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Microwave-Assisted Wolff Rearrangement of Cyclic 2-Diazo-1,3-Diketones: An Eco-compatible Route to α-Carbonylated Cycloalkanones

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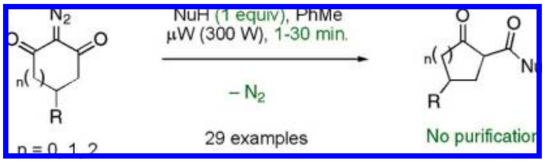
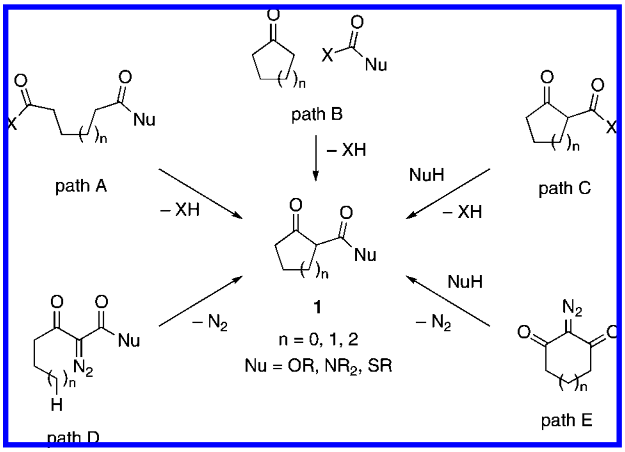
Received September 26, 2008



The microwave-assisted Wolff rearrangement of cyclic 2-diazo-1,3-diketones performed in the presence of a stoichiometric amount of alcohol, amine, or thiol is an efficient, user, and environmentally friendly synthetic protocol for the synthesis of α-carbonylated cycloalkanones. This approach proves superior to existing protocols in scope and eco-compatibility.

SCHEME 1. Synthetic Strategies toward 1



Simple 1,3-dicarbonyl compounds are exceptional synthetic platforms due to the presence of four contiguous reaction sites with alternative nucleophilic and electrophilic character. They allow a vast array of chemical transformations which can translate to a fast increase of molecular complexity if they are judiciously handled. In connection with our program on the development of Michael-initiated domino and multicomponent reactions,[1] we required an efficient and versatile synthetic access to a variety of α-carbonylated cycloalkanones of type **1** with modulated acidity of the activated α proton and a functionalized Nu group (Scheme 1). Of importance, we required a methodology general enough to provide an access to the scarce α-carbonylated cyclobutanones. Several reliable strategies are in the toolbox of the organic chemist for the preparation of **1**. All of them were used in our laboratory in the past decade, and retrospectively, they all suffer from more or less important drawbacks. The Dieckmann cyclization (path A) requires a carefully chosen base and is often associated with reactivity or regioselectivity problems due to the thermodynamical control involved.[2] The acylation of cycloalkanones (path B) meets the same disadvantages when a substituent is required on the cycle.[2] The transesterification and transamidation strategies (path C) are quite general but usually require an excess of nucleophile, an additive, and prolonged reaction times to proceed efficiently.[3] However, the methods are not suitable with tertiary alcohols, poorly nucleophilic amines, or functionalized nucleophiles. The metal carbenoid insertion in the C−H bond (path D) is essentially limited to the formation of five-membered rings and generally proceeds with moderate efficiency with substituted substrates.[4] The ring contraction of cyclic 2-diazo-1,3-diketones (Wolff rearrangement) followed by trapping of the transient α-oxoketene[5] with a nucleophile is a general method to prepare substrates of type **1** (path E).[6] Although some transition-metal-catalyzed Wolff rearrangements have been described,[7] the reaction usually occurs at high temperatures or requires some specific reactors for photoactivation (ultraviolet) or sonication, precluding the presence of sensitive or reactive functional groups.

