Three-Component Reaction of Isocyanides and 2-Formylbenzoic Acid with Dibenzylamine Catalyzed by Silica Nanoparticles under Solvent-Free Conditions

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Reaction of an isocyanide with an iminium ion intermediate, formed by reaction between 2-formylbenzoic acid and dibenzylamine in the presence of silica nanoparticles (silica NP, *ca.* 42 nm) proceeds smoothly at room temperature to afford isocoumarin (=1*H*-2-benzopyran-1-one) derivatives in high yields (*Scheme 1* and *Table 1*).

Introduction. – Recently, multicomponent condensation reactions have become one of the most powerful methods for the synthesis of small-molecule libraries, due to the fact that products are formed in a single step by simultaneous reactions of several reagents, and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component [1–6].

In recent years, nanoparticles (NP) have attracted tremendous attention in catalysis because of their improved efficiency under mild and environmentally benign conditions in the context of ecological (Green) synthesis [7][8]. Due to their enormously large and highly reactive surface area, NP have potential to exhibit superior catalytic activity in comparison to bulk counterparts [9][10].

In this article, we wish to report a simple and practical procedure for the preparation of isocoumarin (=1*H*-2-benzopyran-1-one) derivatives through a multi-component condensation reaction (MCR) in the presence of silica nanoparticles (silica NP, *ca.* 42 nm).

Results and Discussion. – As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds [11–32], we report here a simple, one-pot, three-component reaction between isocyanides **3**, dibenzylamine (**2**), and 2-formylbenzoic acid (**1**) in the presence of silica NP at room temperature, leading after 5 h to isocoumarin derivatives **4** (*Scheme 1* and *Table 1*).

Silica nanoparticles were prepared by thermal decomposition of rice hulls [33]. The results from X-ray diffraction (XRD) showed that the sample was silica NP as indicated by broadened peaks around $2\theta = 22^\circ$ (*Fig. 1*). The morphology and grain size of the silica NP was investigated by scanning electron microscopy (SEM) (*Fig. 2*).

Silica NP were found to catalyze the synthesis of isocoumarin derivatives **4** from 2-formylbenzoic acid (**1**), isocyanides (**3**), and dibenzylamine (**2**) under solvent-free conditions with high efficiency (*Table 1*). We also used silica gel powder (*Merck*)

Scheme 1. *Three-Component Synthesis of Isocoumarin Derivatives* **4** *in the Presence of Silica Nanoparticles* (NP). See *Table 1* for R.

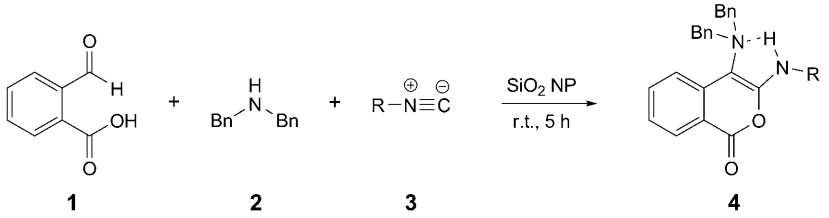


Table 1. *SiO_2 NP-Promoted Synthesis of Isocoumarin Derivatives* **4**[a])

4	R	Yield [%][b])
a	*t*-Bu	97
b	cyclohexyl	94
c	1,1,3,3-tetramethylbutyl	97
d	Bn	96
e	2,6-dimethylphenyl	70

[a]) See *Scheme 1*; 0.3 g of SiO_2 NP/mmol reactants were applied. [b]) Yield of isolated **4**.

