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Microwave-Assisted Paal–Knorr Reaction. A Rapid Approach to Substituted Pyrroles and Furans

Giacomo Minetto, Luca F. Raveglia,† and Maurizio Taddei*

Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena,
Via A. Moro, 53100 Siena, Italy, and NiKem Research srl, Via Zambeletti 25 20021
Baranzate di Bollate, Milano, Italy

taddei.m@unisi.it

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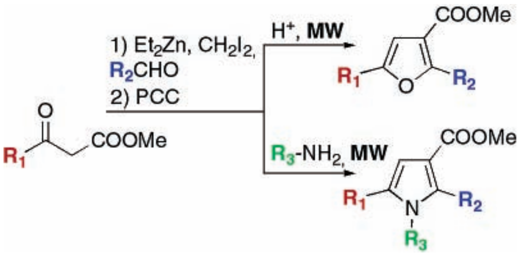
ABSTRACT



An array of tetrasubstituted pyrroles (and trisubstituted furans) was obtained using a simple three-step procedure. Functional homologation of a *β*-ketoester with an aldehyde followed by oxidation gave a series of differently substituted 1,4-dicarbonyl compounds that can be rapidly cyclized with the Paal–Knorr procedure carried out under microwave irradiation.

Pyrrole is one of the most prominent heterocycles, having been known for more than 150 years,[1] and it is the structural skeleton of several natural products, synthetic pharmaceuticals, and electrically conducting materials.[2]

Within these large classes of relevant products, tetrasubstituted pyrroles are extremely important, displaying antibacterial, antiviral, anticonvulsant, and antioxidant activities and inhibiting cytokine-mediated diseases.[3]

One of the most common approaches to pyrrole synthesis is the Paal−Knorr reaction in which 1,4-dicarbonyl compounds are converted to pyrrole via acid-mediated dehydrative cyclization in the presence of a primary amine.[4] In this reaction, the 1,4-dicarbonyl compound provides the four carbons of the pyrrole with the possible substituents, whereas the amine provides the nitrogen with its substituent. The main limitations to intensive use of this reaction are the strong reaction conditions required for cyclization (use of boiling acetic acid for extended times) and the low availability of

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[†] NiKem Research srl.

(1) The name pyrrole comes from πυρροσ and ϵλαιον (red oil): Runge, R. *Ann. Physik*. **1834**, *31*, 67. See also: Bayer, A; Emmerlung. H. *Chem. Ber*. **1870**, *3*, 517.

(2) Gossauer, A. *Die Chemie der Pyrrole*; Springer-Verlag: Berlin, 1974. Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207. Fürstner, A. *Synlett* **1999**, 1523. Higgins, S. *Chem. Soc. Rev*. **1997**, *26*, 247.

(3) Kaiser, D. G.; Glenn, E. M. *J. Pharm. Sci*. **1972**, *61*, 1908. Daisone, G.; Maggio, B.; Schillaci, D. *Pharmazie* **1990**, *45*, 441. Almerico, A. M.; Diana, P.; Barraja, P.; Dattolo, G.; Mingoia, F.; Putzolu, M.; Perra, G.; Milia, C.; Musiu, C.; Marongiu, M. E. *Il Farmaco* **1997**, *52*, 667. Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem*. **1999**, *34*, 991. Chong, P. H.; Bachenheimer, B. S. *Drugs* **2000**, *11*, 351. Pinna, G. A.; Loriga, G.; Murineddu, G.; Grella, G.; Mura, M.; Vargiu, L.; Murgioni, C.; La Colla, P. *Chem. Pharm. Bull*. **2001**, *49*, 1406. Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. *Tetrahedron Lett*. **2003**, *44*, 4443.

(4) Some recent applications of the Paal−Knorr synthesis: Dong, Y.; Naranjan, N.; Ablaza, S. L.; Yu, S.-X.; Bolvig, S.; Forsyth, D. A.; Le Quesne, P. W. *J. Org. Chem*. **1999**, *64*, 2657. Haubmann, C.; Huebner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett* **1999**, *9*, 3143. Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 3389. Wurtz, N. R.; Turner, J. M.; Baird, E. E.; Dervan, P. B. *Org. Lett*, **2001**, *3*, 1201. Ballini, R.; Bosica, G.; Fiorini, G.; Giarlo, G. *Synthesis* **2001**, 2003. Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett*. **2001**, *3*, 3297. Arrowsmith, J.; Jennings, S. A.; Clark, A. S.; Stevens, M. F. G. *J. Med. Chem*. **2002**, *45*, 5458. For other syntheses of pyrroles, see: Bartolo, G.; Salerno, G.; Fazio, A. *J. Org. Chem*. **2003**, *68*, 7853 and references therein.

