[1] a) *Molecular Similarity in Drug Design* (Ed.: P. M. Dean), Chapman & Hall, Glasgow, **1995**; b) G. Schneider, W. Schrödl, G. Wallukat, J. Müller, E. Nissen, W. Rönspeck, P. Wrede, R. Kunze, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12179–12184; c) P. Willett, J. M. Barnard, G. M. Downs, *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 983–996.

[2] a) G. W. Milne, M. C. Nicklaus, S. Wang, *SAR QSAR Environ. Res.* **1998**, *9*, 23–38; b) H. Briem, I. D. Kuntz, *J. Med. Chem.* **1996**, *39*, 3401–3408.

[3] a) J. Sadowski, J. Gasteiger, *Chem. Rev.* **1993**, *93*, 2567–2581; b) R. S. Bohacek, C. McMartin, *Curr. Opin. Chem. Biol.* **1997**, *1*, 157–161.

[4] a) R. D. Brown, Y. C. Martin, *SAR QSAR Environ. Res.* **1998**, *8*, 23–39; b) H. Matter, *J. Med. Chem.* **1997**, *40*, 1219–1229.

[5] G. Schneider, P. Wrede, *Prog. Biophys. Mol. Biol.* **1998**, *70*, 175–222, and references therein.

[6] a) G. Moreau, P. Broto, *Nouv. J. Chim.* **1980**, *4*, 757–764; b) M. Wagener, J. Sadowski, J. Gasteiger, *J. Am. Chem. Soc.* **1995**, *117*, 7769–7775; c) S. Anzali, W. W. K. R. Mederski, M. Osswald, D. Dorsch, *Bioorg. Med. Chem. Lett.* **1997**, *8*, 11–16; d) D. D. Jones, *J. Theor. Biol.* **1975**, *50*, 167–183.

[7] M. Vieth, J. D. Hirst, C. L. Brooks III, *J. Comput. Aided Mol. Des.* **1998**, *12*, 563–72.

[8] a) C. Kettner, E. Shaw, *Methods Enzymol.* **1981**, *80*, 824–826; b) P. D. Grootenhuis, M. Karplus, *J. Comput. Aided Mol. Des.* **1996**, *10*, 1–10.

[9] a) S. I. Ertel, E. A. Ertel, *Trends Pharmacol. Sci.* **1997**, *18*, 37–42; b) D. Sarsero, T. Fujiwara, P. Molenaar, J. A. Angus, *Br. J. Pharmacol.* **1998**, *125*, 109–119.

[10] The cloned T-type Ca^{2+} channel was expressed in HEK293 cells, and the inhibition by the compounds was monitored using a fluorescence assay. T. Giller, unpublished results.

[11] J. Qar, J. P. Galizzi, M. Fosset, M. Lazdunski, *Eur. J. Pharmacol.* **1987**, *141*, 261–268.

[12] D. R. Liu, P. G. Schultz, *Angew. Chem.* **1999**, *111*, 36–56; *Angew. Chem. Int. Ed.* **1999**, *38*, 36–54.

Cascade Reactions in Quantitative Solid-State Syntheses[**]

Gerd Kaupp,[*] Jens Schmeyers, Axel Kuse, and Adnan Atfeh[*]

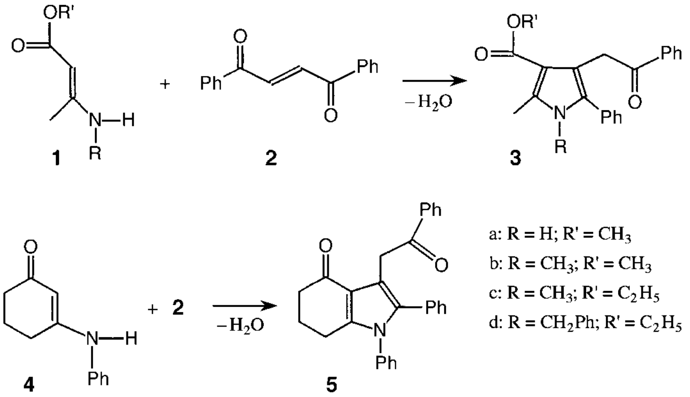
Solvent-free reactions of solids with solids profit from crystal packing effects and are usually highly selective.[1, 2] In contrast to gas–solid reactions[3] no multistep syntheses are known in this field. We report herein on a one-pot synthesis of highly substituted pyrroles (see Scheme 1), which gives moderate yields in solution, but quantitative yields in the solid–solid variant at much lower temperatures, although at least four reaction steps are required in these reactions, not counting proton transfers from N and O. Such reaction cascades[4] have not yet received due recognition in academic teaching, because some particularly elegant examples, which exhibit environmentally friendly and resource-saving behavior due to the lack of workup requirements for intermediates, and which use generally accessible starting materials,[5] were not mentioned in the leading reviews.[6] Rather, the complexity of the starting materials in these reviews require complicated multistep syntheses and thus question both sustainability and broader applications. The execution of the present cascade reactions in the absence of liquid phases avoids product workup because of the 100% yield and is thus truely resource-saving and environmentally friendly.