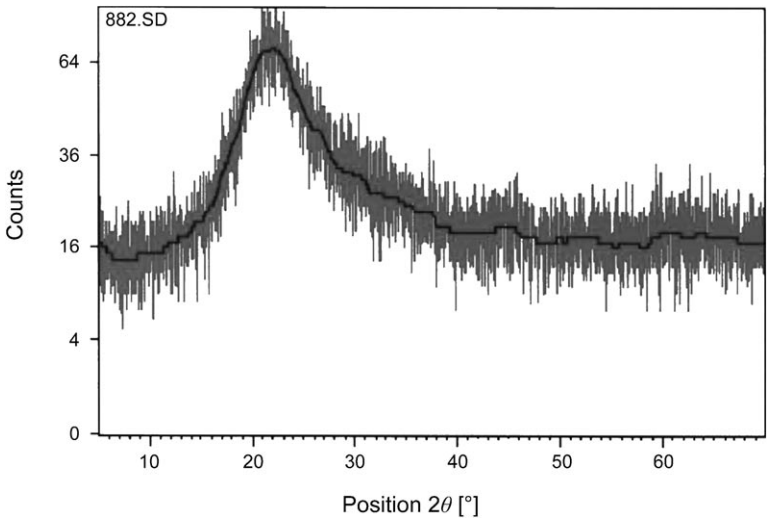


Fig. 1. *X-Ray diffraction pattern of the synthesized silica nanoparticles*

instead of silica NP in this reaction, but increase of reaction times and decrease of isocoumarin yields were observed (*Table 2*). The use of just 0.3 g of silica NP per mmol of reactants was sufficient to push the reaction forward. Higher amounts of silica NP (0.4 g) did not improve the result to a great extent (*Table 2*, *Entries 5–7*).

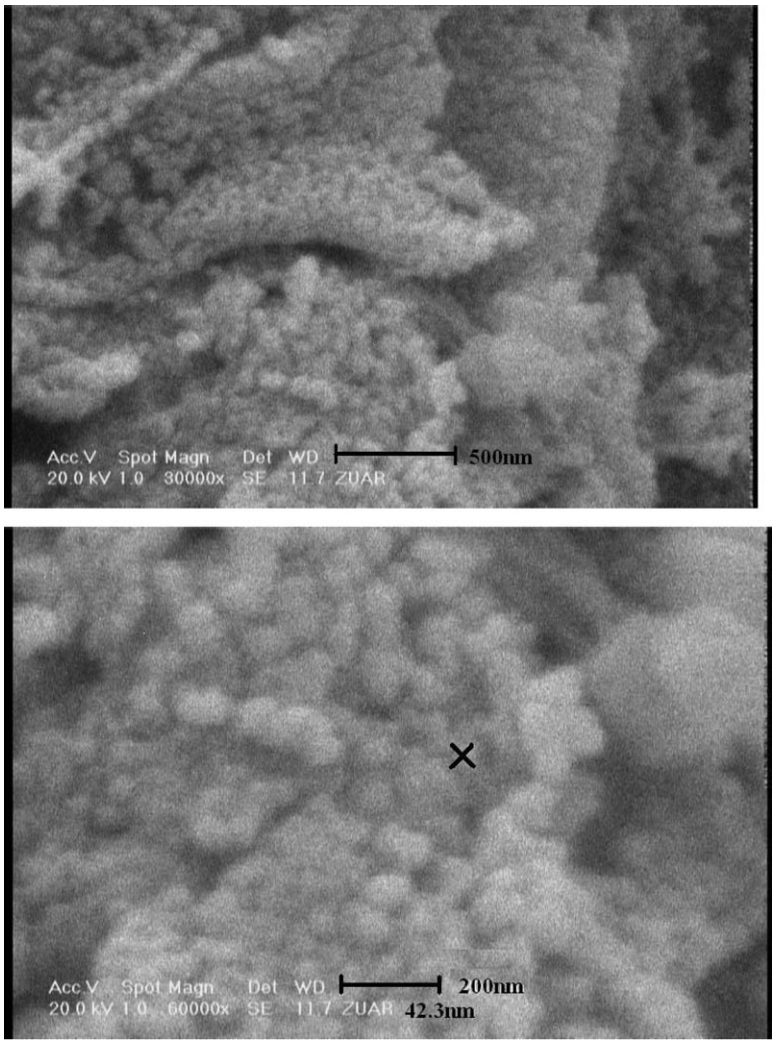


Fig. 2. *SEM of the synthesized silica nanoparticles*

To investigate the effects of other reaction media in this reaction, we carried out the described condensation of **1**–**3** in CH_2Cl_2, H_2O, and solvent-free (neat) systems without silica (*Table 2*, *Entries 1–3*). The reactions proceeded with dibenzylamine in fairly low to moderate yields. We also used other secondary amines (diethylamine, pipyridine, and benzyl(methyl)amine) instead of dibenzylamine in this reaction in the presence of CH_2Cl_2, H_2O, silica NP, and silica gel powder, and also in solvent-free and catalyst-free (neat) systems, but in all cases, several products were observed (based on TLC investigations). So, the reactions with other than dibenzylamine have no synthetic value.