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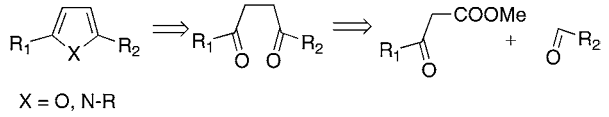
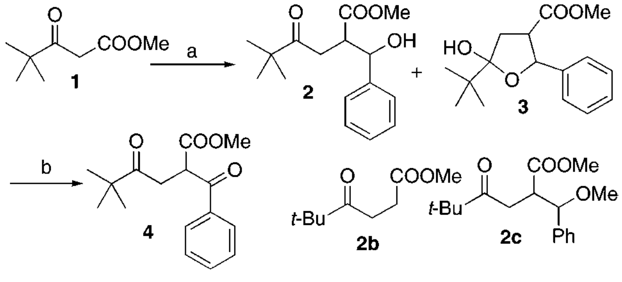
nonsymmetrically substituted 1,4-dicarbonyl compounds. The classical approach to this class of products is the condensation of enolates with phenacyl bromides,[5] thus limiting the preparation to pyrroles with aryl substituents. Alternative approaches need several steps of reactions with chromatographic separations to obtain the intermediates for cyclization. Consequently, there is still room for improvement to the synthesis, particularly with regard to rapid access of pyrroles starting from commercially available intermediates.

Scheme 1



As part of a program assessing the application of microwave chemistry in parallel synthesis of biologically relevant products,[6] we considered the possibility of preparing polysubstituted pyrroles via the Paal−Knorr reaction. The synthesis of pyrrole by microwave (MW)-assisted dehydrogenation of pyrrolidines with MnO_2 and by reaction of 2,4-hexandione with amines neat or in montmorillonite in a microwave cavity has been previously reported.[7] Before approaching a systematic study of the Paal−Knorr cyclization, we took into account the preparation of differentially substituted 1,4-diketones. In this respect, we found the functional homologation of a β-ketoester with an aldehyde recently reported by Zercher and co-workers to be very attractive.[8] Following this report, we reacted methyl 4,4-dimethyl-3-oxopentanoate **1** with Et_2Zn, CH_2I_2, and benzaldehyde, obtaining product **2** as a mixture of diasteroisomers. In this reaction, hemiacetal **3** was also formed as evidenced by chromatographic and ^1H NMR analysis (Scheme 2). Instead of trying to separate and isolate the components of the mixture, we carried out the oxidation of the crude reaction with PCC in CH_2Cl_2 at room temperature. Inspection on the TLC of the reaction showed a simplification of the mixture. After removing the Cr salts originating from the PCC, we observed the exclusive formation of compound **4** that was isolated as a crude product suitable for use in the next steps.

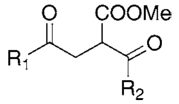
Scheme 2[a]



[a] Conditions: (a) Et_2Zn, CH_2I_2 followed by PhCHO, SiO_2. (b) PCC, CH_2Cl_2, SiO_2.

This synthetic sequence was found to have general application for the substrates described in Table 1 where the yields of the 1,4-dicarbonyl compounds **4**−**9** obtained with this reaction are reported. To speed up the procedure, the mixture obtained after the addition of the aldehyde was quenched with silica gel. After the mixture was stirred for an additional 30 min and filtering under vacuum, the solvent was evaporated and the crude product obtained was directly submitted to PCC oxidation. Again, after a complete oxidation, filtration on a short path of silica provided pure 1,4-dicarbonyl compounds without any hydrolytic workup.[9]

Table 1. 1,4-Dicarbonyl Compounds Prepared as Reported in Scheme 2



R_1	R_2	product	yield (%)
t-Bu	Ph	**4**	90
t-Bu	CH_2-CH_2-Ph	**5**	86
Et	Ph	**6**	91
Et	CH_2Ph	**7**	90
Et	C_3H_7	**8**	91
Et	*p*-Cl−C_6H_4	**9**	92