If the primary or secondary enamine esters **1a–d** or the enamine ketone **4** are treated with *trans*-1,2-dibenzoylethene (**2**) in solution or in a ball-mill without liquid phase, the pyrroles **3** or indole **5** are obtained in moderate or quantitative yields (Table 1), despite the multistep course of reaction (Scheme 1). A thermal after-treatment is only required in the case of **3c** in order to complete the elimination of water (from **8c**, see Scheme 2).

Table 1. Reactions of **1** and **4** with **2** to give **3** and **5**, respectively.

Compound	M.p. [°C] (starting material)	Yield [%] in solution	Yield [%] in crystal	M.p. [°C] (product)	Milling time [h] (T [°C])
1a	81–83	68	100	144–146	3 (25)
1b	67–68	81	100	152	3 (25)
1c	1–2	78[a]	100[a]	122–124	3 (−20)
1d	21	55	100	130–131	3 (0)
4	182	46	100	240–241	3 (25)

[a] After short heating (150 °C) of the 1:1 mixture (78%; solution) or 2:3 mixture (solid) of **3c** and **8c**.



Scheme 1. One-pot synthesis of pyrrole derivatives from easily accessible starting materials.

The complex cascade reactions are remarkable in view of their high selectivity (Table 1) and apparently broad versatility.[7] The constitution of the compounds **3** and **5** is derived from analytical and spectroscopic data.[8] The neighborhood of the phenyl group to the pyrrole-N atom becomes evident from the $\delta(^{13}C)$ values of C4 and C3 in **3b** (C2 and C3 in **5**), which were determined to be 110.1 and 115.1 (114.2 and 119.2). These values correspond much better to the calculated chemical shifts[9] of 112.7 and 117.9 (117.4 and 120.0) than those of the isomeric structure in which the phenyl and benzoylmethyl groups are exchanged: 106.5 and 124.7 (127.5

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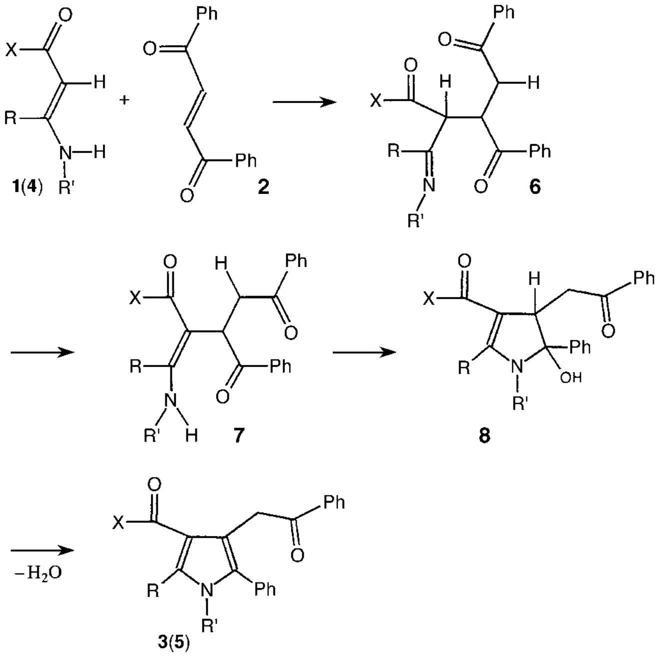
and 126.8). The correspondence with the expectations is excellent. The C–C bond formation is largely preferred over any N–C reaction.

