 55.2 (q), 55.4 (q),

62.2 (t), 67.0 (d), 73.3 (d), 113.7 (d, 2C), 114.5 (d, 2C), 114.9 (d, 2C), 117.1 (d, 2C), 118.5 (s), 121.7 (d), 121.9 (d), 128.7 (d, 2C), 128.9 (d, 2C), 129.3 (d, 4C), 144.5 (s), 145.0 (s), 148.5 (s), 155.2 (s), 160.1 (s), 161.4 (s), 166.8 (s) ppm; MS: m/z (%) = 561 (M^+, 3), 251 (100).

Ethyl 1,6-bis-(4-methoxyphenyl)-3,8-diphenyl-1,5,6,8a-tetrahydro[1,2,4]triazolo[4,3-d][1,2,4]triazine-5-carboxylate (**14c**; $C_{33}H_{31}N_5O_4$)

Yield 0.43 g (31%); m.p.: 109–112°C (MeOH); prisms; IR (KBr): $\nu_{max} = 1731\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.14$ (t, $J = 7$ Hz, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 4.09–4.23 (m, 2H), 5.67 (s, 1H), 6.26 (s, 1H), 6.69–6.76 (overlapping parts of AA′BB′, 4H), 6.84 (part of AA′BB′, $N = 9$ Hz, 2H), 6.93 (part of AA′BB′, $N = 9$ Hz, 2H), 7.32–7.34 (m, 3H), 7.46–7.53 (m, 3H), 7.59–7.62 (m, 2H), 7.68–7.70 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (q), 55.5 (q, 2C), 62.1 (t), 68.7 (d), 74.3 (d), 114.0 (d, 2C), 114.2 (d, 2C), 118.1 (d, 2C), 122.2 (d, 2C), 126.7 (s), 127.3 (d, 2C), 127.9 (d, 2C), 128.2 (d, 2C), 128.6 (d), 129.1 (d, 2C), 130.6 (d), 135.9 (s), 139.3 (s), 142.1 (s), 144.9 (s), 155.3 (s), 155.4 (s), 156.4 (s), 166.7 (s) ppm; MS: m/z (%) = 561 (M^+, 2), 251 (15), 134 (100).

Ethyl 3,8-diacetyl-1,6-diphenyl-1,5,6,8a-tetrahydro[1,2,4]triazolo[4,3-d][1,2,4]triazine-5-carboxylate (**14e**; $C_{23}H_{23}N_5O_4$)

Yield: 0.58 g (54%); m.p.: 133–136°C (MeOH); yellow prisms; IR (KBr): $\nu_{max} = 1754$, $1672\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.22$ (t, $J = 7$ Hz, 3H), 2.35 (s, 3H), 2.50 (s, 3H), 4.23 (q, $J = 7$ Hz, 2H), 6.67 (s, 1H), 7.04 (m_c, 1H), 7.13 (m_c, 1H), 7.32–7.41 (m, 7H), 7.47–7.49 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (q), 24.6 (q), 26.7 (q), 62.9 (t), 65.1 (d), 70.1 (d), 116.0 (d, 2C), 116.8 (d, 2C), 122.6 (d), 124.1 (d), 128.6 (d, 2C), 129.4 (d, 2C), 139.1 (s), 143.4 (s), 143.5 (s), 145.9 (s), 165.6 (s), 190.1 (s), 195.5 (s) ppm; MS: m/z (%) = 433 (M^+, 7), 177 (95), 104 (100).

