Silica Nanoparticles as a Highly Efficient Catalyst for the One-Pot Synthesis of 2-Hydroxyacetamide Derivatives from Isocyanides and Electron-Poor Aromatic Aldehydes

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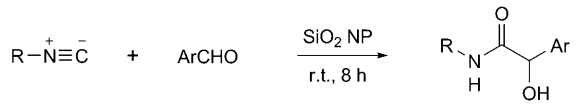
Reaction of an isocyanide with an electron-poor aromatic aldehyde in the presence of silica nanoparticles (silica NP; *ca.* 42 nm) proceeds smoothly at room temperature to afford 2-hydroxyacetamide derivatives in high yields (*Scheme 1* and *Table 1*).

Introduction. – As part of our ongoing program to develop efficient and robust methods for the preparation of organic compounds [1–22], we wish to report now a simple and practical procedure for the preparation of 2-hydroxyacetamide derivatives **3** through reaction of alkyl isocyanides **1** and electron-poor aromatic aldehydes **2** in the presence of silica nanoparticles (silica NP; *ca.* 42 nm) at room temperature for 8 h (*cf. Scheme 1* and *Table 1*).

Results and Discussion. – Silica NP were prepared by thermal decomposition of rice hulls [22][23]. The results from XRD showed that the sample was silica NP as indicated by broadened peaks around $2\theta = 22^\circ$ [22]. The morphology and grain size of the silica NP was investigated by scanning electron microscopy (SEM) [22].

Silica NP were found to catalyze the formation of 2-hydroxyacetamide derivatives **3** from alkyl isocyanides **1** and electron-poor aromatic aldehydes **2** under solvent-free conditions in high yields (*Scheme 1* and *Table 1*). We also have used silica-gel powder instead of silica NP in this reaction, but increasing reaction times and decreasing yields of the 2-hydroxyacetamides were observed (*Table 2*). The use of just 0.2 g of silica NP (per mmol of reactants) was sufficient to push the reaction forward. Higher amounts of silica NP (0.3 g) did not improve the result to a great extent (*Table 2*).

Scheme 1. *Synthesis of 2-Hydroxyacetamide Derivatives* **3** *in the Presence of Silica Nanoparticles* (NP) (see *Table 1*)



1 **2** **3**

Table 1. *Synthesis of 2-Hydroxyacetamide Derivatives* **3** *in the Presence of Silica Nanoparticles*[a])

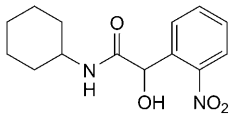
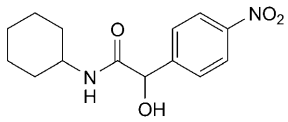
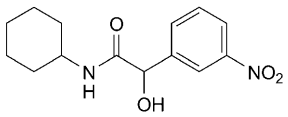
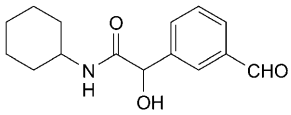
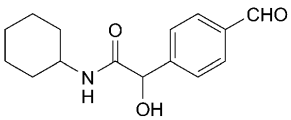
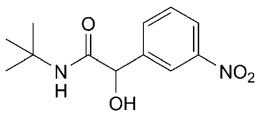
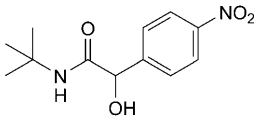
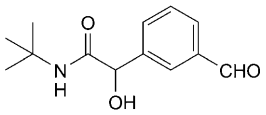
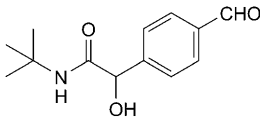
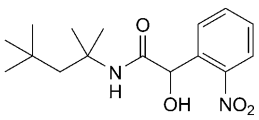
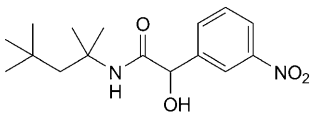
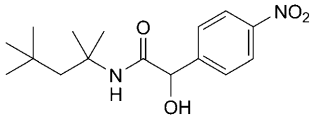
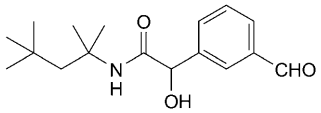
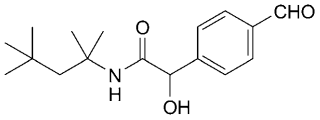
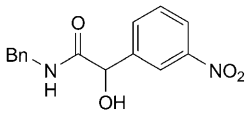
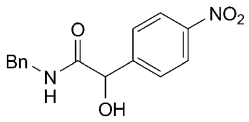
R	Ar	Product	Yield [%][b])
Cyclohexyl	2-$NO_2C_6H_4$	**3a** 	91
Cyclohexyl	4-$NO_2C_6H_4$	**3b** 	96
Cyclohexyl	3-$NO_2C_6H_4$	**3c** 	96
Cyclohexyl	3-HC(O)C_6H_4	**3d** 	90
Cyclohexyl	4-HC(O)C_6H_4	**3e** 	96
t-Bu	3-$NO_2C_6H_4$	**3f** 	95
t-Bu	4-$NO_2C_6H_4$	**3g** 	97
t-Bu	3-HC(O)C_6H_4	**3h** 	93
t-Bu	4-HC(O)C_6H_4	**3i** 	97
1,1,3,3-Tetramethylbutyl	2-$NO_2C_6H_4$	**3j** 	87
1,1,3,3-Tetramethylbutyl	3-$NO_2C_6H_4$	**3k** 	93

Table 1 (cont.)

R	Ar	Product	Yield [%][b])
1,1,3,3-Tetramethylbutyl	4-$NO_2C_6H_4$	**3l** 	95
1,1,3,3-Tetramethylbutyl	3-$HC(O)C_6H_4$	**3m** 	88
1,1,3,3-Tetramethylbutyl	4-$HC(O)C_6H_4$	**3n** 	92
Bn	3-$NO_2C_6H_4$	**3o** 	82
Bn	4-$NO_2C_6H_4$	**3p** 	83

[a]) *Cf. Scheme 1*; 0.2 g of SiO_2 NP/mmol reactants were applied, reaction time 8 h. [b]) Yield of isolated **3**.