The most reasonable reaction course by four sequential steps is formulated in Scheme 2. After an initial vinylogous Michael addition (including hydrogen transfer) to give **6** and imine/enamine rearrangement to give **7**, the amino group formed adds to the more favorably situated carbonyl function leading to the formation of a five-membered ring to give **8**, from which the pyrrole **3** is obtained by elimination of water.



Scheme 2. Cascade reactions to give **3** (**5**) with four discrete sequential reaction types.

An analogous mechanism can be assumed for **5** starting from **4**. Both, the orientational specificity (an initial Michael addition of the enamine nitrogen, cyclizing addition of the enamine double bond, rearrangement to the enamine, and elimination of water would exchange the positions of phenyl and benzoylmethyl groups in **3** and **5**) and the same preference in solution and in the crystal are remarkable. The moderate yields in solution, which are also influenced by the necessary workup procedures, are sharply contrasted by the quantitative yields of the solid–solid reactions given in Table 1. The peculiarity of slower dehydration for **3c** is found in both media.

As might have been expected, the solid-state reaction cascades succeed at considerably lower temperatures, because of the lack of weakening of the reactivities by solvation, if the crystal lattices do not impede the necessary molecular movements.[3] The basic mechanistic understanding of solid–solid reactions was established by atomic force microscopy (AFM) and scanning near-field optical microscopy (SNOM): The experimentally found far-reaching molecular movements that occur in the crystals give rise to clearly distinguishable phase rebuilding, phase transformation, and crystal disintegration in the reaction zone of single-step reactions.[3, 10] In the case of reaction cascades the conditions are more complicated because of the interaction of numerous physical and chemical processes, and indeed, mechanical help is required in the present cases. Thus, no reaction is detected if finely ground powders of **2** and **4** are mixed and stored, and even the AFM analysis[3] indicates the lack of surface changes of single crystals of **4** (or **2**) with finely ground dusts **2** (or **4**; strongly aggregated grains of ca. 1 μm in diameter) in the absence of mechanical treatment. Thus, after the mixtures had been left to stand for four days, and the dust was subsequently blown away, clearly resolved molecular terraces were not removed and no significant change whatsoever was detected on the main faces of **4** (or **2**). No opacity was observed, also on the other faces. Such behavior points to difficulties with the phase rebuilding step, which are overcome by using a ball-mill. The continuous mechanical treatment creates new contacts over and over again between the reacting crystals and it is assumed that it is also helpful for promoting the intramolecular reactions that follow by generating reactive conformers of the intermediate products. These interpretations are supported by the unusually long reaction times of 3 h in these cases. These unusual observations are further elucidated by the evaluation of the known crystal structures of **2**[11] and **4**.[12] The molecules **2** pack densely in successive layers that interlock slightly (Figure 1). Such packing permits cooperative movements of extended molecules in the crystal lattice at best, but not of adduct molecules from **4** and **2**. Furthermore, the packing of **4** (Figure 2) does not permit molecular movements underneath its surface.

Unlike previously studied solid–solid reactions,[2, 3, 10] in which molecular movements were detected in the crystal (reaction zone), we find here the interesting feature that efficient mechanical help apparently gives rise to a surface reaction that proceeds molecular layer by molecular layer in acceptable time and leads to a quantitative reaction. Figures 1 and 2 indicate that easily detachable surface molecules of **2**, which are readily accessible on (001) at the ends of the layers,