Ethyl 3,8-diacetyl-1,6-bis-(4-methylphenyl)-1,5,6,8a-tetrahydro[1,2,4]triazolo[4,3-d][1,2,4]triazine-5-carboxylate (**14f**; $C_{25}H_{27}N_5O_4$)

Yield: 0.65 g (56%); m.p.: 134–137°C (MeOH); yellow prisms; IR (KBr): $\nu_{max} = 1750$, 1675, $1661\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.22$ (t, $J = 7$ Hz, 3H), 2.31 (s, 6H), 2.33 (s, 3H), 2.48 (s, 3H), 4.22 (q, $J = 7$ Hz, 2H), 6.64 (s, 1H), 7.12–7.25 (m, 6H), 7.29 (s, 1H), 7.36 (part of AA′BB′, $N = 9$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (q), 20.7 (q, 2C), 24.5 (q), 26.6 (q), 62.8 (t), 65.3 (d), 70.3 (d), 116.1 (d, 2C), 117.3 (d, 2C), 129.1 (d, 2C), 129.9 (d, 2C), 132.4 (s), 133.8 (s), 138.9 (s), 141.0 (s), 141.4 (s), 145.6 (s), 165.6 (s), 189.9 (s), 195.4 (s) ppm; MS: m/z (%) = 461 (M^+, 7), 191 (100), 118 (95).

Triethyl 1,6-bis-(4-bromophenyl)-1,5,6,8a-tetrahydro[1,2,4]triazolo[4,3-d][1,2,4]triazine-3,5,8-tricarboxylate (**14g**; $C_{25}H_{25}Br_2N_5O_6$)

Yield: 1.12 g (69%); m.p.: 109–113°C (MeOH); yellow prisms; IR (KBr): $\nu_{max} = 1746$, $1708\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.22$ (t, $J = 7$ Hz, 3H), 1.23 (t, $J = 7$ Hz, 3H), 1.33 (t, $J = 7$ Hz, 3H), 4.09–4.24 (m, 2H), 4.26 (q, $J = 7$ Hz, 2H), 4.33 (q, $J = 7$ Hz, 2H), 6.57 (s, 1H), 7.11 (s, 1H), 7.24/7.40 (AA′BB′, $N = 9$ Hz, 4H), 7.31/7.46 (AA′BB′, $N = 9$ Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.9$ (q, 2C), 14.0 (q), 61.4 (t), 62.8 (t), 63.1 (t), 65.0 (d), 70.3 (d), 114.9 (s), 116.7 (s), 117.5 (d, 2C), 118.1 (d, 2C), 131.5 (d, 2C), 132.2 (d, 2C), 132.5 (s), 141.8 (s), 142.6 (s), 143.4 (s), 158.3 (s), 162.3 (s), 165.3 (s) ppm; MS: m/z (%) = 649/651/653 (M^+, 5), 255/257 (100), 182/184 (79).

(5-Ethoxy-1,3-oxazol-2-yl)-phenyl-ketone phenylhydrazone (**15a**; $C_{18}H_{17}N_3O_2$)

Yield: 0.32 g (21%); m.p.: 109–112°C (EtOH); yellow needles; IR (KBr): $\nu_{max} = 1598\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.40$ (t, $J = 7$ Hz, 3H), 4.12 (q, $J = 7$ Hz, 2H), 6.33 (s, 1H), 6.89–6.93 (m, 1H),

7.28–7.42 (m, 7H), 7.76–7.79 (m, 2H), 12.66 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (q), 68.3 (t), 99.8 (d), 113.8 (d, 2C), 121.2 (d), 125.5 (s), 127.8 (d), 128.1 (d, 2C), 128.2 (d, 2C), 129.2 (d, 2C), 136.3 (s), 144.3 (s), 148.7 (s), 158.2 (s) ppm; MS: m/z (%) = 307 (M^+, 100), 234 (84).

