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Transformations of tetrahydrobenzo[*b*][1,6]naphthyridines and tetrahydropyrido[4,3-*b*]pyrimidines under the action of dimethyl acetylene dicarboxylate

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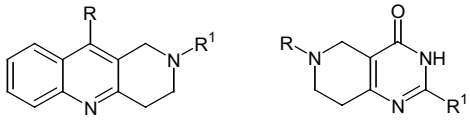
Abstract—10-Cyanotetrahydrobenzo[*b*][1,6]naphthyridines **3**, **4** undergo addition of DMAD, followed by a Stevens rearrangement of the intermediate ylide to yield methyl dioates **8** and **9**. An alternative transformation sequence starts with migration of the dimethyl butenedioate anion to the carbon of the CN group, followed by the addition of 1 mol of water, to provide succinates **10** and **11**. In contrast, tetrahydropyrido[4,3-*b*]pyrimidines **5**–**7** undergo a tandem cleavage process, involving one molecule of solvent. The resulting enamines are easily cleaved by strong acids, to give dihydropyrymidinylethylamines, which are scarcely available by other synthetic means.

Probably due to the lack of efficient synthetic methods, tetrahydrobenzonaphthyridines have not been the focus of much research interest. On the other hand, their naphthyridine and hydronaphthyridine skeletons are found in some bioactive compounds[1,2] and more recently have been shown to be effective lithium[3] or copper[4,5] complexing agents and chiral biomimetic NADH models.[6] Only a few examples of chemical transformations of tetrahydropyridopyrimidines have been reported.[7–9] As part of a project devoted to the synthesis and biological screening of azocine-containing fused heterocycles[10] we focused on the preparation and further tandem cleavage–cyclisation reactions with dimethylacetylene dicarboxylate (DMAD) of tetrahydrobenzo[*b*][1,6]naphthyridines **1**–**4** and pyrido[4,3-*b*]-pyrimidines **5**–**7** (Fig. 1).



1 R=CONH$_2$, R^1=*i*Pr
2 R=CONH$_2$, R^1=Me
3 R=CN, R^1=*i*Pr
4 R=CN, R^1=Me

5 R=Me, R^1=Ph
6 R=Bn, R^1=Ph
7 R=Bn, R^1=Me

Figure 1.

Both of these scaffolds have a tetrahydropyridine (THP) fragment condensed with a π-deficient heterocycle as distinct from the previously studied tetrahydropyrrolopyridines (THPP) and tetrahydropyridoindole (THPI) derivatives. THPP and THPI derivatives undergo cleavage in alcohols with DMAD to produce β-alkoxy-(hydroxy)alkylpyrroles (indoles) in moderate to high yields. The latter compounds are valuable building blocks for the synthesis of fused azocines.[11] Hence, it seemed of interest to investigate the reactivity of compounds **1**–**7** towards DMAD. In this paper, we wish to present the results of these studies.

Compounds **1** and **2** were synthesised according to methods previously described.[12] Condensation of isatin with γ-piperidones in the presence of gaseous ammonia followed by dehydration using phosphorus oxychloride produced nitriles **3** and **4** (Scheme 1). We had to transform amides **1** and **2** into nitriles due to the low solubility of the former in methanol. Tetrahydropyrido-[4,3-*b*]pyrimidines **5**–**7** were synthesised according to a procedure previously described (Scheme 2).[13]

