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A Novel Three-Component Butenolide Synthesis

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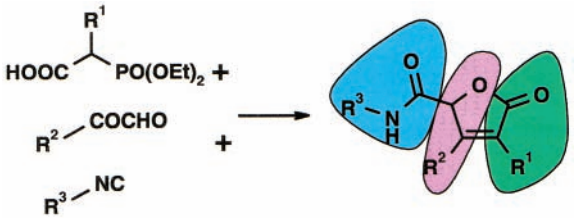
ABSTRACT



5-Acylamino butenolides can be assembled by a multicomponent reaction (MCR) of isocyanides, glyoxals, and acetophosphonic acid diethylesters, followed by a intramolecular Wittig-type reaction. The reaction can be performed either in one pot or with the isolation of the intermediate Passerini product. This versatile reaction offers three independent inputs displayed in the final product. Applications in combinatorial chemistry and natural product synthesis can be envisioned.

Reactions are the tool kits for chemists to create new matter with novel properties. They are the basis for today's organic chemistry art of assembling complex molecules with predefined properties. Interestingly, novel reactions are hardly discovered any more.[1] However, in the field of multicomponent reactions, novel reactions are described frequently.[2] This can be attributed to the tremendous possibilities of MCRs compared to traditional two-component chemistry.[3] The utility of a new reaction can be defined as giving a target molecule in optimal yields while using as few synthetic steps as possible and giving as few side products as possible, thereby using environmentally benign processes. The above criteria are very much approached by the concept of multicomponent reactions.[4]

The concept of divergence and convergence in organic synthesis is very useful. Convergent synthesis pathways generally show advantages over linear or divergent approaches with respect to speed, time, yield, and reproducibility. Among organic reactions, multicomponent reactions are highly convergent.[5] During a multicomponent reaction, more than two starting materials are assembled to afford a complex product. Up to seven-component reactions have been described so far.[6] Therefore, they constitute a superior tool for diversity-oriented and complexity-generating synthesis for drug discovery.[7]

Butenolides, also named 2(5*H*)-furanones, are ubiquitious chemical moieties found in many natural products. They are

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(1) Barton, D. H. R. *Aldrichimica Acta* **1990**, *23*, 3.
(2) Recent examples: (a) Semple, J. E.; Owens T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769−2772. (b) Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem.* **1999**, *64*, 1074−1076. (c) Armstrong, R. W. *J. Org. Chem.* **1998**, *63*, 867−871. (d) Nair, L. G.; Fraser-Reid, B.; Szardenings, A. K. *Org. Lett.* **2001**, *3*, 317. (e) Heck, S.; Dömling, A. *Synlett* **2000**, 424. (f) Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G. *Tetrahedron Lett.* **2001**, *57*, 1395. (g) Dumetsre, P.; El Kaim, L.; Gregoire, A. *Chem. Commun.* **1999**, 775. (h) Shaabani, A.; Yavari, I.; Teimouri, M. B.; Bazigir, A. *Tetrahedron* **2001**, *57*, 1375. (i) Scheffler, G.; Justus, M.; Vasella, A.; Wessel, H. P. *Tetrahedron Lett.* **1999**, *40*, 5845. (j). Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett.*, **2000**, *41*, 9607.
(3) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
(4) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765.
(5) Beck, B.; Hess, S.; Dömling, A. *Biorg. Med. Chem. Lett.* **2000**, *10*, 1701.
(6) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 563.
(7) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709.

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typical products of a polyketide biochemical synthesis pathway. Examples are the cardiotonic digitoxines **1** from *Digitaliz* sp.[8] and the antifungal (−)-incrustoporine[9] **2** (Figure 1). Rofecoxib **3** is a recently launched NSAID with a

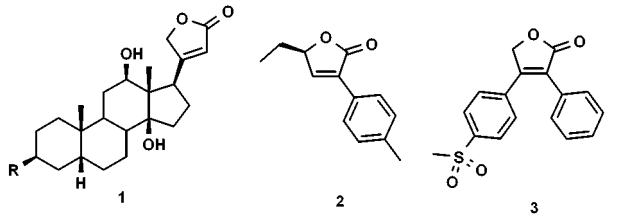
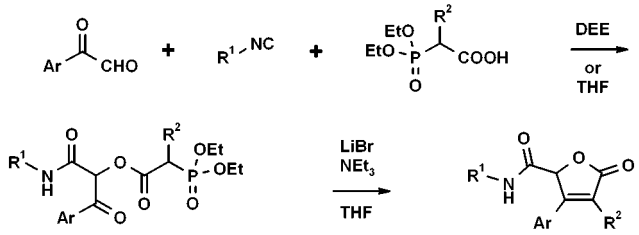