Table 2. *Synthesis of 2-Hydroxyacetamide* **3a** *from the Reaction of 2-Nitrobenzaldehyde and Cyclohexyl Isocyanide under Various Conditions*

Catalyst[a])	Temperature	Time [h]	Yield [%][b])
Silica-gel powder (0.2 g)	r.t.	24	42
Silica-gel powder (0.5 g)	r.t.	24	55
Silica-gel powder (1 g)	r.t.	24	71
Silica-gel powder (1.2 g)	r.t.	24	71
SiO_2 NP (0.1 g)	r.t.	8	80
SiO_2 NP (0.2 g)	r.t.	8	91
SiO_2 NP (0.3 g)	r.t.	8	91

[a]) Amount of SiO_2 catalyst per mmol of reactants. [b]) Yields of isolated **3a**.

The structures of compounds **3a** – **3p** were deduced from their IR and high-field ^{1}H- and ^{13}C-NMR spectra. For example, the IR spectrum of **3a** showed a strong adsorption at 3386 cm^{-1} indicating the presence of an amide group (NH), a sharp band at 1644 cm^{-1} was assigned to the amide C=O group, and two sharp bands at 1529 and 1359 cm^{-1} were assigned to the NO_2 group. The ^{1}H-NMR spectrum of **3a** consisted of three *m*s for the cyclohexyl substituent (δ(H) 0.99 – 1.92 and 3.67 – 3.78), an OH signal

exchangeable by D_2O (δ(H) 4.70), a CH signal (δ(H) 5.23), an amide NH signal (δ(H) 6.79) also exchangeable by D_2O, and partially overlapping coupling patterns of four adjacent aromatic H-atoms (δ(H) 7.41 – 7.48 (H–C(5)), 7.60 – 7.62 (H–C(4), H–C(6)), and 7.89 (*d*, ^3J(H,H) = 7.0 Hz, H–C(3))). The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 14 distinct resonances; partial assignment of these resonances is given in the *Exper. Part*. The ^{1}H- and ^{13}C-NMR spectra of compounds **3b** – **3p** were similar to those of **3a**, except for the aromatic moieties and the alkyl groups, which exhibited characteristic signals with appropriate chemical shifts.

Finally, the structure of **3a** was confirmed unambiguously by single-crystal X-ray analysis (*Fig. 1*). Enantiomorphic crystals of **3a** were formed by slow evaporation from light petroleum ether/AcOEt 3 : 1. The crystal-structure determination was performed on one of the enantiomers refined in the chiral space group $P2_12_12_1$. However, it should be stressed that the absolute configuration could not be established unambiguously by anomalous dispersion effects (see *Exper. Part*), and therefore, *Fig. 1* may not show the real absolute configuration of the molecule. A summary of the conditions for the data collection and the structure refinement parameters are given in *Table 3*. The values of selected bond lengths and valence angles (*Table 4*) correspond well with those typical for the respective types of chemical connections [24].

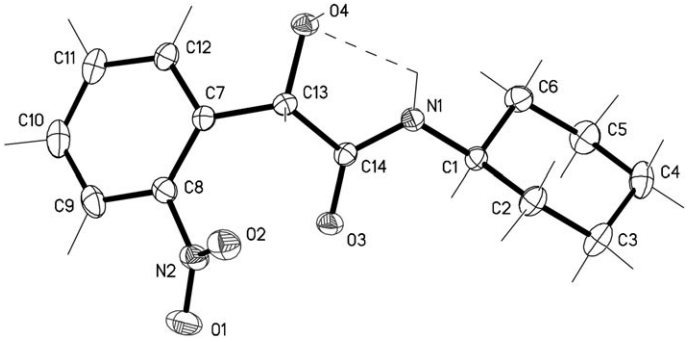


Fig. 1. *Molecular structure of compound* **3a**, *showing the X-ray atom-numbering scheme and intramolecular N–H···O H-bond-forming* S*(5) motif* (dashed line). Displacement ellipsoids represent the 50% probability level.

The central part of molecule **3a** is the 2-hydroxyacetamide moiety, with atoms C(1), N(1), H(N1), C(14), O(3), and C(13) lying in one plane and the OH atom O(4) slightly deviating from this plane by 0.34 Å. As seen from the torsion angles C(1)–N(1)–C(14)–C(13)/O(3) (– 179.69(7)/1.05(12)°), compound **3a** is a *trans* (*Z*) isomer. Synperiplanar orientation of the OH atom O(4) with respect to the amide atom N(1), reflected in the O(4)–C(13)–C(14)–N(1) torsion angle of 14.57(9)°, is stabilized by the intramolecular H-bond N–H···O forming an *S*(5) motif, as shown in *Fig. 2*. The amide moiety is inclined at an angle of *ca.* 63° with respect to the phenyl ring, as confirmed by the torsion angle C(8)–C(7)–C(13)–C(14) of 62.63(9)°. The NO_2 group is twisted relative to the phenyl ring by *ca.* 38°, which is reflected in the torsion angle O(2)–N(2)–C(8)–C(7) of 37.92(10)°. Such a twist of the NO_2 group is accompanied by a weak intramolecular interaction C(13)–H(13)···O(2) forming an *S*(6) motif

Table 3. *Crystallographic Data of Compound* **3a**

Crystallized from	petroleum ether/AcOEt	Scan type	ω and φ
Empirical formula	$C_{14}H_{18}N_2O_4$	Index range	$-17 \le h \le 12$,
M_r	278.30		$-19 \le k \le 19$,
Crystal color, habit	colorless, block		$-21 \le l \le 19$
Crystal dimensions [mm]	$0.40 \times 0.32 \times 0.28$	Measured reflections	35165
Radiation type, λ [Å]	MoK_α, 0.71073	Independent reflections	4375
Temperature [K]	86(2)	Reflections with $I > 2\sigma(I)$	3863
Crystal system	orthorhombic	R_{int}	0.027
Space group	$P2_12_12_1$	Completeness to $\theta = 30°$	99.5%
Z	4	Refinement on	F^2
θ Range [°]	4.27–38.43	Data, restraints, parameters	4375, 0, 253
Unit cell parameters:		R ($F_o^2 > 2\sigma(F_o^2)$)	$R_1 = 0.032$[a]),
a [Å]	10.132(3)		$wR_2 = 0.086$[a])
b [Å]	11.388(4)	R (all data)	$R_1 = 0.037$,
c [Å]	12.305(4)		$wR_2 = 0.089$
V [Å^3]	1419.8(8)	Goodness-of-fit S	1.00
D_x (calc.) [g cm^{-3}]	1.302	Weighting parameter a/b	0.0670/0.0
μ [mm^{-1}]	0.096	$\Delta\rho$ (max; min) [e Å^{-3}]	0.33; −0.24
F(000) [e]	592		

[a]) $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$; $wR_2 = \sqrt{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]}$. Weighting scheme: $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$.