Table 2. *Synthesis of Isocoumarin* **4a** *from 2-Formylbenzoic Acid, Dibenzylamine*[a]*), and* tert-*Butyl Isocyanide under Various Conditions*

Entry	Catalyst[b]) or solvent	Temp [°]	Time [h]	Yield [%][c])
1	CH_2Cl_2	r.t.	12	30
2	H_2O	r.t.	12	57
3	neat	r.t.	12	35
4	silica gel powder (0.3 g; *Merck*)	r.t.	12	47
5	SiO_2 NP (0.2 g)	r.t.	5	88
6	SiO_2 NP (0.3 g)	r.t.	5	97
7	SiO_2 NP (0.4 g)	r.t.	5	97

[a]) We also used other secondary amines (diethylamine, pipyridine, and benzyl(methyl)amine) instead of dibenzylamine in these reactions, but in all cases, several products were observed (based on TLC investigations). So, this reactions have no synthetic value. [b]) Amount of SiO_2 catalyst per mmol of reactants in parentheses. [c]) Yields of isolated **4a**.

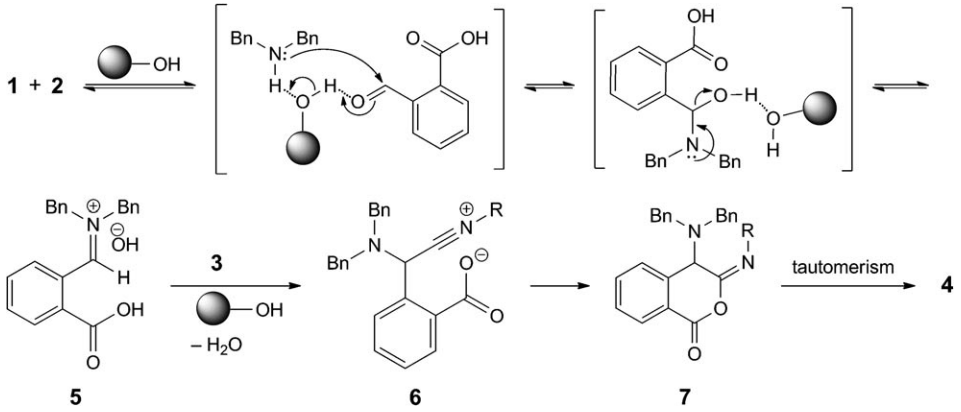
The structures of compounds **4a**–**4e** were deduced from their IR, ^{1}H- and ^{13}C-NMR, and mass spectra. For example, the IR spectrum (KBr) of **4a** showed a strong absorption at 3344 cm^{-1} in accordance with the presence of an NH group in the molecule. The ^{1}H-NMR spectrum ($CDCl_3$) of **4a** consisted of a *s* for the Me groups (Me_3C, δ(H) 1.08), an *AB* system for the two PhCH_2 groups (δ(H) 4.17 and 4.25, $^2J_{AB} = 12.6$ Hz), indicating strong intramolecular H-bonding in the molecule (*Scheme 1*), an amine H-atom (δ(H) 5.22) which was exchangeable with D_2O, two *m*s for the aromatic H-atoms (δ(H) 7.06–7.34 and 7.43–7.64), and one *d* for H–C(8) (δ(H) 8.13 ($^3J = 8.0$ Hz)). The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 16 distinct resonances, the partial assignment of these resonances is given in the *Exper. Part*. The ^{1}H- and ^{13}C-NMR spectra of compounds **4b**–**4e** were similar to those of **4a**, except for the aromatic moieties and the alkyl groups which exhibited characteristic signals with appropriate chemical shifts.

Although we have not established the mechanism of the reaction in an experimental manner, a plausible reaction sequence that accounts for the formation of **4** is shown in *Scheme 2*. Thus, condensation of 2-formylbenzoic acid (**1**) and dibenzylamine (**2**) would give the iminium ion intermediate **5**, which would react with the alkyl isocyanide **3** to afford intermediate **6**. This intermediate would cyclize to lactone **7**. Tautomerization of **7** could then lead to the formation of the isocoumarin derivatives **4**.

It may be speculated that the polar amphoteric surface (OH groups of the silica NP) facilitates the interaction of adsorbed weak acidic and basic components due to stabilization of the corresponding transition states and intermediates by H-bonding. This interaction with the neighboring silanol groups is shown in *Scheme 2* for the first reaction step. Participation of two proximate silanol groups (one as a H-bond donor and the other as a H-bond acceptor) in the reaction mechanism also seems to be plausible.