Microwave-assisted organic chemistry (MAOS) is no longer a laboratory curiosity and will soon be regarded as a common activation mode of chemical transformations. The synthetic community starts to realize the true benefits of microwave activation, and, as a testimony, a number of monographs and review articles have been made available in the past few years

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(1) For recent representative work, see: (a) Liéby-Muller, F.; Constantieux, T.; Rodriguez, J. *J. Am. Chem. Soc.* **2005**, *127*, 17176–17177. (b) Liéby-Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR Comb. Sci.* **2006**, *25*, 432–438. (c) Coquerel, Y.; Bensa, D.; Doutheau, A.; Rodriguez, J. *Org. Lett.* **2006**, *8*, 4819–4822. (d) Coquerel, Y.; Bensa, D.; Moret, V.; Rodriguez, J. *Synlett* **2006**, 2751–2754. (e) Liéby-Muller, F.; Constantieux, T.; Rodriguez, J. *Synlett* **2007**, 1323–1325. (f) Liéby-Muller, F.; Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Commun.* **2008**, 4207–4209. (g) Coquerel, Y.; Filippini, M.-H.; Bensa, D.; Rodriguez, J. *Chem.—Eur. J.* **2008**, *14*, 3078–3092.

(2) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065–1114.

(3) For transesterifications, see: (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470. (b) Mottet, C.; Hamelin, O.; Garavel, G.; Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380–1382. For transamidations, see: (c) Cossy, J.; Thelland, A. *Synthesis* **1989**, 753–754. (d) Ponde, D. E.; Deshpande, V. H.; Bulbule, V. J.; Sudalai, A.; Gajare, A. S. *J. Org. Chem.* **1998**, *63*, 1058–1063. (e) Stefane, B.; Polanc, S. *Tetrahedron* **2007**, *63*, 10902–10913.

(4) For a review, see: (a) Adams, J.; Spero, D. M *Tetrahedron* **1991**, *47*, 1765–1808. For more recent work, see, for example: (b) Kan, T.; Kawamoto, Y.; Asakawa, T.; Furuta, T.; Fukuyama, T *Org. Lett.* **2008**, *10*, 169–171.

(5) For a review, see: Wentrup, C.; Heilmayer, W.; Kollens, G. *Synthesis* **1994**, 1219–1248.

(6) For a review, see: Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193–2256.

(7) For silver-catalyzed rearrangements, see: (a) Sudrik, S.; Sharma, J.; Chavan, V. B.; Chaki, N. K.; Sonawane, H. R.; Vijayamohanan, K. P *Org. Lett.* **2006**, *8*, 1089–1092, and references thereinFor rhodium-catalyzed rearrangements, see: (b) Lee, Y. R.; Suk, J. Y.; Kim, B. S. *Tetrahedron Lett.* **1999**, *40*, 8219–8221.

10.1021/jo8021567 CCC: $40.75 © 2009 American Chemical Society
Published on Web 11/21/2008