Figure 1. Examples of pharmaceutically relevant butenolides.

butenolide core structure and is efficacious in treating rheumatoid arthritis.[10] There are many ways to synthesize the butenolide moiety, but no one-pot multicomponent approach has been published to the best of our knowlegde.[11]

In this Letter we report a new MCR of isocyanides, arylglyoxals, and α-substituted diethylcarboxylicmethanephosphonates producing butenolides. The total transformation is a combination of the Passerini three-component reaction followed by a intramolecular Wittig-type reaction (Scheme 1). In the first step, the Passerini three-component reaction

Scheme 1



of diethylcarboxylicmethanephosphonates, isocyanides, and arylglyoxals takes place in good yield.[12]

Typically, the yield was nearly quantitative, and in many cases the reaction product precipitates during the reaction. The cyclization of this Passerini intermediate, using a Horner−Wadsworth−Emmons modification of the Wittig reaction with LiBr and Et_3N in THF according to the Rathke procedure, furnished the butenolides in good to acceptable yield.[13] The overall transformation can be run with isolation of the intermediate Passerini product or in a one-pot procedure. The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. The products belong to the class of 3,4-disubstituted 5-aminoacyl-2(5*H*)-furanones. A X-ray structure of a typical example **4** is shown in Figure 2.[14]

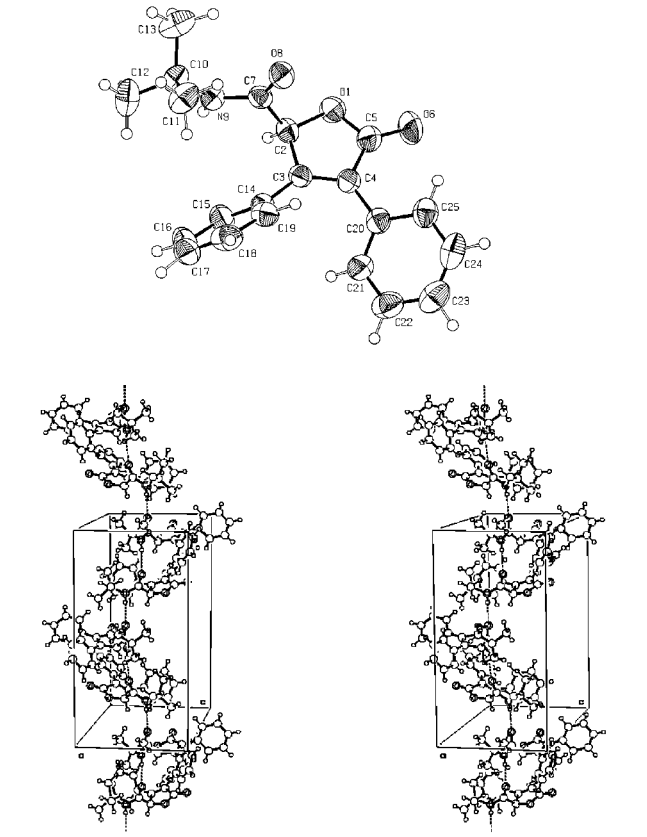
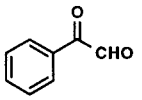
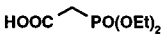
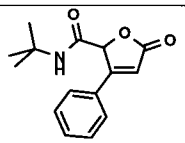
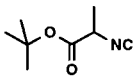
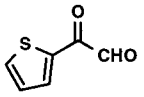
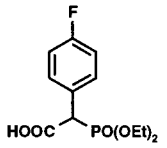
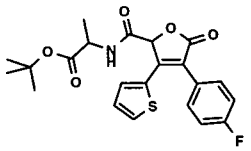
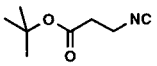
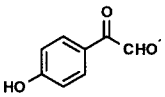
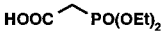
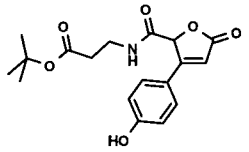
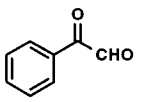
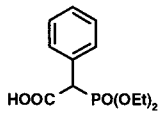
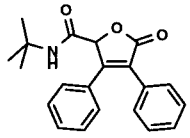
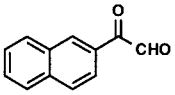
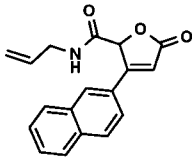
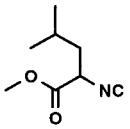
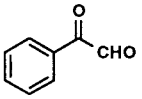
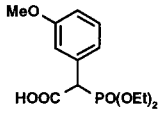
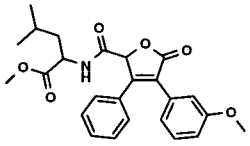
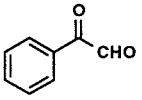
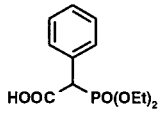
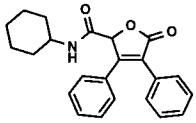
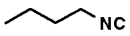
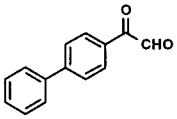
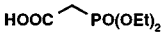
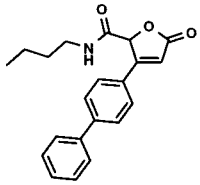
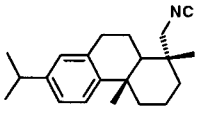
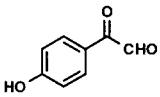
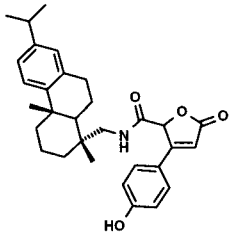