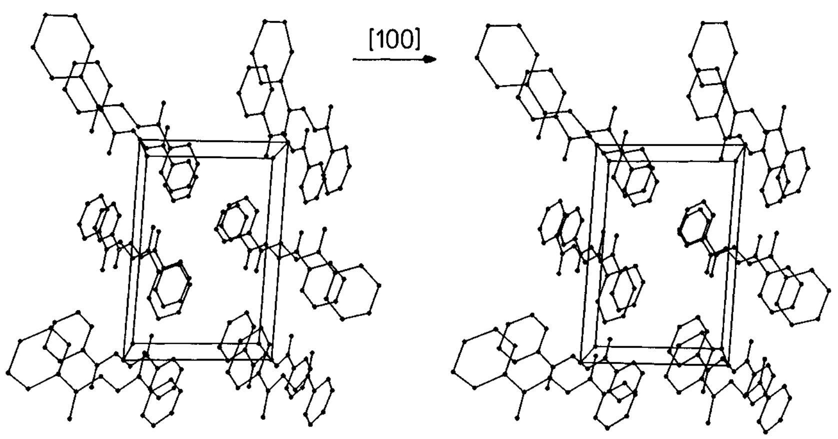


Figure 1. Stereoscopic perspective representation of the crystal packing of **2** ($P2_1/c$) on (010); the layers from bottom to top that are parallel to (100) show the molecules in two orientations that are tilted by 85°; the hydrogens are omitted for clarity; the (001) face is on top.

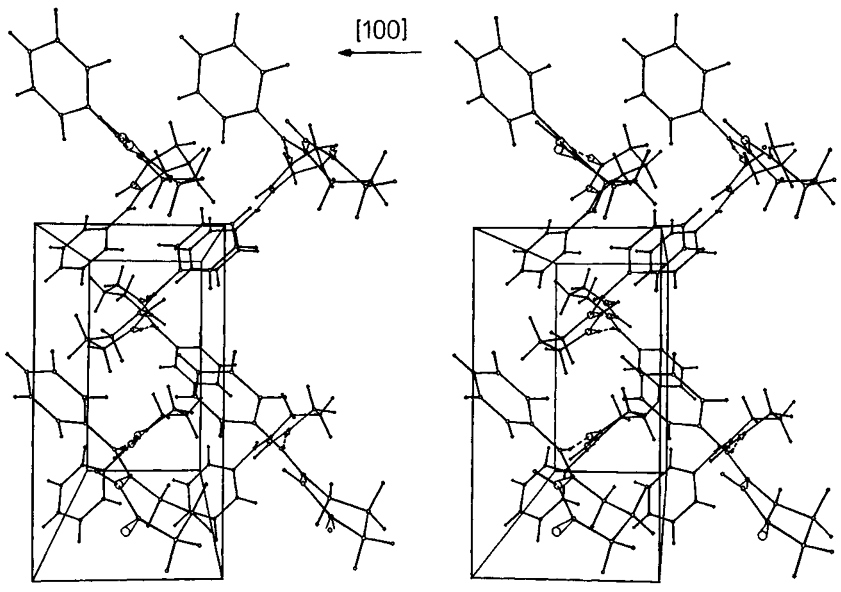
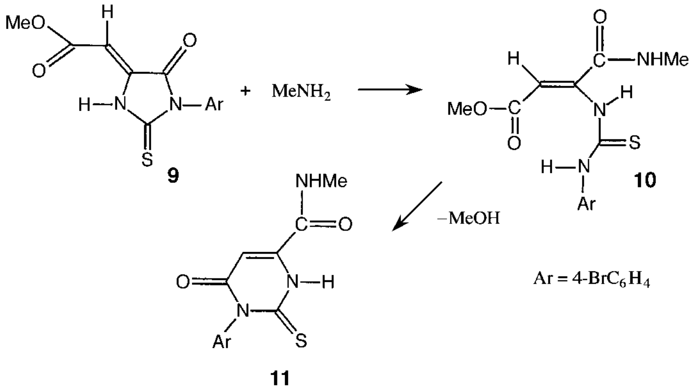


Figure 2. Stereoscopic perspective representation of the crystal packing of **4** ($P2_1/c$) on (001) with marked C=O and C=C double bonds and (dotted) hydrogen bonds [N(H)O distance: 2.851 Å]; the hydrogen-bonded molecular chains are three-dimensionally interlocked; the enamine ketone double bond of the surface molecules in front is sterically shielded.

move to the hydrogen-bridged reaction partner **4** and react with the slightly shielded enamine ketone double bond. Thereafter, the product molecules must detach from the surface of the crystal **4** by breakage of their hydrogen bond, in order to release further reactive molecules at the surface. According to microscopic inspection these processes occur in the ball-mill (mortars and pestles are inefficient here) at 1 μm grains. In view of the recent mechanistic experiences[3, 10] amorphous product layers would be impeding. We therefore assume that immediate product crystallization and the absence of stable mixed crystals are additional requirements for the reactivity.