Keywords: Pyridine; Cleavage; Acetylene; Rearrangement.
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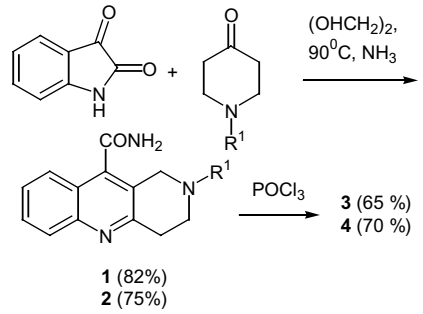
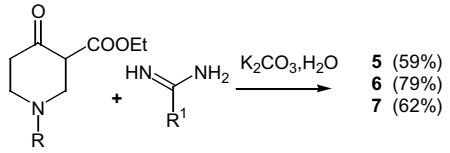
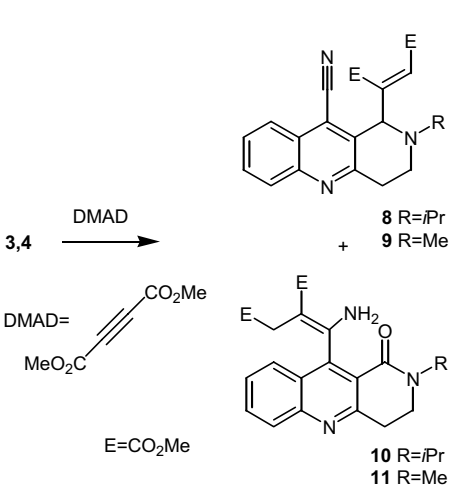


Scheme 1.



Scheme 2.



Scheme 3.

Nitriles **3** and **4** were treated with DMAD in methanol at room temperature. In both cases the reactions proceeded smoothly, giving two products, the chromatographic separation of which led to the isolation of unexpected products **8**–**11** (Scheme 3).[14]

X-ray crystallographic analysis was carried out on compounds **8** and **10**, which were obtained as suitable monocrystals by recrystallisation from ethyl acetate (slow evaporation; rt) to arrive at unequivocal structural assignments and elucidate their three-dimensional structures. The refined X-ray crystal structures of **8**[15] and **10**[16] are shown in Figures 2 and 3. In both compounds the double bonds have the *Z*-configuration. We presume that the reaction proceeds via the intermediate zwitterion **A**, resulting from the Michael addition of the tertiary nitrogen to the DMAD molecule. An internal proton transfer then gives ylide **B** (Scheme 4).

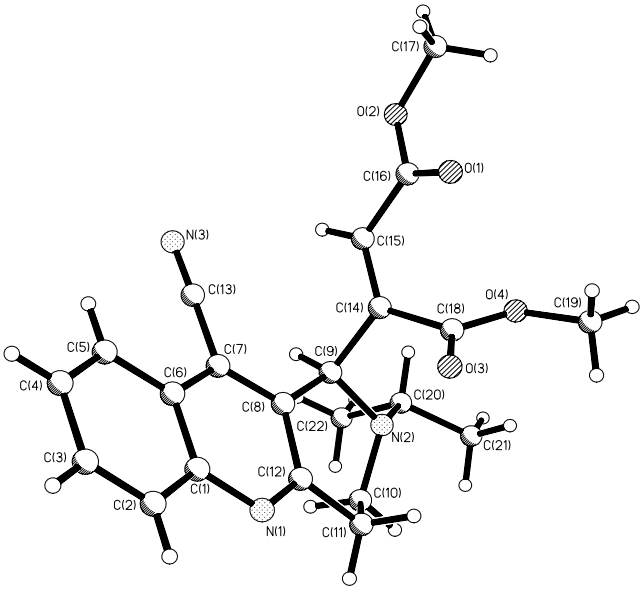


Figure 2. X-ray crystal structure of **8**.