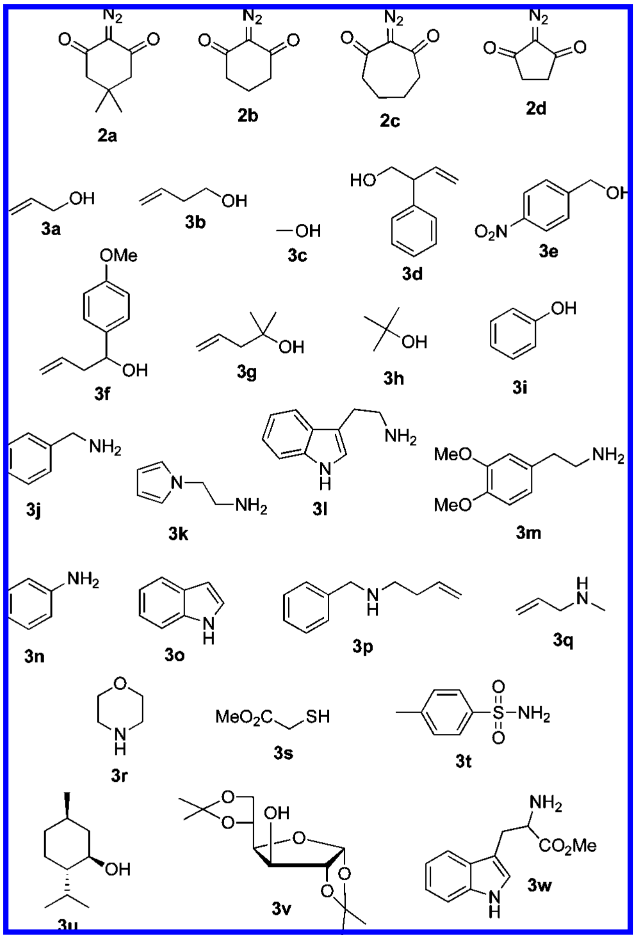

FIGURE 1. Substrates used in the study.

on both the theory and the development of the technique.[8] A microwave effect can be observed in many reactions. Its origin can be from a purely thermal/kinetic effect according to the Arrhenius equation as a consequence of the extremely rapid and internal localized heating of the reaction mixture to a putative, highly controversial, microwave-specific nonthermal effect.[9] It is, however, universally recognized that polar substrates and solvents are microwave active, and owing to their high dipole moments, α-diazo ketones fall into this category. Indeed, in a couple of recent reports, microwave activation has been shown to efficiently promote the Wolff rearrangement of α-diazo ketones in peptide chemistry,[10a,b] α-diazo sulfoxides,[10c] and some microwave specific nonthermal effect has been suggested.[11] Herein, we disclose that a broad range of cyclic 1,3-dicarbonyl compounds of type **1** can be prepared with high efficiency through a microwave-assisted Wolff rearrangement of cyclic 2-diazo-1,3-diketones in the presence a stoichiometric amount of alcohol, amine, or thiol. The overall eco-compatibility[12] of the process is highlighted.

As a test reaction, we submitted a 1:1 mixture of 5,5-dimethyl-2-diazo-1,3-cyclohexandione (**2a**) and allyl alcohol (**3a**) in toluene to microwave irradiation (300 W) for 3 min in a sealed tube and were pleased to find that the desired five-membered ring β-ketoester **1aa** could be obtained with high purity and almost quantitative yield after simple evaporation of the solvent (Table 1, entry 1). Stimulated by this result, we examined the scope of the protocol with several five- to seven-membered cyclic 2-diazo-1,3-diketones[13] and a variety of nucleophiles (Figure 1). The results are reported in Table 1. The reactions systematically afforded the pure one-ring-carbon-contracted products in good to excellent yields and, with a few exceptions, without need for purification. The reaction virtually allows the efficient and expeditious synthesis of four- to six-membered α-carbonylated cycloalkanones with all the nucleophiles shown in Figure 1. Indeed, even poorly nucleophilic alcohols and amines such as phenol (**3i**, entry 7) and *p*-toluenesulfonamide (**3t**, entry 15) could be used, and the *p*-toluenesulfonyl β-ketoamide **1at** would be difficultly available by other methods.[14] Almost no loss of efficiency was observed with the hindered tertiary alcohols **3g** and **3h** (entries 6, 19, 28), allowing the straightforward preparation of challenging substrates such as *tert*-butyl 2-oxocyclobutanecarboxylate (**1dh**, entry 28).[15] Although secondary amines **3o**−**r** reacted efficiently to give the corresponding tertiary amides (entries 10−13 and 26), as expected, total chemoselectivities were observed with substrates exhibiting two nucleophilic nitrogen atoms such as **3w** and **3l** (entries 17 and 21). Additionally, thanks to the neutral reaction conditions, nucleophiles bearing a methyl ester functional group as **3s** and **3w** (entries 14, 17, and 29) could be used. Chiral auxiliaries could be easily introduced (entries 16 and 24). This methodology also provided a nice synthetic access to the valuable product **1ac** (entry 3) which was used in the synthesis of hirsutenes[16] and compounds **1bk**, **1bl**, **1bm**, and **1 cm** (entries 20−22 and 25) which were recently used in domino reactions.[17]