In contrast to the previously studied solid-state reactions the present examples cannot be predicted from the crystal structures. Nevertheless, the new mechanism is of considerable importance: it shows that even solid–solid reactions that do not appear promising from crystal structure considerations or that failed previously should be tried in efficient ball-mills, the advantages of which are evidently not restricted to the comfortable handling of sensitive materials.[10]



Scheme 3. Transformation of the thiohydantoin **9** to give the thioorotic acid amide **11**.

The present results suggest that already known cascade reactions[5, 6] would be more efficient and perhaps quantitative in the solid-state with efficient milling or in the gas–solid variant than in solution or liquid phase. They also suggest the development of new cascade reactions. The methodological variability of this method is illustrated by the reaction of thiohydantoin **9**[13] (m.p. 247 °C; 1.0 g), which is easily accessible from dimethylacetylenedicarboxylate, potassium rhodanide, and 4-bromoaniline, with gaseous methylamine (250 mL, 1 bar, left overnight at room temperature), leading to the quantitative formation of the thioorotic acid amide **11** (m.p. 280 °C, decomp; no change after recrystallization from ethanol), (Scheme 3). In this reaction cascade methylamine must add to **9** with ring-opening and formation of the intermediate product **10**. Subsequent cyclization and elimination of methanol without liquefying yields quantitatively the product **11** which is analytically pure after vacuum treatment.

Several quantitative gas–solid cascades and tetrasubstitutions are already known.[3, 5i, 10] Further environmentally friendly solid-state cascade reactions with 100% yield, with and without mechanical treatment will certainly emerge before long.

Experimental Section

Solution reactions: *trans*-1,2-Dibenzoylethylene (**2**) (20 mmol, Aldrich) and **1a–d** (22 mmol; from ethyl acetoacetate and the respective amine) were dissolved in methanol (100 mL) and heated under reflux for 3 h. After cooling to room temperature water was added until crystallization started. It was cooled to 0 °C overnight to complete the crystallization. The crystals were filtered off with suction and dried. In the case of **3c** the methanol was evaporated prior to recrystallization and the solid residue was heated to melting for 5 min, in order to complete the elimination of water.

The related reaction of **4** with **2** was achieved by refluxing in a xylene mixture (30 mL) for 1.5 h. The solvent was evaporated, and the residue crystallized from ethanol.

Solid-state reactions: A heatable/coolable ball-mill (Retsch MM2000) with 10-mL-mill beakers made from stainless steel and two stainless steel balls (6.5 g) was run at 20–30 Hz for 3 h in order to achieve quantitative conversions. Milling of **1a–d** or **4** (2.00 mmol) and **2** (2.00 mmol; m.p. 111 °C) gave dust-dry powders that were heated to 80 °C for removal of the water of reaction. Compound **3c** was obtained as a 2:3 mixture with its precursor **8c** and was obtained in pure form after heating to 150 °C for 5 min in order to complete the elimination and removal of water.

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[1] F. Toda in *Comprehensive Supramolecular Chemistry, Vol. 6* (Eds.: D. D. McNicol, F. Toda, R. Bishop), Pergamon, Oxford, **1996**, pp. 465–516.
[2] J. Schmeyers, F. Toda, J. Boy, G. Kaupp, *J. Chem. Soc. Perkin Trans. 2* **1998**, 989.

[3] a) G. Kaupp in *Comprehensive Supramolecular Chemistry, Vol. 8* (see also color plates 3–22) (Ed.: J. E. D. Davies, J. A. Ripmeester), Elsevier, Oxford, **1996**, pp. 381–423; b) G. Kaupp, *Chemie Unserer Zeit* **1997**, *31*, 129–139 (English translation in http://kaupp.chemie.uni-oldenburg.de); c) G. Kaupp, A. Kuse, *Mol. Cryst. Liq. Cryst.* **1998**, *313*, 361; d) G. Kaupp, J. Schmeyers, M. Haak, T. Marquardt, A. Herrmann, *Mol. Cryst. Liq. Cryst.* **1996**, *276*, 315; e) G. Kaupp, A. Herrmann, *J. Prakt. Chem.* **1997**, *339*, 256; f) A. Herrmann, G. Kaupp, T. Geue, U. Pietsch, *Mol. Cryst. Liq. Cryst.* **1997**, *293*, 261.