Table 4. *Selected Interatomic Distances, Valence Angles, and Torsion Angles of* **3a**

Bond lengths [Å]			
O(1)–N(2)	1.2317(11)	O(4)–C(13)	1.4116(9)
O(2)–N(2)	1.2296(11)	N(1)–C(1)	1.4665(10)
O(3)–C(14)	1.2383(10)	N(1)–C(14)	1.3284(10)
Valence angles [°]			
C(14)–N(1)–C(1)	123.24(7)	C(9)–C(8)–N(2)	115.73(7)
O(2)–N(2)–O(1)	123.92(8)	O(3)–C(14)–N(1)	124.32(7)
O(2)–N(2)–C(8)	118.13(7)	O(3)–C(14)–C(13)	119.44(6)
O(1)–N(2)–C(8)	117.84(8)	N(1)–C(14)–C(13)	116.24(6)
Torsion angles [°]			
C(14)–N(1)–C(1)–C(6)	146.99(8)	O(1)–N(2)–C(8)–C(7)	–145.62(8)
C(14)–N(1)–C(1)–C(2)	– 88.72(9)	O(2)–N(2)–C(8)–C(7)	37.92(10)
C(1)–N(1)–C(14)–O(3)	1.05(12)	C(8)–C(7)–C(13)–O(4)	–174.59(7)
C(1)–N(1)–C(14)–C(13)	– 179.69(7)	C(8)–C(7)–C(13)–C(14)	62.63(9)
N(1)–C(1)–C(2)–C(3)	– 179.55(7)	O(4)–C(13)–C(14)–O(3)	–166.13(7)
N(1)–C(1)–C(6)–C(5)	– 179.20(7)	C(7)–C(13)–C(14)–O(3)	–43.46(9)
C(13)–C(7)–C(8)–C(9)	– 174.09(7)	O(4)–C(13)–C(14)–N(1)	14.57(9)
N(2)–C(8)–C(9)–C(10)	174.84(8)	C(7)–C(13)–C(14)–N(1)	137.24(7)

(*Table 5*). The cyclohexyl substituent at N(1) adopts a typical chair conformation, the *Cremer* and *Pople* puckering parameters [25] being $Q = 0.580(1)$ Å, $\Theta = 1.5(1)°$, $\Phi = 107(4)°$, and endocyclic torsion angles averaging 56.5°.

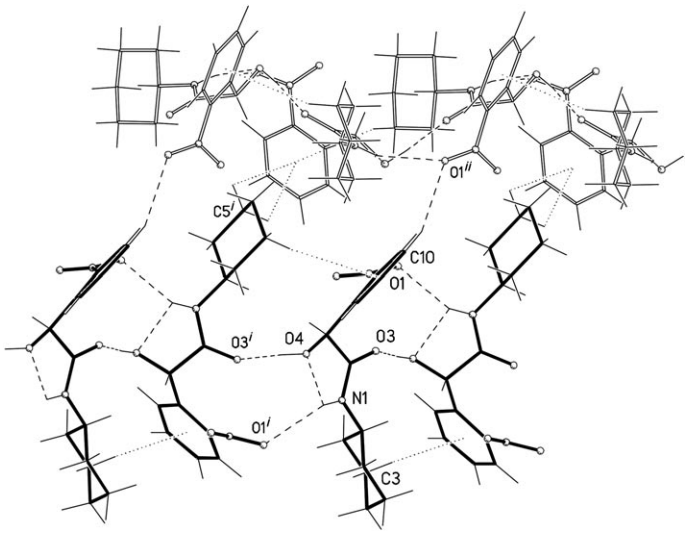


Fig. 2. *Two ribbons* (solid and open lines) *joined by weak C–H···O interactions* (dashed lines) *and bifurcated C–H···π contacts* (dotted lines) *in the crystal lattice of* **3a**. Symmetry codes are given in *Table 5*.

Table 5. *Geometry of Proposed H-Bonds and C–H···O Close Contacts of* **3a**

D–H···A	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
O(4)–H(4)···O(3)^{i}	0.88(2)	1.74(2)	2.618(1)	172(2)
N(1)–H(1*N*)···O(4)	0.85(2)	2.22(2)	2.653(1)	112(2)
N(1)–H(1*N*)···O(1)^{i}	0.85(2)	2.51(2)	3.235(2)	144(2)
C(1)–H(1)···O(3)	0.97(2)	2.49(2)	2.838(2)	101(1)
C(10)–H(10)···O(1)^{ii}	1.02(2)	2.64(2)	3.457(2)	138(2)
C(12)–H(12)···O(4)	0.98(2)	2.28(2)	2.700(2)	105(1)
C(13)–H(13)···O(2)	0.93(2)	2.39(2)	2.920(2)	116(1)

Symmetry codes: *i*, $x + 1/2, -y + 1/2, -z + 1$; *ii*, $-x, y - 1/2, -z + 1/2$.

The crystal packing in **3a** is determined mainly by the H-bonds O–H···O and N–H···O involving the 2-hydroxyacetamide moiety and atom O(1) of the NO_2 group (see *Fig. 3* and *Table 5*), and reveals arrangement of the molecules into ribbons running down the *a*-axis. The structure of the ribbon is additionally stabilized by weak C–H···π contacts (dotted lines in *Fig. 2*) with a H(3*B*)^{i}···ring-centroid(Ph) distance of *ca.* 3.2 Å. Each ribbon is further linked with four adjacent ones *via* interactions C(10)–H(10)···O(1)^{ii} in a manner shown in *Fig. 2* (symmetry code in *Table 5*) giving rise to the three-dimensional network. Additional stabilization of the crystal structure comes from bifurcated C–H···π contacts formed between the adjacent ribbons, with H(5*A*)···ring-centroid(Ph)^{iii} and H(5*B*)···ring-centroid(Ph)^{iii} distances of *ca.* 3.1 and 3.2 Å, respectively (dotted lines in *Fig. 2*; *iii*: $-x, y + 1/2, -z + 3/2$).