As demonstrated, the scope of the reaction is broad, but one may also consider the eco-compatibility[12] issues of the protocol in terms of waste, energy, and human resource economy. In the current era, the efficiency of a chemical process is more

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(8) For recent edited volumes on MAOS, see: (a) *Microwave in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006. (b) *Topics in Current Chemistry, Vol. 266: Microwave Methods in Organic Synthesis*; Larhed, M., Olafsson, K., Eds.; Springer: Berlin/Heidelberg, 2006. For recent representative reviews on MAOS and its applications, see: (c) Kappe, C. O *Chem. Soc. Rev.* **2008**, *37*, 1127–1139. (d) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125–1132. (e) de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A *Chem. Soc. Rev.* **2005**, *34*, 164–178. (f) Hayes, B. L. *Aldrichim. Acta* **2004**, *37* (2), 66–77. (g) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A *Green Chem* **2004**, *6*, 128–141. For recent special issues on MAOS, see: (h) *Macromol. Rapid Commun.* **2007**, *28* (4), 368−513. (i) *Tetrahedron* **2006**, *62* (19), 4635−4732.

(9) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36–47.

(10) (a) Patil, B. S.; Vasanthakumar, G.-R.; Babu, V. V. S. *Lett. Pept. Sci.* **2002**, *9*, 231–233. (b) Kantharaju; Patil, B. S.; Babu, V. V. S *Indian J. Chem. B* **2005**, *44B*, 2611–2613. (c) O'Sullivan, O. C. M.; Collins, S. G.; Maguire, A. R. *Synlett* **2008**, 659–662.

(11) Sudrik, S. G.; Chavan, S. P.; Chandrakumar, K. R. S.; Pal, S.; Date, S. K.; Chavan, S. P.; Sonawane, H. R. *J. Org. Chem.* **2002**, *67*, 1574–1579.

(12) We define eco-compatibility as both economical and ecological compatibility.

(13) 2-Diazo-1,3-diketones were obtained from the corresponding 1,3-diketones either by treatment with *p*-toluenesulfonyl azide according to: (a) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 179−183; or, in a much eco-compatible manner, by treatment with a polystyrene-supported benzenesulfonyl azide according to: (b) Green, G. M.; Peet, N. P.; Metz, W. A *J. Org. Chem.* **2001**, *66*, 2509–2511.

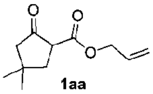
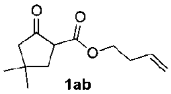
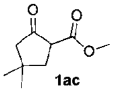
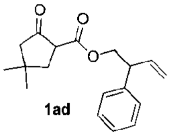
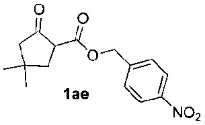
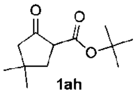
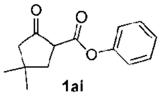
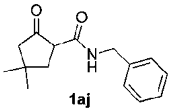
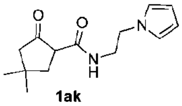
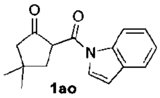
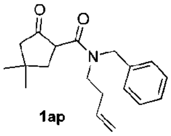
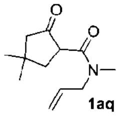
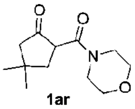
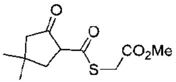
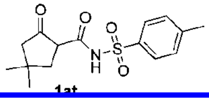
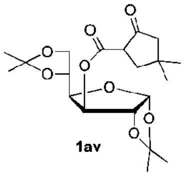
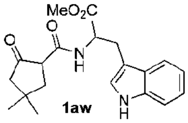
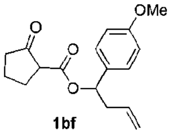
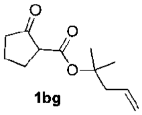
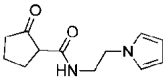
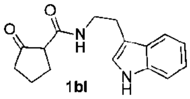
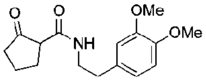
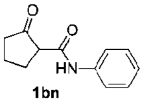
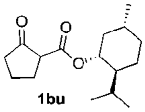
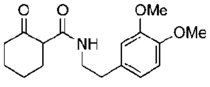
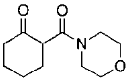
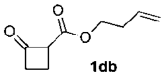
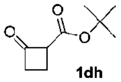
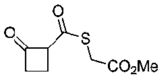
(14) Following the standard transamidation protocol of ref 3c, treatment of commercial methyl 2-oxocyclopentanecarboxylate with *p*-toluenesulfonamide (1 equiv) in the presence of dimethylaminopyridine (DMAP, 1.5 equiv) in refluxing toluene for 24 h left the starting material unchanged. However, the present protocol was unsuccessful with the very poorly nucleophilic bis-*p*-toluenesulfonamide (Ts_2NH).