[4] The frequently used terms "tandem" (no time sequence!) or "domino" (table game with 28 divided plates with differing numbers of points) are less appropriate for sequential reactions that do not mutually interfere. On the other hand "cascades" describe sequential or stepwise events.

[5] a) G. Kaupp, K. Sailer, *J. Prakt. Chem.* **1996**, *338*, 47; G. Kaupp, K. Sailer, *Angew. Chem.* **1990**, *102*, 917; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 933; b) G. Kaupp, U. Pogodda, A. Atfah, H. Meier, A. Vierengel, *Angew. Chem.* **1992**, *104*, 783; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 768; c) G. Kaupp, in *Photochemical Key Steps in Organic Synthesis* (Eds.: J. Mattay, A. Griesbeck), VCH, Weinheim, **1994**, pp. 224–225; d) S. N. Denisenko, E. Pasch, G. Kaupp, *Angew. Chem.* **1989**, *101*, 1397; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1381; e) G. Kaupp, *Top. Curr. Chem.* **1989**, *146*, 57–98; f) G. Kaupp, H. Voss, H. Frey, *Angew. Chem.* **1987**, *99*, 1327; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1280; g) G. Kaupp, M. Stark, *Angew. Chem.* **1977**, *89*, 555; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 552; h) G. Kaupp, H. Rösch, *Angew. Chem.* **1976**, *88*, 185; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 163; i) G. Kaupp, U. Pogodda, J. Schmeyers, *Chem. Ber.* **1994**, *127*, 2249.

[6] a) F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; b) F. Tietze, *Chem. Rev.* **1996**, *96*, 115; c) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137; d) J. D. Winkler, *Chem. Rev.* **1996**, *96*, 167; e) I. Ryu, N. Sonoda, D. P. Curran, *Chem. Rev.* **1996**, *96*, 177; f) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195; g) K. K. Wang, *Chem. Rev.* **1996**, *96*, 207; h) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; i) M. Malacria, *Chem. Rev.* **1996**, *96*, 289; j) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307; k) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339; l) E. Negishi, C. Coperet, S. Ma, S. Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365.

[7] Recently, *cis*-1,2-diacetylethene and **1a** were allowed to react in benzene with analogous result (80% yield): G. Adembri, A. M. Celli, A. Sega, *J. Heterocycl. Chem.* **1997**, *34*, 541.

[8] All new compounds gave correct IR, ^{1}H, ^{13}C NMR, and (highly resolved) mass spectra, for example **3b**: IR (KBr): $\tilde{\nu} = 1691$ cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 8.00$ (d, 2H), 7.35 (m, 8H), 4.22 (s, 2H), 3.54 (s, 3H), 3.41 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta = 199.12$, 165.93, 137.43, 136.91, 133.13, 132.53, 131.33, 130.66 (2C), 128.43 (2C), 128.36 (2C), 128.01 (2C), 127.87, 115.10, 110.13, 50.24, 36.53, 31.77, 12.01; HR-MS: calcd. for $C_{22}H_{21}NO_3$: 347.1521; found: 347.1521. **5**: IR (KBr): $\tilde{\nu} = 1695$ (C=O), 1652 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 8.03$ (d, 2H), 7.51 (m, 3H), 7.30 (m, 3H), 7.11 (m, 7H), 4.42 (s, 2H), 2.69 (t, $J = 6.05$ Hz, 2H), 2.48 (t, $J = 6.6$ Hz, 2H), 2.14 (quint, $J = 6.05$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta = 198.69$, 195.12, 144.55, 137.67, 137.51, 132.71, 130.71, 130.31 (2C), 129.07 (3C), 128.48 (2C), 128.39 (2C), 128.19 (2C), 127.92, 127.80 (2C), 127.43, 119.16, 114.19, 38.33, 35.95, 23.70, 23.26; HR-MS: calcd. for $C_{28}H_{23}NO_2$: 405.1667; found: 405.1698. **11**: IR (KBr): $\tilde{\nu} = 3305$ (NH, sharp), 1680 (sh, C=O), 1658 (C=O), 1270, 1218 cm^{-1} (C=S); ^{1}H NMR (CDCl$_3$/[D$_6$]DMSO ca. 4/1, 300 MHz): $\delta =$ 8.08 (2NH), 7.52 (d, 2ArH), 7.01 (d, 2ArH), 6.40 (s, 1H), 2.82 (s, 3H); ^{13}C NMR (CDCl$_3$/[D$_6$]DMSO, 75 MHz): $\delta = 180.2$, 164.3, 152.7, 141.2, 131.2 (2C), 130.6 (2C), 124.3, 119.6, 101.4, 25.3; HR-MS: calcd. for $C_{12}H_{10}BrN_3O_2S$: 340.9684; found: 340.9687.