(5-Ethoxy-1,3-oxazol-2-yl)-(4-methoxyphenyl)-ketone phenylhydrazone (**15b**; $C_{19}H_{19}N_3O_3$)

Yield: 0.13 g (8%); m.p.: 112–114°C (EtOH); yellow needles; IR (KBr): $\nu_{max} = 1598\,cm^{-1}$; ^{1}H NMR ($CDCl_3$): $\delta = 1.43$ (t, $J = 7$ Hz, 3H), 3.84 (s, 3H), 4.17 (q, $J = 7$ Hz, 2H), 6.36 (s, 1H), 6.88–6.93 (m, 1H), 6.95/7.71 (AA′BB′, $N = 9$ Hz, 4H), 7.28–7.30 (m, 4H), 12.54 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (q), 55.3 (q), 68.3 (t), 99.8 (d), 113.57 (d, 2C), 113.63 (d, 2C), 120.9 (d), 125.3 (s), 128.9 (s), 129.2 (d, 2C), 129.3 (d, 2C), 144.4 (s), 148.7 (s), 158.2 (s), 159.4 (s) ppm; MS: m/z (%) = 337 (M^+, 60), 264 (100).

(5-Ethoxy-1,3-oxazol-2-yl)-phenyl-ketone (4-methoxyphenyl)hydrazone (**15c**; $C_{19}H_{19}N_3O_3$)

Yield: 0.11 g (7%); m.p.: 111–114°C (EtOH); yellow needles; IR (KBr): $\nu_{max} = 1603\,cm^{-1}$; ^{1}H NMR ($CDCl_3$): $\delta = 1.44$ (t, $J = 7$ Hz, 3H), 3.79 (s, 3H), 4.18 (q, $J = 7$ Hz, 2H), 6.36 (s, 1H), 6.88/7.25 (AA′BB′, $N = 9$ Hz, 4H), 7.31–7.35 (m, 1H), 7.39–7.43 (m, 2H), 7.76–7.78 (m, 2H), 12.59 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (q), 55.6 (q), 68.3 (t), 99.7 (d), 114.7 (d, 2C), 114.8 (d, 2C), 124.4 (s), 127.6 (d), 128.0 (d, 2C), 128.1 (d, 2C), 136.4 (s), 138.2 (s), 148.8 (s), 154.6 (s), 158.1 (s) ppm; MS: m/z (%) = 337 (M^+, 70), 264 (100).

(5-Ethoxy-1,3-oxazol-2-yl)-phenyl-ketone (4-nitrophenyl)hydrazone (**15d**; $C_{18}H_{16}N_4O_4$)

Yield: 1.53 g (87%); m.p.: 202–206°C (acetone); deep yellow needles; IR (KBr): $\nu_{max} = 1596\,cm^{-1}$; ^{1}H NMR ($CDCl_3$): $\delta = 1.47$ (t, $J = 7$ Hz, 3H), 4.22 (q, $J = 7$ Hz, 2H), 6.43 (s, 1H), 7.31/8.19 (AA′BB′, $N = 9$ Hz, 4H), 7.42–7.48 (m, 3H), 7.75–7.78 (m, 2H), 13.04 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (q), 68.6 (t), 100.1 (d), 112.9 (d, 2C), 125.9 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.8 (d), 129.8 (s), 135.2 (s), 141.1 (s), 147.8 (s), 149.4 (s), 158.8 (s) ppm; MS: m/z (%) = 352 (M^+, 100), 279 (93).

1-(5-Ethoxy-1,3-oxazol-2-yl)-1-(phenylhydrazono)propan-2-one (**15e**; $C_{14}H_{15}N_3O_3$)

Yield: 0.34 g (25%); m.p.: 103–104°C (EtOH); yellow needles; IR (KBr): $\nu_{max} = 1684\,cm^{-1}$; ^{1}H NMR ($CDCl_3$): $\delta = 1.46$ (t, $J = 7$ Hz, 3H), 2.56 (s, 3H), 4.23 (q, $J = 7$ Hz, 2H), 6.29 (s, 1H), 7.06–7.11 (m, 1H), 7.34–7.39 (m, 4H), 13.38 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.8$ (q), 26.2 (q), 68.7 (t), 99.1 (d), 115.4 (d, 2C), 124.0 (d), 125.0 (s), 129.7 (d, 2C), 142.8 (s), 147.7 (s), 159.0 (s), 194.8 (s) ppm; MS: m/z (%) = 273 (M^+, 100), 200 (38).