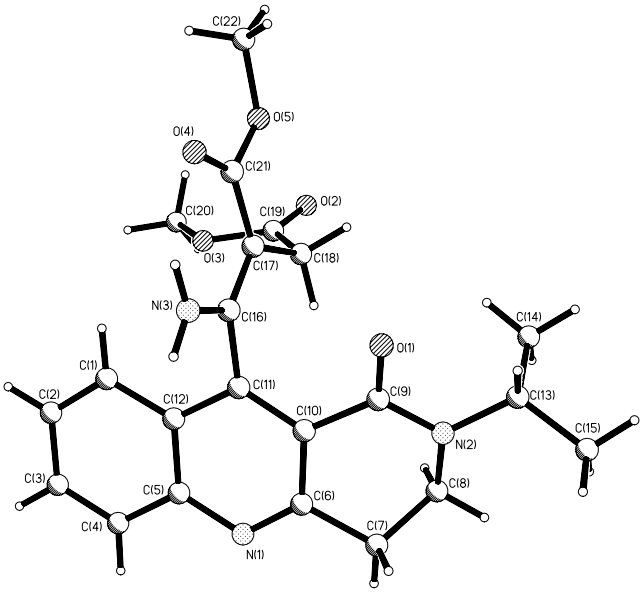
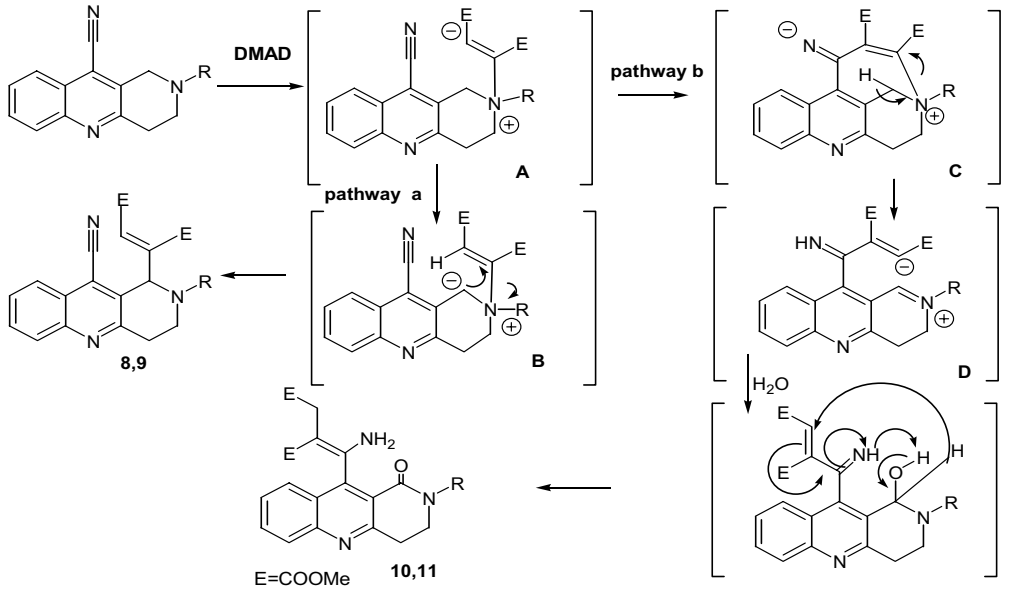


Figure 3. X-ray crystal structure of **10**.

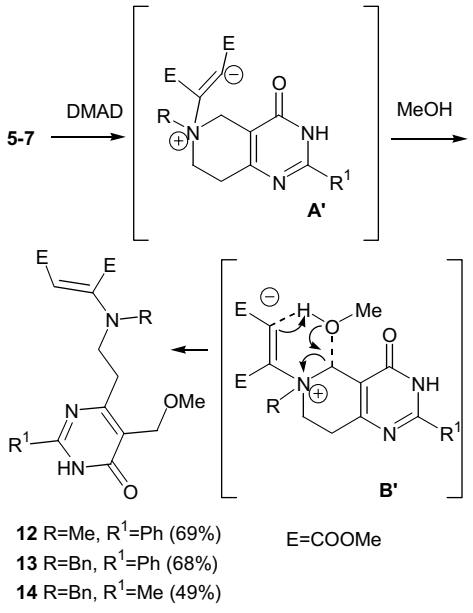
Stevens rearrangement[17] of the ylide (pathway a) yields compounds **8**[18] and **9**. The alternative transformation (pathway b) starts with migration of the dimethyl butenedioate anion to the carbon of the CN group, resulting in the formation of the iminium zwitterion **C**, which, upon reaction with water, followed by the rearrangement of the intermediate imine **D** yields the enamines **10**[19] and **11** via an internal redox process.

Pyridopyrimidines **5**–**7** were also treated with DMAD in methanol at 50 °C (no reaction occurred at lower temperatures). In all cases a tandem cleavage process involving one molecule of solvent took place (Scheme 5).