Although we have not established the mechanism of the reaction in an experimental manner, a plausible reaction sequence that accounts for the formation

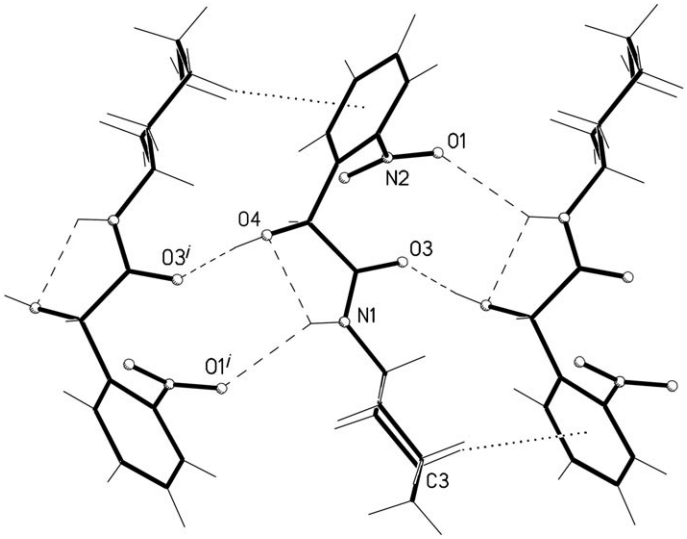
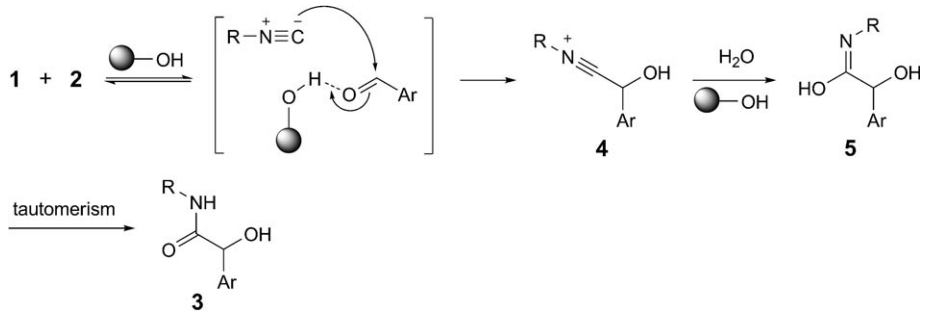


Fig. 3. *The arrangement of* **3a** *molecules within the ribbons running down the* a-*axis.* Intra- and intermolecular H-bonds are shown with dashed lines, C–H $\cdots$ π contacts with dotted lines. The symmetry code is given in *Table 5*.

of **3** is shown in *Scheme 2*. Thus, intermediate **4** was produced by nucleophilic reaction of alkyl isocyanide **1** and electron-poor aromatic aldehyde **2**, followed by nucleophilic attack of H_2O on the nitrilium moiety and production of compound **5**. Finally, tautomerization of **5** leads to the 2-hydroxyacetamide derivatives **3** (*Scheme 2*).

Scheme 2. *Proposed Mechanism for the Preparation of 2-Hydroxyacetamide Derivatives* **3** *in the Presence of Silica Nanoparticles*



The recycling potential of the silica-NP catalyst was studied by coupling cyclohexyl isocyanide and 2-nitrobenzaldehyde in five consecutive cycles. The silica NP could be recycled and reused by separating them from the reaction mixture through centrifugation, frequent washing with EtOH, and drying under vacuum to remove the residual solvent. The results show that the yield of product, after five runs, was only slightly reduced (*Fig. 4*).

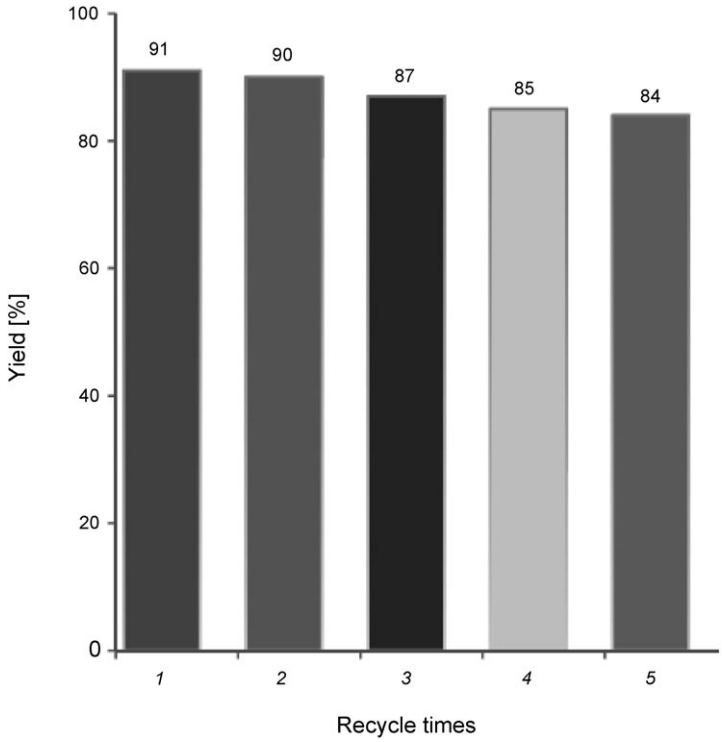


Fig. 4. *Recycle of the catalyst*

Conclusions. – We have developed an efficient route for the one-pot synthesis of 2-hydroxyacetamide derivatives **3** from simple and readily available alkyl isocyanides **1** and electron-poor aromatic aldehydes **2** in the presence of silica NP (*Scheme 1* and *Table 1*). The ease of workup and high yields of products make this procedure a useful addition to modern synthetic methods. Furthermore, this solvent-free reaction has many advantages: reduced pollution, low costs, and simplicity in process and handling. These factors may be important, especially in industry.

This research was supported by the Zanjan University.