Figure 2. Above: X-ray structure of one molecule of **4A**. Below: A stereoview of a unit cell. Two crystallographic independent molecules **A** and **A′** are in the asymmetric unit. They are connected by weak hydrogen bonds building a chain **A**···**A′**···**A** running parallel to the *b*-axis of the unit cell.

Three substituents in the products can be varied independently of each other (Table 1). Each type of starting material is easily accessible from its corresponding precursor. A variety of α-substituted diethylcarboxylicmethanephos-

(8) Review: Repke, K. R. H.; Megges, R.; Weiland, J.; Schön, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 282.
(9) Zapf, S.; Anke, T.; Sterner, O. *Acta Chem. Scand.* **1995**, *49*, 233.
(10) Scott, L. I.; Lamb, H. M. *Drugs* **1999**, *3*, 499.
(11) For a review on butenolide synthesis, see: (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. The reaction of α-acidic acetic acids (cyan acetic acid, arensulfonylacetic acids, 2-nitrophenylacetic acid) with glyoxals and isocyanides followed by Dieckmann-type condensations resulting in 5-aminoacyl-2(5*H*)-furanones has been reported: (b) Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *Synthesis* **1993**, 783. (c) Bossio, R.; Marcaccini, S.; Pepino, R. *Liebigs Ann. Chem.* **1994**, 5, 527. (d) Marcaccini, S.; Pepino, R.; Marcos, C. F.; Polo, C.; Torroba, T. *J. Heterocyl. Chem.* **2000**, 37, 1501.
(12) Passerini, M. *Gazz. Chim. Ital.* **1924**, *54*, 529.
(13) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.
(14) X-ray single-crystal structure determination of **4** (crystallized from acetic acid ethylester). Crystal data: $C_{21}H_{21}NO_3$, $M_r = 335.39$, orthorhombic, space group $Pbc2_1$ (nonstandard $Pca2_1$; No. 29), $a = 9.9119(3)$, $b = 19.0265(7)$, $c = 19.2249(5)$ Å, $V = 3625.6(2)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.229$ g cm^{-3}, $F(000) = 1424$, μ(Cu Kα) = 0.659 mm^{-1}, $T = 293$ K. Data collection: Nonius CAD4 diffractometer, λ(Cu Kα) = 1.54180 Å, colorless crystal 0.15 × 0.25 × 0.28 mm^{-3}, unit cell parameters by least-squares for 25 reflections with 80.0° < 2θ < 89.5°. Structure solution and refinement: direct methods (SHELXS-86[a]), full-matrix least-squares on F^2 (SHELXL-97[b]). (a) Sheldrick G. M. *SHELXS-86*, University of Göttingen: Germany, 1997. (b) Sheldrick G. M. *SHELXL-97*, University of Göttingen: Germany, 1997.