[9] SpecTool for Windows, Version 2.1, Chemical Concepts GmbH, Weinheim, **1994**.

[10] a) G. Kaupp, J. Schmeyers, J. Boy, *Eur. J. Chem.* **1998**, *4*, 2467; b) G. Kaupp, J. Boy, J. Schmeyers, *J. Prakt. Chem.* **1998**, *340*, 346.

[11] J. C. J. Bart, G. M. J. Schmidt, *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 231.

[12] V. Bertolasi, P. Gilli, V. Ferretti, G. Gilli, *Acta Crystallogr. Sect. B* **1998**, *54*, 50.

[13] P. C. Thieme, E. Hädicke, *Justus Liebigs Ann. Chem.* **1978**, 227.

Novel Fluorescent Probes for Singlet Oxygen**

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Tetsuo Nagano*

Singlet oxygen ($^{1}O_2$), an excited state of molecular oxygen, has aroused much interest as a chemical and biological oxidant. The chemical reactivity of $^{1}O_2$ is well characterized since $^{1}O_2$ is useful for organic synthesis and has unique reactivity.[1] Singlet oxygen is thought to be an important toxic species in vivo[2] since it can oxidize various kinds of biological molecules such as DNA, proteins, and lipids, and its reactivity toward DNA bases has been especially well characterized by Foote et al.[3] Furthermore, Sies et al. and other researchers have reported that $^{1}O_2$ plays a role as an activator of gene expression.[4]

Although many $^{1}O_2$ traps have been reported,[5] it is still difficult to detect $^{1}O_2$ generated in biological systems because of its short lifetime. The most widely used $^{1}O_2$ trap is 9,10-diphenylanthracene (DPA), which reacts rapidly with $^{1}O_2$ specifically to form a thermostable endoperoxide at a rate of $k = 1.3 \times 10^{6}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$.[6] The decrease in absorbance at 355 nm is used as a measure of the formation of the endoperoxide. Many water-soluble DPA derivatives have been developed,[7] but the quenching of $^{1}O_2$ by water means that they are difficult to apply to biological systems. Steinbeck et al. have achieved the direct detection of $^{1}O_2$ generation from phagocytes with DPA by adapting the method to avoid $^{1}O_2$ quenching.[8]

DPA derivatives are not very sensitive as probes because the detection is based on the measurement of absorbance. Hence, we designed and synthesized novel fluorometric probes for $^{1}O_2$ in order to improve the sensitivity. In general, fluorescence measurement is more sensitive, and so is easier to use in imaging studies, for example, fura-2 is used in Ca^{2+} imaging.

We designed 9-[2-(3-carboxy-9,10-diphenyl)anthryl]-6-hydroxy-3*H*-xanthen-3-one (DPAX-1, Scheme 1) as a suitable fluorescent probe. We chose fluorescein as a fluorophore since it has a high fluorescence quantum yield in aqueous solution and is able to be excited at long wavelength. Excitation by visible light is preferable for biological applications as it minimizes cell damage and autofluorescence. We then fused this fluorophore with the reactive moiety of DPA. When DPAX reacts with $^{1}O_2$ to yield DPAX-endoperoxide (DPAX-EP) the conjugation between the DPA structure and xanthene ring is greatly altered, so we expected a change in fluorescence properties.

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