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A New Water-Compatible Dehydrating Agent DPTF

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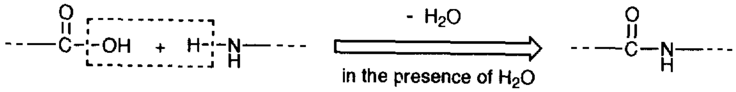
Abstract: The dehydration of a carboxylic acid and an amine to form an amide linkage was performed by the use of a new water-compatible dehydrating agent, 2,2-dichloro-5-(2-phenylethyl)-4-(trimethylsilyl)-3-furanone (DPTF). The application of this new agent to the peptide bond formation is also described. Copyright © 1996 Elsevier Science Ltd

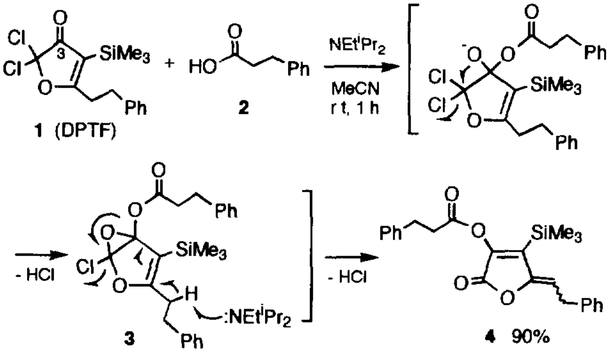
The dehydration and linking together of two organic molecules is one of the most fundamental transformations in organic chemistry. The interlinkage of important biopolymers like proteins and nucleic acids occurs by dehydration of their monomeric units. In vivo, a complex association of enzymes and coenzymes permits removal of the elements of water from two specific molecules *in the presence of water*. It is a challenge to achieve dehydration under aqueous conditions by a chemical method.

A very wide variety of reagents for dehydration of a carboxylic acid and an amine to form an amide linkage have been developed.[1] Those chemical procedures involve (i) the activation of a carboxy group by attachment of a leaving group, and (ii) aminolysis of the activated carboxy derivative. Since an amine is more nucleophilic than water, aminolysis of the activated carboxy derivative is favored over hydrolysis even under aqueous conditions. In contrast, anhydrous conditions are normally preferred for generation of reactive carboxy derivatives, like acyl chloride, *N*-carboxyanhydride,[2] and acyloxypyridinium salt.[3] In the cases with carbodiimide reagents, a carboxy component can be activated under aqueous conditions in the presence of a nucleophilic component, which is directly acylated.[4] Activation with benzoxazolium salts[5] or with uronium salts[6] is also operable in aqueous solution. We now report a new agent, 2,2-dichloro-3-furanone which performs dehydration in the presence of water. An amide linkage is formed from a carboxylic acid and an amine through separate steps of activation and aminolysis.



$$\text{---}\overset{\overset{O}{\|}}{C}\text{-OH} + \text{H-}\underset{H}{N}\text{---} \xrightarrow[\text{in the presence of } H_2O]{- H_2O} \text{---}\overset{\overset{O}{\|}}{C}\text{—}\underset{H}{N}\text{---}$$

We have recently reported a general preparative method of 2,2-dichloro-3-furanones.[7] Whereas 2,2-dichloro-3-furanones undergo methanolysis, they are rather inert toward water. In particular, 2,2-dichloro-5-(2-phenylethyl)-4-(trimethylsilyl)-3-furanone (**1**, DPTF), a crystalline substance, is stable for long-term storage. When DPTF was treated with 3-phenylpropionic acid (**2**) in the presence of two equivalents of Hünig's base in acetonitrile at room temperature for 1 h, a furyl ester (**4**) was produced in 90% isolated yield as a mixture of *Z*- and *E*-isomers (*ca.* 4:1). Recrystallization from hexane-ether gave pure crystalline *Z*-**4**. In addition to full spectroscopic and analytical characterization,[8] the solid state structure was determined by a single crystal X-ray diffraction study.[9] An ORTEP diagram is shown in Figure 1. On the basis of the fact that