Table 1. Representative Examples of Butenolides Synthesized by the New 3-CR; Total Yields over Both Steps Are Given

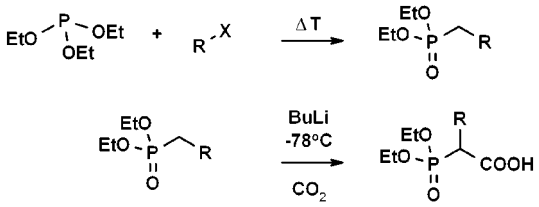
No	Isocyanide	Glyoxal	Phosphono acetic acid diethylester	Butenolide	Yield %
1					87
2					47[a]
3					81
4					36
5					75
6					13[b]
7					42
8					85
9					52[c]

[a] de = 82%. [b] de = 54% as determined by ^{1}H NMR. [c] de could not be determined by ^{1}H NMR. The relative stereochemistry could not be determined by ^{1}H NMR.

phonates have been synthesized using the Arbuzov reaction of halides with triethyl phosphite followed by treatment with BuLi and carboxylation (Scheme 2).[15] Although many general methods toward isocyanides are known, the most versatile access to isocyanides starts from primary amines via formylation and dehydration.[16] Many different syntheses

(15) Coutrot, P.; Ghribi, A. *Synthesis* **1986**, 661.

Scheme 2



have been described toward glyoxals. For example, arylglyoxals can be made by oxidation of the corresponding acetophenones.[17]

In conclusion, we are reporting a new MCR, yielding butenolides, by a sequence of a Passerini reaction and an intramolecular Wittig-type ring closure. The reaction is highly versatile. The one-pot MCR protocol has several distinct advantages over sequential multistep procedures. These include superior atom economy,[18] simplified workup procedures, greater efficiency, and superior overall yields.[19] Currently, we are investigating solid-phase procedures of the above-described three-component butenolide synthesis.

Supporting Information Available: General procedures for the two-step synthesis as well as the one-pot synthesis, ^{1}H and ^{13}C NMR spectra of several butenolides and a Passerini intermediate, and the data for the X-ray structure analysis of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Formamide dehydration: (a) Ugi, I.; Meyr, R. *Angew. Chem.* **1958**, *70*, 702. (b) Ugi, I.; Meyr, R. *Chem. Ber*. **1960**, *93*, 239. Hoffmann's carbylamine method: (c) Weber, W. P.; Gokel, G. W.; Ugi, I. *Angew. Chem., Int. Ed. Engl*. **1972**, *11*, 520. Meyer's method (AgCN): (d) Meyer, E. *J. Prakt. Chem*. **1866**, 147. (e) Boullanger, P.; Descotes, G. *Tetrahedron Lett*. **1976**, *38*, 4327. Gassman's merhod (epoxides, TMS−CN): (f) Gassman, P. G.; Guggenheim, T. L. *J. Am. Chem. Soc*. **1982**, *104*, 5849. Appels method (PPh_3, CCl_4, NEt_3): (g) Appel, R.; Kleistück, R.; Ziehn, K. D. *Angew. Chem., Int. Ed. Engl*. **1971**, *10*, 132.

(17) (a) SeO_2, dioxan/water: Edlin, C. D.; Faulkner, S.; Parker, D.; Wilkinsom, M. P. *J. Chem. Soc., Chem. Commun*. **1996**, 1249. (b) Aqueous $Cu(OAc)_2$: Evans, W. E.; Carr, C. J.; Krantz, J. C. *J. Am. Chem. Soc*. **1938**, *60*, 1628. (c) dmso, HBr: Ushami, K.; Isobe, M. *Tetrahedron* **1996**, *37*, 12061.

(18) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(19) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.