Experimental Part

General. Freshly distilled solvents were used throughout, and anh. solvents were dried according to *Perrin* and *Armarego* [26]. The silica-NP samples were characterized with a scanning electron microscope (SEM) (*Philips XL 30*) with gold coating. M.p.: *Electrothermal-9100* apparatus; uncorrected. X-Ray powder diffraction (XRD) measurements: *X'pert* diffractometer of *Philips* company with monochromatized CuK_α radiation. IR Spectra: *Jasco-6300* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-DRX-250-Avance* spectrometer at 250.0 and 62.5 MHz, resp.; $CDCl_3$ or (D_6)DMSO soln.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

General Procedure. Silica NP (0.2 g) were added to a mixture of an electron-poor aromatic aldehyde (1 mmol) and an isocyanide (1 mmol) at r.t., followed by 8 h of stirring. After completion of the reaction,

flash column chromatography (silica gel (powder), petroleum ether/AcOEt 5:2) of the residue gave the 2-hydroxyacetamide derivative.

N-*Cyclohexyl-2-hydroxy-2-(2-nitrophenyl)acetamide* (**3a**): Colorless crystals. M.p. 132–134°. IR: 3388, 3256, 2937, 2858, 1647, 1534, 1449, 1361. ^{1}H-NMR ($CDCl_3$): 0.99–1.92 (2*m*, 5 CH_2 of Chx); 3.67–3.78 (*m*, CH–N of Chx); 4.70 (*s*, OH); 5.53 (*s*, CH); 6.79 (*d*, ^3J(NH,CH) = 6.8, NH); 7.41–7.48 (*m*, H–C(5) of C_6H_4); 7.60–7.62 (*m*, H–C(4), H–C(6) of C_6H_4); 7.89 (*d*, ^3J(H,H) = 7.0, H–C(3) of C_6H_4). ^{13}C-NMR ($CDCl_3$): 24.47, 24.50 (2 $CH_2(\beta)$ of Chx); 25.35 ($CH_2(\gamma)$ of Chx); 32.53, 32.70 (2 $CH_2(\alpha)$ of Chx); 48.64 (CH–N of Chx); 68.53 (CH); 124.52, 128.98, 129.33, 133.84 (4 CH of C_6H_4); 135.46, 148.68 (2 C of C_6H_4); 169.73 (CONH). Anal. calc. for $C_{14}H_{18}N_2O_4$: C 60.42, H 6.52, N 10.07; found: C 60.39, H 6.48, N 10.04.

N-*Cyclohexyl-2-hydroxy-2-(4-nitrophenyl)acetamide* (**3b**): Yellow crystals. M.p. 145–147°. IR: 3367, 3278, 2931, 2857, 1638, 1519, 1451, 1349. ^{1}H-NMR ($CDCl_3$): 0.88–1.82 (2*m*, 5 CH_2 of Chx); 3.64–3.73 (*m*, CH–N of Chx); 3.87 (*s*, OH); 5.13 (*s*, CH); 6.27 (*d*, ^3J(NH,CH) = 6.8, NH); 7.63 (*d*, ^3J(H,H) = 8.3, H–C(2,6) of C_6H_4); 8.20 (*d*, ^3J(H,H) = 8.3, H–C(3,5) of C_6H_4). ^{13}C-NMR ($CDCl_3$): 24.65 (2 $CH_2(\beta)$ of Chx); 25.31 ($CH_2(\gamma)$ of Chx); 32.81 (2 $CH_2(\alpha)$ of Chx); 48.52 (CH–N of Chx); 73.13 (CH); 123.78, 127.35 (4 CH of C_6H_4); 135.40, 148.27 (C of C_6H_4); 169.67 (CONH). Anal. calc. for $C_{14}H_{18}N_2O_4$: C 60.42, H 6.52, N 10.07; found: C 60.38, H 6.47, N 10.03.

N-*Cyclohexyl-2-hydroxy-2-(3-nitrophenyl)acetamide* (**3c**): Yellow crystals. M.p. 143–145°. IR: 3351, 3322, 2938, 2857, 1646, 1525, 1452, 1350. ^{1}H-NMR ($CDCl_3$): 1.12–1.81 (*m*, 5 CH_2 of Chx); 3.64–3.73 (*m*, CH–N of Chx); 3.80 (*s*, OH); 5.12 (*s*, CH); 6.47 (*s*, NH); 7.52–7.59 (*m*, H–C(5) of C_6H_4); 7.77 (*s*, H–C(6) of C_6H_4); 8.14 (*s*, H–C(4) of C_6H_4); 8.30 (*s*, H–C(2) of C_6H_4). ^{13}C-NMR ($CDCl_3$): 24.67 (2 $CH_2(\beta)$ of Chx); 25.31 ($CH_2(\gamma)$ of Chx); 32.79 (2 $CH_2(\alpha)$ of Chx); 48.48 (CH–N of Chx); 72.92 (CH); 121.42, 123.25, 129.55, 132.78 (4 CH of C_6H_4); 141.74, 148.27 (2 C of C_6H_4); 169.98 (CONH). Anal. calc. for $C_{14}H_{18}N_2O_4$: C 60.42, H 6.52, N 10.07; found: C 60.37, H 6.49, N 10.02.

N-*Cyclohexyl-2-(3-formylphenyl)-2-hydroxyacetamide* (**3d**): White oil. IR: 3348, 2931, 2855, 1699, 1653, 1532, 1451. ^{1}H-NMR ($CDCl_3$): 1.13–1.81 (*m*, 5 CH_2 of Chx); 3.59–3.78 (*m*, CH–N of Chx); 4.09 (*s*, OH); 5.07 (*s*, CH); 6.33 (*s*, NH); 7.52 (*t*, ^3J(H,H) = 7.5, H–C(5) of C_6H_4); 7.69 (*d*, ^3J(H,H) = 7.8, H–C(6) of C_6H_4); 7.8 (*d*, ^3J(H,H) = 7.3, H–C(4) of C_6H_4); 7.92 (*s*, H–C(2) of C_6H_4); 9.98 (*s*, CH=O). ^{13}C-NMR ($CDCl_3$): 24.68 (2 $CH_2(\beta)$ of Chx); 25.35 ($CH_2(\gamma)$ of Chx); 32.80 (2 $CH_2(\alpha)$ of Chx); 48.42 (CH–N of Chx); 73.37 (CH); 127.63, 129.40, 129.78, 132.71 (4 CH of C_6H_4); 136.61, 140.41 (2 C of C_6H_4); 170.51 (CONH); 192.11 (CH=O). Anal. calc. for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 68.88, H 7.38, N 5.32.