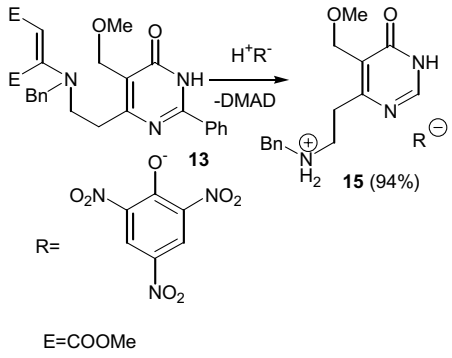
As in the previous case, the reaction most probably starts with Michael addition of the THP N-atom onto



Scheme 4.



Scheme 5.



Scheme 6.

DMAD. Cleavage of the C(1)–N bond then occurs via the six-membered transition state **B′** in which a molecule of alcohol facilitates a S_N2 reaction. The resulting pyrimidines **12**–**14** were isolated in good yields.[18] To obtain additional information about the structures of **12**–**14** (i.e., about the configuration of the enamine double bond and hydroxy(oxo)pyrimidine fragment) we tried to obtain a suitable monocrystal for X-ray analysis, but our attempts were unsuccessful. We therefore decided to convert compound **13** into its picrate. Under the reaction conditions (an equimolar amount of picric acid, ethanol, 40–50 °C), the enamine fragment of **13** was cleaved, to produce picrate **15** in almost quantitative yield (Scheme 6). An X-ray analysis of **15**[19] was carried out on a monocrystal obtained by recrystallisation from ethanol by slow evaporation at room temperature. The refined X-ray crystal structure of **15** (cation) is shown in Figure 4. It is worth pointing out that the benzyl and pyrimidine rings are almost coplanar and the latter exists in its oxo-form. Further experiments showed

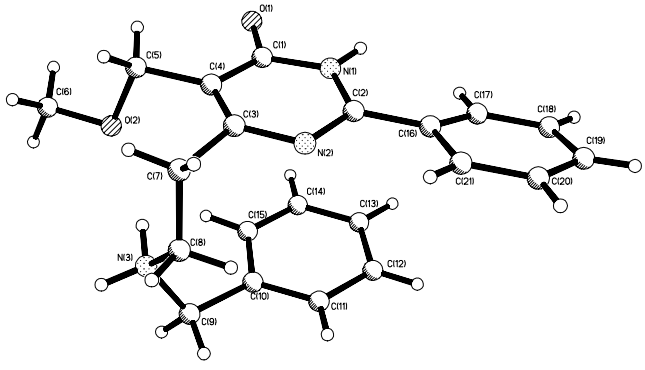
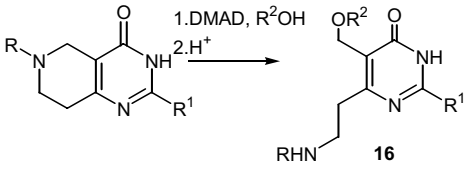


Figure 4. X-ray crystal structure of **15** (cation).



Scheme 7.

that the enamine bond in compounds **12**–**14** is cleaved by any strong acid (e.g., HCl, H_2SO_4).

This fact, along with the good yields and the availability of the starting materials encouraged us to elaborate a one-pot procedure for the synthesis of substituted pyrimidinyl-4-ethylamines of general formula **16**, having three points of diversity (hardly available by other synthetic means) (Scheme 7).[20]

In conclusion, we have demonstrated, that 10-cyano tetrahydrobenzo[*b*][1,6]naphthyridines **3**, **4** undergo unusual reactions with DMAD, leading to the formation of diesters **8**–**11** having good synthetic potential. We have also demonstrated, that the readily available tetrahydropyrido[4,3-*b*]pyrimidines react with DMAD undergoing a tandem cleavage process involving one molecule of methanol. The resulting enamines are readily cleaved under acidic conditions providing in high yields the corresponding dihydropyrymidinylethylamines which are hardly available by other synthetic means. A one-pot protocol for this transformation has been elaborated.