The first step of the reaction was extremely sensitive to the presence of acid that could quench the intermediate anion generated by rearrangement of the oxycyclopropyl derivative (produced by reaction of the β-keto ester in the enolic form).[8] The presence of traces of water generated the ketoester **2b** and even when an aldehyde having a NHCbz group was used, the main reaction product was the same ester. Only when the reaction mixture was stirred for more than 2 h did we observe the formation of the methoxy derivative **2c** as previously reported by Zercher.[8] It is obvious that in this case we had to purify the product by flash chromatography. The main byproduct observed in the first step was the unreacted aldehyde that was probably transformed in the next step into acid, separable in the short-path chromatography. Regarding the second step, we observed higher yields using PCC freshly prepared[10] instead of using commercially available samples. The oxidation took 12−24 h, and in some

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(5) See for example: Pinna, G. A.; Curzu, M. M.; Sechi, M.; Chelucci, G.; Maciocco, E. *Il Farmaco* **1999**, *54*, 542.

(6) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M.; Taddei, M. *J. Comb. Chem*. **2003**, *5*, 465. Lampariello, L. R.; Piras, D.; Rodriquez, M.; Taddei, M. *J. Org. Chem*. **2003**, *68*, 7893.

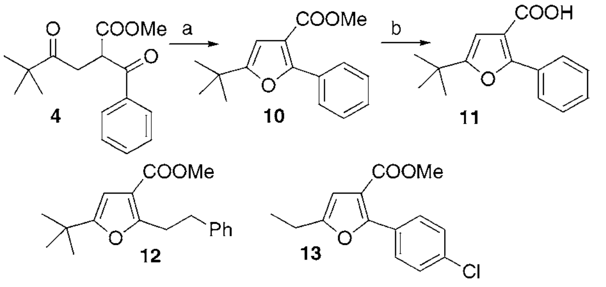
(7) (a) Oussaid, B.; Garrigues, B.; Soufiaoui, M. *Can. J. Chem*. **1994**, *72*, 2483. (b) Ruault, P.; Pilard, J. F.; Touaux, B.; Texier-Boullet, F.; Hamelin, J. *Synlett* **1994**, 935. (c) Danks, T. N. *Tetrahedron Lett*. **1999**, *40*, 3957.

(8) Lai, S.; Zercher, C. K.; Jasinski, J. P.; Reid, S. N.; Taples, R. J. *Org. Lett*. **2001**, *3*, 4169.

(9) This procedure was carried out in our laboratory using a parallel synthesizer such as Syncore from Buchi.

(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett*, **1975**, 2647.

Scheme 3[a]



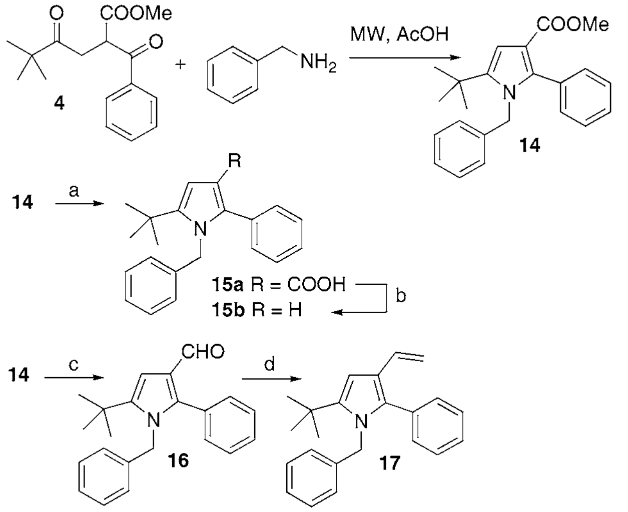
[a] Conditions: (a) EtOH, HCl, MW, 3 min. (b) NaOH, EtOH/H_2O reflux, 6 h.

cases, additional amounts of PCC were needed to induce a complete conversion of the starting material into the desired 1,4-diketones. Attempts to speed up the reaction by heating (traditional and microwave) gave lower yields of the products. Also, the use of other oxidant (PDC, MnO_2, TEMPO in the presence of different co-oxidants) gave unsatisfactory results.