N-*Cyclohexyl-2-(4-formylphenyl)-2-hydroxyacetamide* (**3e**): White crystals. M.p. 99–101°. IR: 3363, 2933, 2855, 1699, 1632, 1536, 1450. ^{1}H-NMR ((D_6)DMSO): 1.13–1.62 (*m*, 5 CH_2 of Chx); 3.80–3.86 (*m*, CH–N of Chx); 4.99 (*s*, OH); 6.36 (*s*, CH); 7.92 (*s*, NH); 7.61 (*d*, ^3J(H,H) = 8.0, H–C(2,6) of C_6H_4); 7.84 (*d*, ^3J(H,H) = 8.0, H–C(3,5) of C_6H_4); 9.96 (*s*, CH=O). ^{13}C-NMR ((D_6)DMSO): 25.06 (2 $CH_2(\beta)$ of Chx); 25.52 ($CH_2(\gamma)$ of Chx); 32.60 (2 $CH_2(\alpha)$ of Chx); 47.81 (CH–N of Chx); 73.43 (CH); 127.49, 129.67 (4 CH of C_6H_4); 135.79, 148.61 (2 C of C_6H_4); 170.77 (CONH); 193.28 (CH=O). Anal. calc. for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 68.90, H 7.28, N 5.33.

N-*(*tert*-Butyl)-2-hydroxy-2-(3-nitrophenyl)acetamide* (**3f**): Yellow crystals. M.p. 96–98°. IR: 3383, 3118, 2973, 2859, 1648, 1532, 1457, 1349. ^{1}H-NMR ((D_6)DMSO): 1.21 (*s*, *Me*$_3$C); 4.98 (*d*, ^3J(OH,CH) = 5.3, OH); 6.57 (*d*, ^3J(CH,OH) = 5.5, CH); 7.44 (*s*, NH); 7.60 (*t*, ^3J(H,H) = 8.0, H–C(5) of C_6H_4); 7.82 (*d*, ^3J(H,H) = 7.5, H–C(6) of C_6H_4); 8.10 (*d*, ^3J(H,H) = 8.0, H–C(4) of C_6H_4); 8.22 (*s*, H–C(2) of C_6H_4). ^{13}C-NMR ((D_6)DMSO): 28.67 (*Me*$_3$C); 50.71 (Me$_3$*C*NH); 72.64 (CH); 121.27, 122.79, 130.05, 136.53 (4 CH of C_6H_4); 143.87, 147.92 (2 C of C_6H_4); 171.04 (CONH). Anal. calc. for $C_{12}H_{16}N_2O_4$: C 57.13, H 6.39, N 11.10; found: C 57.08, H 6.33, N 11.07.

N-*(*tert*-Butyl)-2-hydroxy-2-(4-nitrophenyl)acetamide* (**3g**): Yellow crystals. M.p. 115–117°. IR: 3390, 3324, 2928, 2859, 1648, 1525, 1458, 1349. ^{1}H-NMR ((D_6)DMSO): 1.22 (*s*, *Me*$_3$C); 4.99 (*s*, OH); 6.43 (*s*, CH); 7.41 (*s*, NH); 7.66 (*d*, ^3J(H,H) = 8.0, H–C(2,6) of C_6H_4); 8.18 (*d*, ^3J(H,H) = 8.0, H–C(3,5) of C_6H_4). ^{13}C-NMR ((D_6)DMSO): 28.76 (*Me*$_3$C); 50.61 (Me$_3$*C*NH); 73.05 (CH); 123.54, 127.94 (4 CH of C_6H_4); 147.21, 149.49 (2 C of C_6H_4); 170.66 (CONH). Anal. calc. for $C_{12}H_{16}N_2O_4$: C 57.13, H 6.39, N 11.10; found: C 57.10, H 6.34, N 11.05.

N-*(*tert*-Butyl)-2-(3-formylphenyl)-2-hydroxyacetamide* (**3h**): White oil. IR: 3380, 3226, 2969, 1703, 1650, 1540, 1457. ^{1}H-NMR ($CDCl_3$): 1.32 (*s*, *Me*$_3$C); 3.88 (*s*, OH); 4.99 (*s*, CH); 6.11 (*s*, NH); 7.53 (*t*, ^3J(H,H) = 7.5, H–C(5) of C_6H_4); 7.68 (*d*, ^3J(H,H) = 7.8, H–C(6) of C_6H_4); 7.84 (*d*, ^3J(H,H) = 7.3, H–C(4) of C_6H_4); 7.92 (*s*, H–C(2) of C_6H_4); 10.00 (*s*, CH=O). ^{13}C-NMR ($CDCl_3$): 28.62 (*Me*$_3$C); 51.60 (Me$_3$*C*NH); 73.59 (CH); 127.64, 129.49, 129.81, 132.70 (4 CH of C_6H_4); 136.70, 141.16 (2 C of C_6H_4); 170.44 (CONH); 192.05 (CH=O). Anal. calc. for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95; found: C 66.40, H 7.22, N 5.93.

N-*(*tert*-Butyl)-2-(4-formylphenyl)-2-hydroxyacetamide* (**3i**): White crystals. M.p. 139–141°. IR: 3363, 3263, 2974, 1703, 1649, 1536, 1460. ^{1}H-NMR ($CDCl_3$): 1.31 (*s*, *Me*$_3$C); 3.84 (*s*, OH); 4.99 (*s*, CH); 6.00 (*s*, NH); 7.57 (*d*, ^3J(H,H) = 8.0, H–C(2,6) of C_6H_4); 7.88 (*d*, ^3J(H,H) = 8.0, H–C(3,5) of C_6H_4); 10.01 (*s*, CH=O). ^{13}C-NMR ($CDCl_3$): 28.59 (*Me*$_3$C); 51.68 (Me$_3$*C*NH); 73.77 (CH); 127.22, 130.16 (4 CH of C_6H_4); 136.29, 146.40 (2 C of C_6H_4); 170.10 (CONH); 191.84 (CH=O). IR: 3359, 3259, 2926, 1698, 1648, 1533, 1447, 1209. Anal. calc. for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95, found: C 66.31, H 7.25, N 5.92.