Acknowledgements

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14. General experimental procedure: To a solution of 1 mmol of the benzonaphthyridine derivative **3**, **4** in 10 mL of methyl alcohol, 1.2 mmol of DMAD was added. The reaction mixture was stirred for 4–6 h at room temperature (TLC monitoring). The solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography using 1:2 ethyl acetate–hexane mixture as eluent. The first fraction provided the corresponding derivatives **8** and **9.** Further elution provided compounds **10** and **11**. (In the case of benzonaphthyridine **4**, LC–MS analysis of the reaction mass carried out within 2 h after the reaction start showed a small peak (approx. 7–8%) due to a compound with *m*/*z* 333, which was neither isolated nor identified.) Selected physical data for *dimethyl (2Z)-2-(10-cyano-2-isopropyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridin-1-yl)but-2-enedioate* (**8**): pale-yellow crystals, mp 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (m, 2H), 7.80 (m, 1H), 7.68 (m, 1H), 5.84 (s, 1H), 5.32 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.39 (m, 1H), 3.22–2.90 (m, 4H), 1.14 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 166.8, 164.5, 157.9, 150.2, 146.5, 131.5, 130.9, 129.2, 128.4, 124.7, 124.6, 122.8, 117.4, 113.9, 61.2, 52.1, 51.8, 50.4, 39.9, 31.2, 20.9, 18.4. EIMS: *m*/*z* (%): 393 (M^+, 16), 378 (30), 350 (21), 334 (23), 251 (20), 250 (100), 234 (18), 208 (40), 206 (20), 193 (15). Selected physical data for *dimethyl (2Z)-2-[amino(2-isopropyl-1-oxo-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridin-10-yl)methylene]succinate* (**10**): yellow crystals, mp 205–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 8.1 Hz, 1H), 7.61 (t, J = 8.1 Hz, 1H), 6.60 (br s, 2H), 5.10 (spt, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.60–3.40 (m, 2H), 3.35 (s, 3H), 3.31–3.22 (m, 2H), 2.80 (d, J = 17.1 Hz, 1H), 2.60 (d, J = 17.1 Hz, 1H), 1.22 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 164.4, 156.1, 152.6, 152.1, 143.1, 138.6, 126.5, 123.2, 122.0, 121.9, 119.7, 115.2, 85.2, 46.2, 45.7, 38.8, 32.5, 28.4, 28.2, 14.6, 14.2. EIMS: *m*/*z* (%): 411 (M^+, 55), 379 (15), 352 (100), 337 (75), 320 (20), 306 (60), 292 (25), 278 (30), 250 (30), 235 (25), 224 (25), 206 (22), 192 (15).
15. Crystal structure analysis for **8**: $C_{22}H_{23}N_3O_4$, M_r = 393.43 g mol^{-1}, monoclinic, space group $P2_1/c$, a = 9.784(3), b = 17.546(4), c = 12.229(3) Å, β = 100.01(3)°, V = 2067.4(9) Å^3, Z = 4, ρ = 1.264 g cm^3, μ = 0.088 cm^{-1}, $F(000)$ = 832, crystal size: 0.12 × 0.06 × 0.02 mm. Crystal data was collected on a Cad-4 diffractometer (λ Mo K_α radiation, graphite monochromator; ω scaning, $2\theta_{макс.}$ = 50°). A total of 3860 reflections ($2.05 < \theta < 24.97°$) were collected of which 3610 were unique (R(int) = 0.0958). The structure was solved with the program SHELXS-97[21] and refined using SHELXL-97[22] to R_1 = 0.0520 and $wR(F^2)$ = 0.1450 for 2377 reflections with $I > 2\sigma(I)$; max.\min. residual electron density 0.262 and –0.249 e Å^{-3}. All atoms were refined with anisotropic thermal parameters. Crystallographic data (excluding

structure factors) for compound **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 246613.