1-(5-Ethoxy-1,3-oxazol-2-yl)-1-((4-methylphenyl)hydrazono)propan-2-one (**15f**; $C_{15}H_{17}N_3O_3$)

Yield: 0.41 g (29%); m.p.: 128–129°C (EtOH); yellow needles; IR (KBr): $\nu_{max} = 1673\,cm^{-1}$; ^{1}H NMR ($CDCl_3$): $\delta = 1.46$ (t, $J = 7$ Hz, 3H), 2.34 (s, 3H), 2.56 (s, 3H), 4.24 (q, $J = 7$ Hz, 2H), 6.29 (s, 1H), 7.17/7.28 (AA′BB′, $N = 8$ Hz, 4H), 13.37 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (q), 20.8 (q), 25.9 (q), 68.5 (t), 98.8 (d), 115.1 (d, 2C), 124.3 (s), 130.0 (d, 2C), 133.5 (s), 140.3 (s), 147.6 (s), 158.7 (s), 194.6 (s) ppm; MS: m/z (%) = 287 (M^+, 100), 214 (56).

Ethyl ((4-bromophenyl)hydrazono)(5-ethoxy-1,3-oxazol-2-yl)acetate (**15g**; $C_{15}H_{16}BrN_3O_4$)

Yield: 0.29 g (15%); m.p.: 96–97°C (EtOH); yellow needles; IR (KBr): $\nu_{max} = 1715\,cm^{-1}$; ^{1}H NMR ($CDCl_3$): $\delta = 1.42$ (t, $J = 7$ Hz, 3H), 1.47 (t, $J = 7$ Hz, 3H), 4.24 (q, $J = 7$ Hz, 2H), 4.39 (q, $J = 7$ Hz,

2H), 6.33 (s, 1H), 7.27/7.44 (AA′BB′, $N = 9$ Hz, 4H), 13.27 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.3$ (q), 14.5 (q), 61.3 (t), 68.5 (t), 99.5 (d), 115.8 (s), 116.7 (d, 2C), 117.6 (s), 132.2 (d, 2C), 141.9 (s), 147.5 (s), 158.6 (s), 162.8 (s) ppm; MS: m/z (%) = 381/383 (M^+, 100), 308/310 (24).

Diethyl 6-(4-bromophenyl)-1,3-diphenyl-1,5,6,8a-tetrahydro-[1,2,4]triazolo[4,3-d][1,2,4]triazine-5,8-dicarboxylate (**14h**; $C_{28}H_{26}BrN_5O_4$)

To a stirred solution of crude 0.38 g **13g** (1 mmol) and 0.23 g **1a** (1 mmol) in 15 cm^3 of anhydrous benzene, 0.5 cm^3 of triethylamine (*ca.* 3 mmol) were added. The mixture was heated under reflux for 1 h, cooled to room temperature, diluted with 15 cm^3 of light petroleum and, after filtration of the triethylammonium chloride, concentrated *in vacuo*. The residue was chromatographed on silica gel (CH_2Cl_2 as eluent) and recrystallized from MeOH.

Yield: 0.24 g (42%); m.p.: 145–146°C; yellow prisms; IR (KBr): $\nu_{max} = 1735$, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.24$ (t, $J = 7$ Hz, 3H), 1.32 (t, $J = 7$ Hz, 3H), 4.19–4.36 (m, 4H), 5.77 (s, 1H), 6.36 (s, 1H), 6.77/7.29 (AA′BB′, $N = 9$ Hz, 4H), 6.97–7.01 (m, 1H), 7.28–7.33 (m, 2H), 7.44–7.55 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (q), 14.1 (q), 61.5 (t), 63.1 (t), 66.5 (d), 71.0 (d), 116.1 (d, 2C), 116.5 (s), 117.4 (d, 2C), 121.6 (d), 125.8 (s), 127.7 (d, 2C), 128.7 (d, 2C), 129.2 (d, 2C), 131.0 (d), 132.1 (d, 2C), 134.2 (s), 142.5 (s), 148.3 (s), 155.4 (s), 162.6 (s), 165.4 (s) ppm; MS: m/z (%) = 575/577 (M^+, 27), 255/257 (90), 221 (100), 182/184 (89).