Conclusions. – We have developed an efficient route for the one-pot synthesis of isocoumarin derivatives **4** from simple and readily available isocyanides **3**, dibenzyl-

Scheme 2. *Proposed Mechanism for the Formation of Isocoumarins* **4** *in the Presence of Silica Nanoparticles* (NP)



amine (**2**), and 2-formylbenzoic acid (**1**) in the presence of silica NP. The ease of workup and high yields of products make this procedure a useful tool of modern synthetic methods.

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Experimental Part

General. Freshly distilled solvents were used throughout, and anh. solvents were dried according to *Perrin* and *Armarego* [34]. IR Spectra (KBr): *Mattson-1000* FT-IR spectrophotometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-250* spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS: *Finnigan-MAT-8430* mass spectrometer operating at an ionization potential of 20 eV; in *m*/*z* (rel. %). Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

General Procedure. Silica nanoparticles (0.3 g) were added to a mixture of 2-formylbenzoic acid (**1**; 0.15 g, 1 mmol), dibenzylamine (**2**; 0.19 ml, 1 mmol), and *tert*-butyl isocyanide (**2a**; 0.12 ml, 1 mmol) at r.t., followed by 5 h of stirring. After completion of the reaction, flash column chromatography (petroleum ether/Et_2O 10:1) of the residue gave **4a**.

*3-[(*tert*-Butyl)amino]-4-(dibenzylamino)-1*H*-2-benzopyran-1-one* (**4a**): Yellow oil. IR: 3340, 2963, 1751, 1673, 1475. ^{1}H-NMR: 1.08 (*s*, Me_3C); 4.17, 4.25 (*AB*, $^2J_{AB}$ = 12.6, 2 PhCH_2); 5.22 (br. *s*, NH, exchanged by D_2O); 7.06–7.34 (*m*, 2 C_6H_5); 7.43–7.64 (*m*, H–C(5), H–C(6), H–C(7)); 8.13 (*d*, ^3J = 8.0, H–C(8)). ^{13}C-NMR: 29.49 (Me_3C); 51.40 (Me_3*C*NH); 57.99 (2 Ph*C*H_2); 99.41, 114.54, 140.88, 157.39 (4 C of isoc.); 119.60, 121.62, 131.09, 134.32 (4 CH of isoc.); 127.32, 128.37, 129.34 (10 CH of 2 Ph); 139.44 (2 C_{ipso} of 2 Ph); 160.79 (C(1)=O). EI-MS: 409 (5), 328 (13), 223 (54), 149 (19), 132 (15), 104 (24), 91 (100), 57 (19). Anal. calc. for $C_{27}H_{28}N_2O_2$: C 78.61, H 6.84, N 6.79; found: C 78.55, H 6.80, N 6.73.

*3-(Cyclohexylamino)-4-(dibenzylamino)-1*H*-2-benzopyran-1-one* (**4b**): Yellow oil. IR: 3407, 2930, 1738, 1615, 1484. ^{1}H-NMR: 1.04–1.6 (2*m*, 5 CH_2 of Chx); 3.28–3.32 (*m*, CH–N of Chx); 4.17, 4.25 (*AB*, $^2J_{AB}$ = 12.7, 2 PhCH_2); 4.96 (*d*, ^3J = 8.5, NH, exchanged by D_2O); 7.06–7.35 (*m*, 2 C_6H_5); 7.41–7.63 (*m*, H–C(5), H–C(6), H–C(7)); 8.12 (*d*, ^3J = 8.0, H–C(8)). ^{13}C-NMR: 24.57 (2 *C*H_2(β) of Chx); 25.44 (*C*H_2(γ) of Chx); 33.45 (2 *C*H_2(α) of Chx); 49.32 (CH–N of Chx); 58.00 (2 Ph*C*H_2); 99.14, 114.65, 141.22, 157.35 (4 C of isoc.); 119.65, 121.57, 131.12, 134.41 (4 CH of isoc.); 127.30, 128.38, 129.26 (10 CH of 2 Ph); 139.44 (2 C_{ipso} of 2 Ph); 161.02 (C(1)=O). EI-MS: 420 (5), 347 (7), 328 (6), 196 (11), 104 (11), 91 (100), 65 (7). Anal. calc. for $C_{29}H_{30}N_2O_2$: C 79.42, H 6.89, N 6.39; found: C 79.36, H 6.83, N 6.35.