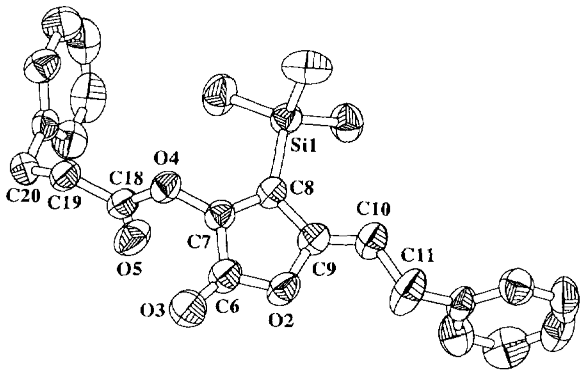
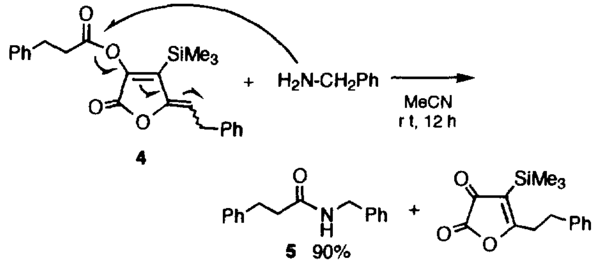


Figure 1. Molecular structure of Z-4 (hydrogen atoms omitted). Only one of the two independent molecules is depicted.

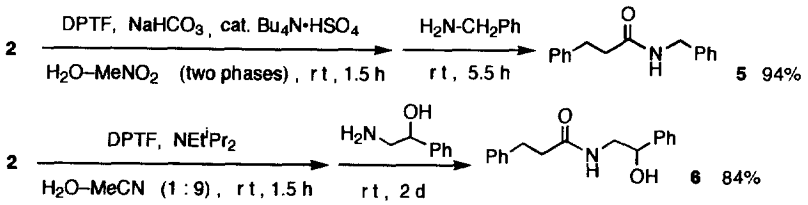


methanolysis of 1 occurs selectively at the 3-position,[7] the following pathway seems likely for the formation of **4**; a carboxylate anion underwent a nucleophilic attack onto the 3-position of DPTF, leading to the formation of epoxyfuran (**3**) as a transient intermediate. Next, de-protonation at the side chain of **3** results in a subsequent electron shift to open the epoxy ring.[10] As a consequence, HCl was eliminated from **3** to furnish **4**.

In contrast to the cases of carbodiimides, the formation of a symmetrical carboxylic anhydride by the subsequent reaction of the ester **4** with the carboxylic acid **2** was not observed, even when two equivalents of **2** were used. This result suggests that the ester **4** is far less electrophilic than DPTF. However, the ester **4** was still reactive with respect to aminolysis, with the furyl moiety acting as the leaving group. Treatment of **4** with benzylamine at room temperature produced an amide **5** in 90% yield.

Isolation of the furyl ester **4** was not necessary, and conveniently, both steps of activation and aminolysis could be sequentially performed in the same reaction vessel. As a result, a water molecule was eliminated from a carboxylic acid and an amine using DPTF as the dehydrating agent.

It is noteworthy that both DPTF and the intermediary active furyl ester **4** are considerably inert to water despite their moderate electrophilic reactivities. This distinguishing property of DPTF and **4** rendered it possible to carry out the whole process of dehydration under aqueous conditions. Treatment of 3-phenylpropionic acid (**2**) with DPTF in a two-phase system, consisting of an aqueous solution of $NaHCO_3$ and nitromethane, followed by the addition of benzylamine resulted in successful dehydration to produce **5** in 94% yield. A quaternary ammonium salt ($Bu_4N{\bullet}HSO_4$) was used as a phase transfer catalyst to accelerate the reaction. Furthermore, dehydration was also possible even in a homogeneous hydrous medium, *i.e.*, in a mixed solvent of acetonitrile and water (9 : 1). The amino group of hydroxyamine was selectively acylated to furnish **6** in 84% yield. The rate of aminolysis of an activated ester



was greatly affected by the solvent system, carboxy, and amino components used, although the reaction conditions were not optimized for each case.

The successful activation of a carboxylic acid in the presence of water by the use of DPTF can be understood on the basis of nucleophilicity. Under neutral conditions, water is more basic, and accordingly more nucleophilic than a carboxylic acid. In contrast, when the reaction conditions are basic enough to convert only a carboxylic acid, rather than water, to the corresponding anionic species, the negatively charged carboxylate anion is a stronger nucleophile than a neutral water molecule. Thus, the minimal electrophilicity of DPTF permits the selective reaction with a carboxylic acid under suitably basic conditions.