2-Hydroxy-2-(2-nitrophenyl)-N-*(1,1,3,3-tetramethylbutyl)acetamide* (**3j**): Yellow crystals. M.p. 132–134°. IR: 3369, 3163, 2927, 2871, 1654, 1540, 1477, 1347. ^{1}H-NMR ($CDCl_3$): 0.82 (*s*, *Me*$_3$C); 1.36, 1.39 (2*s*, *Me*$_2$CNH); 1.62 (*s*, Me$_3$CC*H*$_2$); 4.75 (*d*, ^3J(OH,CH) = 5.3, OH); 5.43 (*d*, ^3J(CH,OH) = 5.0, CH); 6.76 (*s*, NH); 7.42–7.66 (*m*, 3 CH of C_6H_4); 7.90 (*d*, ^3J(H,H) = 8.0, H–C(3) of C_6H_4). ^{13}C-NMR ($CDCl_3$): 28.87, 29.04 (*Me*$_2$CNH); 31.10 (*Me*$_3$C); 31.42 (Me$_3$*C*); 51.69 (Me$_3$C*C*H$_2$); 55.76 (Me$_2$*C*NH); 67.84 (CH); 124.31, 128.89, 129.32, 134.00 (4 CH of C_6H_4); 135.90, 148.63 (2 C of C_6H_4); 168.93 (CONH). Anal. calc. for $C_{16}H_{24}N_2O_4$: C 62.32, H 7.84, N 9.08; found: C 62.23, H 7.87, N 9.12.

2-Hydroxy-2-(3-nitrophenyl)-N-*(1,1,3,3-tetramethylbutyl)acetamide* (**3k**): Yellow crystals. M.p. 109–111°. IR: 3379, 3247, 2952, 2867, 1654, 1528, 1347. ^{1}H-NMR ((D$_6$)DMSO): 0.83 (*s*, *Me*$_3$C); 1.27 (*s*, *Me*$_2$CNH); 1.63 (*s*, Me$_3$CC*H*$_2$); 5.00 (*d*, ^3J(OH,CH) = 5, OH); 6.49 (*d*, ^3J(CH,OH) = 4.8, CH); 7.32 (*s*, NH); 7.57–7.63 (*m*, H–C(5) of C_6H_4); 7.84 (*d*, ^3J(H,H) = 7.8, H–C(6) of C_6H_4); 8.11 (*d*, ^3J(H,H) = 7.0, H–C(4) of C_6H_4); 8.26 (*s*, H–C(2) of C_6H_4). ^{13}C-NMR ((D$_6$)DMSO): 29.38 (*Me*$_2$CNH); 31.53 (*Me*$_3$C); 31.67 (Me$_3$*C*); 50.93 (Me$_3$C*C*H$_2$); 54.44 (Me$_2$*C*NH); 72.70 (CH); 121.41, 122.63, 129.84, 133.59 (4 CH of C_6H_4); 144.00, 147.83 (2 C of C_6H_4); 170.28 (CONH). Anal. calc. for $C_{16}H_{24}N_2O_4$: C 62.32, H 7.84, N 9.08; found: C 62.26, H 7.80, N 9.04.

2-Hydroxy-2-(4-nitrophenyl)-N-*(1,1,3,3-tetramethylbutyl)acetamide* (**3l**): Yellow crystals. M.p. 111–113°. IR: 3356, 3245, 2943, 2866, 1657, 1523, 1344. ^{1}H-NMR ((D$_6$)DMSO): 0.84 (*s*, *Me*$_3$C); 1.28 (*s*, *Me*$_2$CNH); 1.64 (*s*, Me$_3$CC*H*$_2$); 4.99 (*d*, ^3J(OH,CH) = 5.3, OH); 6.50 (*d*, ^3J(CH,OH) = 5.3, CH); 7.28 (*s*, NH); 7.67 (*d*, ^3J(H,H) = 8.8, H–C(2,6) of C_6H_4); 8.75 (*d*, ^3J(H,H) = 8.0, H–C(3,5) of C_6H_4). ^{13}C-NMR ((D$_6$)DMSO): 29.32 (*Me*$_2$CNH); 31.58 (*Me*$_3$C); 31.69 (Me$_3$*C*); 51.11 (Me$_3$C*C*H$_2$); 54.45 (Me$_2$*C*NH); 73.12 (CH); 123.42, 128.03 (4 CH of C_6H_4); 147.21, 149.34 (2 C of C_6H_4); 170.05 (CONH). Anal. calc. for $C_{16}H_{24}N_2O_4$: C 62.32, H 7.84, N 9.08; found: C 62.27, H 7.81, N 9.02.

2-(3-Formylphenyl)-2-hydroxy-N-*(1,1,3,3-tetramethylbutyl)acetamide* (**3m**): White oil. IR: 3388, 2956, 2874, 1702, 1660, 1532, 1479, 1366. ^{1}H-NMR ($CDCl_3$): 0.88 (*s*, *Me*$_3$C); 1.37 (*s*, *Me*$_2$CNH); 1.65 (*s*, Me$_3$CC*H*$_2$); 3.91 (*s*, OH); 4.98 (*s*, CH); 6.08 (*s*, NH); 7.53 (*t*, ^3J(H,H) = 7.5, H–C(5) of C_6H_4); 7.68 (*d*, ^3J(H,H) = 7.8, H–C(6) of C_6H_4); 7.83 (*d*, ^3J(H,H) = 7.5, H–C(4) of C_6H_4); 7.92 (*s*, H–C(2) of C_6H_4); 10.01 (*s*, CH=O). ^{13}C-NMR ($CDCl_3$): 28.70, 29.00 (*Me*$_2$CNH); 31.31 (*Me*$_3$C); 31.53 (Me$_3$*C*); 52.17 (Me$_3$C*C*H$_2$); 55.59 (Me$_2$*C*NH); 73.67 (CH); 127.67, 129.45, 129.76, 132.68 (4 CH of C_6H_4); 136.65, 140.94 (2 C of C_6H_4); 169.89 (CONH); 192.00 (CH=O). Anal. calc. for $C_{16}H_{24}N_2O_4$: C 70.07, H 8.65, N 4.81; found: C 7.02, H 8.61, N 4.82.