*4-(Dibenzylamino)-3-[(1,1,3,3-tetramethylbutyl)amino]-1*H*-2-benzopyran-1-one* (**4c**): Yellow oil. IR: 3354, 2949, 1772, 1691, 1476. ^{1}H-NMR: 0.86 (*s*, *Me*$_3$C); 1.04 (*s*, C(*Me*)$_2$NH); 1.52 (*s*, Me$_3$CC*H*$_2$); 4.17, 4.26 (*AB*, $^2J_{AB}$ = 12.9, 2 PhC*H*$_2$); 5.23 (*s*, NH, exchanged by D$_2$O); 7.06–7.37 (*m*, 2 C$_6$H$_5$); 7.41–7.63 (*m*, H–C(5), H–C(6), H–C(7)); 8.14 (*d*, ^3J = 8.0, H–C(8)). ^{13}C-NMR: 30.06 (C(*Me*)$_2$NH); 31.38 (*Me*$_3$C); 31.64 (Me$_3$*C*); 52.53 (Me$_3$C*C*H$_2$); 55.22 (*C*(Me)$_2$NH); 58.02 (2 Ph*C*H$_2$); 99.89, 114.40, 140.19, 157.30 (4 C of isoc.); 119.66, 121.54, 131.08, 134.27 (4 CH of isoc.); 127.38, 128.44, 129.33 (10 CH of 2 Ph); 139.41 (2 C$_{ipso}$ of 2 Ph); 160.63 (C(1)=O of isoc.). EI-MS: 426 (2), 328 (5), 223 (63), 149 (52), 105 (16), 91 (100), 57 (41). Anal. calc. for $C_{31}H_{36}N_2O_2$: C 79.45, H 7.74, N 5.98; found: C 79.38, H 7.71, N 5.93.

*3-(Benzylamino)-4-(dibenzylamino)-1*H*-2-benzopyran-1-one* (**4d**): Yellow oil. IR: 3365, 2919, 1750, 1677, 1453. ^{1}H-NMR: 4.02 (*d*, ^3J = 6.25, C*H*$_2$NH); 4.22 (*s*, 2 PhC*H*$_2$); 5.22 (*t*, ^3J = 6.2, NH, exchanged by D$_2$O); 7.02–7.32 (*m*, 3 C$_6$H$_5$); 7.39–7.64 (*m*, H–C(5), H–C(6), H–C(7)); 8.13 (*d*, ^3J = 8.0, H–C(8)). ^{13}C-NMR: 45.40 (CH$_2$NH); 57.95 (2 Ph*C*H$_2$); 100.11, 115.03, 140.92, 156.15 (4 C of isoc.); 120.02, 122.31, 131.17, 134.52 (4 CH of isoc.); 127.33, 127.36, 127.39, 128.37, 128.53, 129.17 (15 CH of 3 Ph); 139.44, 138.28 (3 C of 3 Ph); 160.74 (C(1)=O of isoc.). EI-MS: 328 (16), 222 (41), 196 (15), 132 (6), 104 (12), 91 (100), 77 (5). Anal. calc. for $C_{30}H_{26}N_2O_2$: C 80.69, H 5.87, N 6.27; found: C 80.63, H 5.82, N 6.20.

*4-(Dibenzylamino)-3-[(2,6-dimethylphenyl)amino]-1*H*-2-benzopyran-1-one* (**4e**): Yellow oil. IR: 3357, 2915, 1743, 1644, 1465. ^{1}H-NMR: 1.80 (*s*, 2 *Me*); 4.32, 4.39 (*AB*, $^2J_{AB}$ = 13.0, 2 PhC*H*$_2$); 5.61 (*s*, NH, exchanged by D$_2$O); 6.99–7.33 (2*m*, 13 arom. H); 7.42–7.64 (*m*, H–C(5), H–C(6), H–C(7)); 8.15 (*d*, ^3J = 8.2, H–C(8)). ^{13}C-NMR: 18.18 (*Me*$_2$C$_6$H$_3$); 57.96 (2 Ph*C*H$_2$); 99.81, 116.54, 139.09, 155.69 (4 C of isoc.); 120.28, 122.48, 131.28, 134.47 (4 CH of isoc.); 120.12, 127.56, 128.16, 128.64, 129.27 (13 arom. CH); 126.66, 136.10, 138.44 (5 arom. C); 160.85 (C(1)=O of isoc.). Anal. calc. for $C_{31}H_{28}N_2O_2$: C 80.84, H 6.13, N 6.08; found: C 80.77, H 6.08, N 6.02.

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