This process in hydrous media was next applied to the dehydration between amino acids forming peptide bonds, which would merit special consideration. Sequential treatment of *O*-benzylated *Boc*-Ser–OH with DPTF and with H–Val–OMe in water–nitromethane furnished the corresponding dipeptide in 88% yield. No racemization was observed. Other successful examples of the synthesis of dipeptides in hydrous media were exemplified below. All of benzyl (*Z*), tertiary butyl (*Boc*), and 9-fluorenylmethyl (*Fmoc*) carbamates, which are the most widely used amino-protective groups in peptide synthesis, are tolerated under the reaction conditions.

$$\textit{Boc}\text{-Ser}(\textit{Bn})\text{–OH} \xrightarrow[\textit{aq}.\ \mathrm{NaHCO_3–MeNO_2},\ \mathrm{r\,t},\ 3.5\ \mathrm{h}]{\mathrm{DPTF}} \xrightarrow[\mathrm{NEt^iPr_2},\ \mathrm{r\,t},\ 18\ \mathrm{h}]{\text{H–Val–OMe•HCl}} \underset{88\%}{\textit{Boc}\text{-Ser}(\textit{Bn})\text{–Val–OMe}}$$

$$\textit{Z}\text{-Lys}(\textit{Z})\text{–OH} \xrightarrow[\mathrm{H_2O–MeCN},\ \mathrm{r\,t},\ 2\ \mathrm{h}]{\mathrm{DPTF,\ NEt^iPr_2}} \xrightarrow[\mathrm{NEt^iPr_2},\ \mathrm{r\,t},\ 16\ \mathrm{h}]{\text{H–Ala–OMe•HCl}} \textit{Z}\text{-Lys}(\textit{Z})\text{–Ala–OMe} \quad 78\%$$

$$\textit{Fmoc}\text{-Ala–OH} \xrightarrow[\mathrm{H_2O–MeCN},\ \mathrm{r\,t},\ 2\ \mathrm{h}]{\mathrm{DPTF,\ NEt^iPr_2}} \xrightarrow[\mathrm{NEt^iPr_2},\ \mathrm{r\,t},\ 16\ \mathrm{h}]{\text{H–Gly–OMe•HCl}} \textit{Fmoc}\text{-Ala–Gly–OMe} \quad 82\%$$

The present dehydrating system consists of two separate steps, the pre-activation of a carboxylic acid in the absence of an amino component, and the subsequent reaction of the resulting activated ester with an amine. Thus, it was made feasible to use a free amino acid, which is sparingly soluble in organic solvents, as the amino component, *i.e.*, a "salt coupling" technique. Addition of an aqueous solution of a free amino acid to a preformed activated ester in acetonitrile resulted in the formation of a dipeptide having a free carboxy end, which could then be subjected to the second activation by DPTF again without any deprotection procedure. The subsequent addition of the third amino acid produced the corresponding tripeptide **7**. In the synthesis of **7**, elongation of the chain was carried out at the carboxy end, and therefore, detectable racemization occurred (LL : DL = 92.4 : 7.6 determined by HPLC analysis).

$$\textit{Z}\text{-Gly–OH} \xrightarrow[\mathrm{MeCN,\ r\,t,\ 1\ h}]{\mathrm{DPTF,\ NEt^iPr_2}} \xrightarrow[\mathrm{NEt^iPr_2},\ \mathrm{r\,t},\ 2\ \mathrm{h}]{\text{H–Phe–OH / H}_2\text{O}} \xrightarrow[\mathrm{MeCN,\ r\,t,\ 1.5\ h}]{\mathrm{DPTF,\ NEt^iPr_2}} \xrightarrow[\mathrm{NEt^iPr_2,\ r\,t,\ 1\ h}]{\text{H–Val–OMe•HCl}} \textit{Z}\text{-Gly–Phe–Val–OMe}$$

7 57%
(LL : DL = 92.4 : 7.6)

In summary, step-wise dehydration is achieved in the presence of water by the use of the new agent DPTF, which activates a carboxyl group without additional auxiliaries like *N*-hydroxysuccinimide. This new process was applied to the peptide bond formation, making feasible the "salt coupling" strategy. The solubility problem, particularly with longer peptides and even small peptides containing asparagine and glutamine,[11] has been one of the most unpredictable difficulties often encountered in the peptide synthesis. Although haloalkane solvents like dichloromethane possess high solvating ability, their use has been strictly limited due to their environmental impact. The present process allows access to a wide range of multi-solvents systems composed of water and other organic solvents,[12] which may provide a solution to these problems.