2-(4-Formylphenyl)-2-hydroxy-N-*(1,1,3,3-tetramethylbutyl)acetamide* (**3n**): White oil. IR: 3361, 3279, 2957, 2857, 1702, 1640, 1530, 1366. ^{1}H-NMR ($CDCl_3$): 0.88 (*s*, *Me*$_3$C); 1.36 (*s*, *Me*$_2$CNH); 1.72 (*s*, Me$_3$CC*H*$_2$); 4.25 (*s*, OH); 4.61 (*s*, CH); 6.17 (*s*, NH); 7.54 (*d*, ^3J(H,H) = 8.3, H–C(2,6) of C_6H_4); 7.85 (*d*, ^3J(H,H) = 8.0, H–C(3,5) of C_6H_4); 9.99 (*s*, CH=O). ^{13}C-NMR ($CDCl_3$): 28.92 (*Me*$_2$CNH); 31.32 (*Me*$_3$C); 31.53 (Me$_3$*C*); 52.12 (Me$_3$C*H*$_2$); 55.52 (Me$_2$*C*NH); 73.47 (CH); 127.16, 130.00 (4 CH of C_6H_4); 136.12, 146.41 (2 C of C_6H_4); 169.85 (CONH); 191.92 (CH=O). Anal. calc. for $C_{17}H_{25}NO_3$: C 70.07, H 8.65, N 4.81; found: C 7.10, H 8.60, N 4.77.

N-*Benzyl-2-hydroxy-2-(3-nitrophenyl)acetamide* (**3o**): Yellow oil. IR: 3405, 3262, 2925, 2854, 1648, 1513, 1347. ^{1}H-NMR ((D$_6$)DMSO): 4.24 (*d*, ^3J(H,H) = 6.3, PhC*H*$_2$); 5.14 (*d*, ^3J(OH,CH) = 4.8, OH); 6.71 (*d*, ^3J(CH,OH) = 5, CH); 7.21 (*s*, NH); 7.14–7.22, 8.69–8.74 (2*m*, 5 CH of C_6H_5); 7.57–7.63 (*m*, H–C(5)

of C_6H_4); 7.85 (*d*, ^3J(H,H) = 7.8, H–C(6) of C_6H_4); 8.10 – 8.13 (*d*, ^3J(H,H) = 7.3, H–C(4) of C_6H_4); 8.26 (*s*, H–C(2) of C_6H_4). ^{13}C-NMR ((D$_6$)DMSO): 42.24 (Ph*C*H$_2$); 72.75 (CH); 121.23, 122.90, 130.08, 133.61 (4 CH of C_6H_4); 127.25, 127.48, 128.66 (5 CH of C_6H_5); 139.56 (C of C_6H_5); 143.87, 147.92 (2 C of C_6H_4); 172.11 (CONH). IR: 3371, 3275, 2919, 1653, 1527, 1348. Anal. calc. for $C_{15}H_{14}N_2O_4$: C 62.93, H 4.93, N 9.70; found: C 62.88, H 4.90, N 9.73.

N-*Benzyl-2-hydroxy-2-(4-nitrophenyl)acetamide* (**3p**): Yellow oil. IR: 3401, 2930, 2860, 1657, 1530, 1351. ^{1}H-NMR ((D$_6$)DMSO): 4.22 (*d*, ^3J(H,H) = 6.3, PhC*H*$_2$); 5.12 (*s*, OH); 6.56 (*s*, CH); 7.13 (*s*, NH); 7.15 – 7.25, 8.63 – 8.71 (2*m*, 5 CH of C_6H_5); 7.67 (*d*, ^3J(H,H) = 8.8, H–C(2,6) of C_6H_4); 8.16 (*d*, ^3J(H,H) = 8.8, H–C(3,5) of C_6H_4). ^{13}C-NMR ((D$_6$)DMSO): 42.30 (Ph*C*H$_2$); 73.14 (CH); 123.57, 127.98 (4 CH of C_6H_4); 127.15, 127.56, 128.63 (5 CH of C_6H_5); 139.79 (C of C_6H_5); 147.01, 149.22 (2 C of C_6H_4); 171.60 (CONH). Anal. calc. for $C_{15}H_{14}N_2O_4$: C 62.93, H 4.93, N 9.79; found: C 62.88, H 4.91, N 9.75.

X-Ray Crystal-Structure Determination of **3a** (*Table 3* and *Fig. 1*)[1]. Colorless single crystals of **3a** were obtained from its light petroleum ether/AcOEt 3 : 1 soln. by slow evaporation at 20° over 2 d. The colorless single crystals were filtered, washed with cold light petroleum ether/AcOEt 3 : 1, and dried at r.t. (m.p. 132.0 – 134.0°). The crystallographic measurement was performed on a κ-geometry *Xcalibur-PX* automated four-circle diffractometer with graphite-monochromatized MoK_α radiation (λ 0.71073 Å). The data for the crystal were collected at 86(2) K by using an *Oxford-Cryosystems* cooler. Data collection, cell refinement, and data reduction and analysis were carried out with the *Xcalibur-PX* software (*Oxford Diffraction Ltd.*): CrysAlis CCD and CrysAlis RED, resp. [27]. The data were corrected for *Lorentz* and polarization effects. The structure was solved by direct methods with the SHELXS-97 program [28], and refined by a full-matrix least-squares technique by using SHELXL-97 [28] with anisotropic thermal parameters for all non-H atoms. All H-atoms were found in difference *Fourier* maps and were refined isotropically. The absolute configuration could not be established unambiguously by anomalous dispersion effects (the anomalous scattering power was too small, as the heaviest atom is O-atom). Therefore, the choice of enantiomer was made relying on the lower *Flack* parameter (close to 0), and then, in the final refinement cycles, the *Friedel* pairs were averaged by using the MERG 4 instruction. All figures were made with the XP program [29]. *Cremer* and *Pople* puckering parameters [25] were calculated with the PLATON program [30]. A summary of the conditions for the data collection and the structure refinement parameters are given in *Table 3*.

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[1]) CCDC-789360 contains the supplementary crystallographic data for **3a**. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk.

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