Ring opening of triazolotriazines **14a**–**c**; *general procedure*

A solution of the appropriate triazolotriazine **14** (0.5 mmol) in 50 cm^3 of $CHCl_3$ was heated under reflux for 12 h (daylight!) whereupon the solvent was removed *in vacuo*. In the case of **14a**,**b**, the residue was treated with the minimum amount of EtOH to allow crystallization of the phenylhydrazones **16a**,**b** which were collected by filtration (data see below). In the case of **14c**, the residue was chromatographed on silica gel (CH_2Cl_2 as eluent) to give an oil which, after treatment with EtOH, left an inhomogeneous solid showing an intense singlet at 10.44 ppm in its ^{1}H NMR spectrum ($CDCl_3$). Attempts to isolate the product failed.

(1,3-Diphenyl-1H-1,2,4-triazol-5-yl)-phenyl-ketone phenylhydrazone (**16a**; $C_{27}H_{21}N_5$)

Yield: 0.17 g (82%); m.p.: 179–180°C (EtOH) (Ref. [7]: 181–182°C); pale yellow needles; the IR, ^{1}H and ^{13}C NMR data were consistent with the literature data [7].

(4-Methoxyphenyl)-(3-(4-methoxyphenyl)-1-phenyl-1H-1,2,4-triazol-5-yl)-ketone phenylhydrazone (**16b**; $C_{29}H_{25}N_5O_2$)

Yield: 0.22 g (93%); m.p.: 164–166°C (EtOH); pale yellow prisms; ^{1}H NMR ($CDCl_3$): $\delta = 3.70$ (s, 3H), 3.89 (s, 3H), 6.64/7.03 (AA′BB′, $N = 9$ Hz, 4H), 6.89–6.94 (m, 1H), 7.15–7.37 (m, 10H), 7.42–7.55 (m, 1H), 8.22 (part of AA′BB′, $N = 9$ Hz, 2H), 10.18 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 55.2$ (q), 55.4 (q), 113.56 (d, 2C), 113.61 (d, 2C), 114.2 (d, 2C), 121.0 (d), 122.8 (s), 123.9 (d, 2C), 127.7 (d, 2C), 128.1 (d, 2C), 128.5 (d), 128.7 (s), 128.9 (d, 2C), 129.3 (d, 2C), 129.6 (s), 137.4 (s), 144.1 (s), 146.8 (s), 159.4 (s), 161.0 (s), 161.9 (s) ppm; MS: m/z (%) = 475 (M^+, 92), 474 (100).

Crystal structure determination of **14e**

Crystal data: $C_{23}H_{23}N_5O_4$, $M = 433.46$, triclinic, space group $P(-1)$, $a = 9.1925(6)$, $b = 10.0014(6)$, $c = 12.3904(8)$ Å, $\alpha = 68.551(3)$, $\beta = 85.026(3)$, $\gamma = 85.468(3)°$, $U = 1054.9$ Å^3, $Z = 2$, $T = -140$°C. Data collection: A crystal of *ca.* 0.3×0.23×0.2 mm was used to record 13938 intensities on a Bruker

SMART 1000 CCD diffractometer (MoK_α radiation, $2\theta_{max} = 60°$). Structure refinement: The structure was refined anisotropically on F^2 (program SHELXL-97 [17]) to $wR_2 = 0.117$, $R_1 = 0.040$ for 292 parameters and 6080 unique reflections. The hydrogens were refined using a riding model or rigid methyl groups. The data have been deposited at the Cambridge Crystallographic Data Centre (deposition No. CCDC 173739).

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