First attempts to cyclize compound **4** were carried out in acidic conditions.[11] Heating a solution of ketone **4** in EtOH/H_2O in the presence of catalytic amounts of HCl in a sealed tube inserted into a microwave cavity generated the furan **10** in 3 min at 140 °C and a maximum internal pressure of 120 psi.[12] After the mixture was cooled, the furan was extracted with diethyl ether and isolated in 95% yields and in good purity (GC-mass and NMR analysis).[13] The carboxyl group could be removed by saponification followed by decarboxylation with NaOH in boiling EtOH/H_2O. Starting from ketoesters **5** and **9** we obtained furans **12** and **13** (Scheme 3) in very good yields. This procedure allowed the preparation of these furans in two simple steps with chromatography separation required in the last step exclusively for an analytical sample.

For the preparation of the pyrrole, we explored different conditions. Microwave heating of the ketone **4** in the presence of benzylamine used as a solvent (as described in the literature)[7c] did not produce the expected pyrrole. Analogously, when different amounts of acids were used to catalyze the reaction, furan **10** was the main product of the cyclization. Pyrrole **14** was effectively obtained by heating a solution of ketone **4** in the presence of benzylamine in acetic acid in a sealed tube in a microwave cavity heated to 180 °C for 3 min (maximum internal pressure = 120 psi). Exactly the same result was obtained by heating an open round-bottomed flask equipped with a reflux condenser under microwave irradiation (internal temperature 150°) for 5 min.[14]

Scheme 4

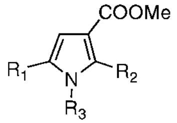


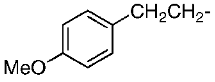
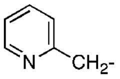
[a] Conditions: (a) NaOH, EtOH/H_2O, reflux, 10 min. (b) Toluene, reflux, 12 h. (c) DIBAL-H, toluene 0 °C, 2 h. (d) $MePPh_3Br$, BuLi, THF 2 h, 66% overall yield.

It is worth noting that, when the reaction was conducted under traditional heating, good yield of pyrrole **14** was not obtained after 12 h of heating at 110 °C (external oil bath 150°). After this period, the starting material was still present in the reaction medium that had begun to become very dark with formation of less than 15% of the desired product.

Microwave-assisted Paal−Knorr cyclization was carried out on different 1,4-diketoesters in the presence of different amines and always gave the expected pyrroles **14**−**22** in good yields (see Table 2). After aqueous alkaline workup, the products were extracted with ethyl acetate and purified by column chromatography. When neutral amines were used,

Table 2. 1,2,3,5-Tetrasubstituted Pyrroles Prepared as Reported in Scheme 3



R_1	R_2	R_3	prod.	yield (%)
t-Bu	Ph	$PhCH_2$-	**14**	70
t-Bu	*p*-Cl-C_6H_4	-C_4H_9	**18**	72
Et	Ph	$PhCH_2$-	**19**	81
Et	CH_2Ph	Me_2CHCH_2-	**20**	78
Et	CH_2Ph		**21**	68
Et	*p*-Cl-C_6H_4		**22**	68

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[11] Knorr, L. *Chem. Ber*. **1884**, *17*, 1635.

[12] All the experiments under microwave irradiation were carried out using a Discover System from CEM.

[13] For a microwave-mediated transformation of a 1,4-diketones into furan, see: Rao, H. S. P.; Jothilingam, S. *J. Org. Chem*. **2003**, *68*, 5392.

[14] Although the boiling temperature of acetic acid is about 118 °C, this was the internal temperature recorded by the Discover System during the experiments. Using the open flask method, we could prepare pyrrole **14** in a 2.5 g scale

we observed also the formation of different amounts of the corresponding acetamides. These kinds of byproducts were not present using amines with an additional basic center, as in the case of the preparation of compound **22** in Table 2. Saponification of **14** with NaOH gave acid **15a**, which could be decarboxylated in boiling toluene to give **15b**.

Alternatively, reduction with DIBAL-H of **14** gave aldehyde **16**, which was submitted to Wittig reaction conditions to give product **17**.

In conclusion, we have described a new rapid and versatile approach to trisubstituted furans and tetrasubstitued pyrroles in few highly efficient steps starting from commercially available β-ketoesters. Additional work is in progress in order to obtain different kinds of heterocycles using the same strategy.

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Supporting Information Available: Experimental general procedure and spectra of compounds **14**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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