REFERENCES AND NOTES

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1. For general reviews on the peptide bond formation, see: a) J. Jones, *The Chemical Synthesis of Peptides*, Oxford Univ. Press, Oxford (1991). b) *The Peptides*, ed. by E. Gross and J. Meienhofer, Academic Press, New York (1979), Vol. 1 and 2. c) M. Bodanszky, *Principles of Peptide Synthesis*, Springer-Verlag, Berlin (1984).
2. S. Mobashery and M. Johnston, *J. Org. Chem.*, **50**, 2200–2202 (1985), and references cited therein.
3. E. Bald, K. Saigo, and T. Mukaiyama, *Chem. Lett.*, **1975**, 1163–1166.
4. a) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067–1068 (1955). b) J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, **21**, 439–441 (1956). c) J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525–2528 (1961).
5. D. S. Kemp, S. J. Wrobel, Jr., S.-W. Wang, Z. Bernstein, and J. Rebek, Jr., *Tetrahedron*, **30**, 3969–3980 (1974).
6. W. Bannwarth, D. Schmidt, R. L. Stallard, C. Hornung, R. Knorr, and F. Müller, *Helv. Chim. Acta*, **71**, 2085–2099 (1988).
7. M. Murakami, M. Hayashi, and Y. Ito, *J. Org. Chem.*, **59**, 7910–7914 (1994).
8. *Z*-**4**: ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 2.86–2.96 (m, 2H), 3.03–3.14 (m, 2H), 3.77 (d, J = 8.0 Hz, 2H), 5.49 (t, J = 8.0 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ -1.0, 30.4, 32.3, 35.3, 116.3, 126.5, 128.3, 128.4, 128.6, 128.7, 138.7, 139.6, 140.5, 146.2, 148.7, 163.2, 169.4. Anal. Found: C, 70.78; H, 6.54%. Calcd for $C_{24}H_{26}O_4Si$: C, 70.90; H, 6.45%.
9. crystal data: $C_{24}H_{26}O_4Si$, M = 406.6, triclinic, space group $P\bar{1}$, a = 11.740 (4), b = 20.100 (5), c = 10.965 (3) Å, α = 96.38 (3), β = 117.82 (2), γ = 87.90 (3)°, U = 2274 (1) Å^3, Z = 4, D_c = 1.187 g/cm^3, μ = 11.00 cm^{-1}. Intensity data were measured on a Mac Science MXC^3 diffractometer (ω-2θ scan) with graphite monochromated Cu K_α radiation (λ = 1.54178 Å). 6967 unique reflections ($3 \le 2\theta \le 130°$) were collected. The data were corrected for Lorentz and polarization effects. The structure was refined by the full-matrix least-squares to R = 0.060 (R_w = 0.070) for 5078 reflections [$I > 3.0\sigma(I)$], using a Crystan GM package program. The crystal contains two independent molecules of *Z*-**4** in an asymmetric unit. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the refinement at the calculated distances (0.96 Å) with isotropic temperature factors calculated from those of the bonded atoms.
10. For precedent ring opening reactions of epoxyfurans, see: a) K. P. Manfredi and P. W. Jennings, *J. Org. Chem.*, **54**, 5186–5188 (1989). b) B. M. Adger, C. Barrett, J. Brennan, M. A. McKervey, and R. W. Murray, *J. Chem. Soc., Chem. Commun.*, **1991**, 1553–1554. c) W. Adam, K. Peters, and M. Sauter, *Synthesis*, **1994**, 111–119, and references cited therein.
11. M. Ueki, T. Saito, J. Sasaya, S. Ikeda, and H. Oyamada, *Bull. Chem. Soc. Jpn.*, **61**, 3653–3657 (1988).
12. Recently, the racemization-suppressing effect of an aqueous two-phase system has been reported: G.-J. Ho, K. M. Emerson, D. J. Mathre, R. F. Shuman, and E. J. J. Grabowski, *J. Org. Chem.*, **60**, 3569–3570 (1995).

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