16. Crystal structure analysis for **10**: $C_{22}H_{25}N_3O_5$, $M_r = 411.45$ g mol^{-1}, triclinic, space group *P*-1, $a = 11.148(8)$, $b = 11.823(8)$, $c = 16.679(9)$ Å, $\alpha = 75.85(3)°$, $\beta = 86.40(3)°$, $= 76.22(3)$, $V = 2070(2)$ Å^3, $Z = 4$, $\rho = 1.320$ g cm^3, $\mu = 0.095$ cm^{-1}, $F(000) = 872$, crystal size: $0.35 \times 0.25 \times 0.08$ mm^3. Crystal data was collected on a Bruker AXS SMART 1000 area detector diffractometer[10] (three-circle goniometer with 1K CCD detector, Mo K_α radiation, graphite monochromator; hemispere data collection in ω at 0.3° scan, $2\theta_{makc.} = 46°$). A total of 3512 reflections ($1.26 < \theta < 23.10°$) were collected of which 3480 were unique (R(int) = 0.0870). The structure was solved with the program SHELXS-97 and refined using SHELXL-97 to $R_1 = 0.0805$ and $wR(F^2) = 0.2279$ for 3480 reflections with $I > 2\sigma(I)$; max.\min. residual electron density 0.338 and −0.281 e Å^{-3}. All nonhydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were fixed with $U_H = 0.08E^2$. Crystallographic data (excluding structure factors) for compound **10** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 246612.
17. For Stevens rearrangement see: (a) Brewster, J. H.; Kline, M. M. *J. Am. Chem. Soc.* **1953**, *74*, 5179; (b) Jenney, E. F.; Druey, J. *Angew. Chem., Int. Ed.* **1962**, *1*, 155.
18. General experimental procedure: To a stirred solution of pyridopyrimidines **5**–**7** (1 mmol) in 15 mL of methanol at 50 °C, 1.2 mmol of DMAD was added and stirring was continued for an additional 3 h (TLC monitoring). Methanol was evaporated under reduced pressure and the resulting residue was recrystallised from ethanol to give compounds **12**–**14**. Selected physical data for *dimethyl-2-(benzyl{2-[5-(methoxymethyl)-6-oxo-2-phenyl-1,6-dihydropyrimidin-4-yl]ethyl}amino)but-2-enedioate* (13): White crystals, mp 174–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, $J = 7.1$ Hz, 2H), 7.70–7.51 (m, 3H), 7.50–7.1 (m, 5H), 5.00 (br s, 1H), 4.42 (s, 2H), 4.35 (s, 2H), 3.94 (s, 3H), 3.66 (s, 3H), 3.57 (t, $J = 7.1$, 2H), 3.40 (s, 3H), 2.95 (t, $J = 7.1$,2H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.2, 166.1, 165.2, 164.8, 155.5, 154.1, 135.7, 132.2, 131.6, 128.8, 128.7, 127.9, 127.8, 127.6, 119.4, 85.4, 64.2, 58.5, 54.6,52.9, 50.82, 48.0, 31.4. ESI MS: 492 (M^++1).
19. Crystal structure analysis for **15**: $C_{27}H_{26}N_6O_9$, $M_r = 578.54$ g mol^{-1}, monoclinic, space group *Cc*, $a = 38.553(9)$, $b = 6.882(2)$, $c = 27.215(7)$ Å, $\alpha = 90°$, $\beta = 128.14(2)°$, $\gamma = 90$, $V = 5679(3)$ Å^3, $Z = 8$, $\rho = 1.353$ g cm^3, $\mu = 0.104$ mm^{-1}, $F(000) = 2416$, crystal size: $0.53 \times 0.33 \times 0.23$ mm^3. Crystal data was collected on a Cad-4 diffractometer (Mo K_α radiation, graphite monochromator; ω scaning, $2\theta_{makc.} = 30.4°$). A total of 4795 reflections ($1.34 < \theta < 25.15°$) were collected of which 4754 were unique (R(int) = 0.0177). The structure was solved with the program SHELXS-97 and refined using SHELXL-97 to $R_1 = 0.0391$ and $wR(F^2) = 0.0850$ for 4754 reflections with $I > 2\sigma(I)$; max.\min. residual electron density 0.267 and −0.200 e Å^{-3}. Crystallographic data (excluding structure factors) for compound **15** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 246614.
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