(15) Only a few methods are available for the synthesis of *tert*-butyl β-ketoesters: Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H *Tetrahedron Lett.* **1986**, *27*, 2383–2386. See also refs 2 and 3a.

(16) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728–6733.

(17) (a) Pilling, A. W.; Boehmer, J.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5428–5430. (b) In this paper, no experimental protocol or characterization data are provided for compounds **1bk**, **1bl**, **1bm**, and **1 cm**. For a similar multicomponent approach, see ref 1e.

TABLE 1. Wolff Rearrangement of Cyclic 2-Diazo-1,3-diketones

entry	diazo	NuH	cond.[a]	product	yield (%)[b]
1	**2a**	**3a**	3 min. 0.3M	 **1aa**	96
2	**2a**	**3b**	3 min. 0.3M	 **1ab**	96
3	**2a**	**3c**	2.2 min. 0.8M	 **1ac**	96
4	**2a**	**3d**	1.75 min. 0.4M	 **1ad**	99[c]
5	**2a**	**3e**	0.25 min 3M	 **1ae**	96
6	**2a**	**3h**	1.5 min. 1M	 **1ah**	89
7	**2a**	**3i**	3 min. 0.1M	 **1ai**	95
8	**2a**	**3j**	3 min. 0.1M	 **1aj**	99
9	**2a**	**3k**	1.1 min. 0.9M	 **1ak**	71[d]
10	**2a**	**3o**	3 min. 0.3M	 **1ao**	99
11	**2a**	**3p**	1.75 min. 0.4M	 **1ap**	93
12	**2a**	**3q**	3 min. 0.1M	 **1aq**	96
13	**2a**	**3r**	3 min. 0.1M	 **1ar**	99
14	**2a**	**3s**	3 min. 0.1M	 **1as**	93
15	**2a**	**3t**	0.95 min. 0.3M	 **1at**	55[d]
16	**2a**	**3v**	5.7 min. 0.2M	 **1av**	55[c,d]
17	**2a**	**3w**	5.35 min. 0.3M	 **1aw**	69[c,d]
18	**2b**	**3f**	1.7 min. 0.5M	 **1bf**	97[c]
19	**2b**	**3g**	1.55 min. 0.6M	 **1bg**	90
20	**2b**	**3k**	3 min. 0.1M	 **1bk**	94
21	**2b**	**3l**	1.1 min. 0.7M	 **1bl**	79[d]
22	**2b**	**3m**	2.15 min. 0.7M	 **1bm**	85[d]
23	**2b**	**3n**	2.25 min. 0.3M	 **1bn**	98
24	**2b**	**3u**	1.45 min. 0.3M	 **1bu**	99[c]
25	**2c**	**3m**	3 min. 0.2M	 **1cm**	55[d]
26	**2c**	**3r**	5.9 min. 0.1M	 **1cr**	99
27	**2d**	**3b**	5.45 min. 0.5M	 **1db**	98
28	**2d**	**3h**	30 min. 0.1M	 **1dh**	84
29	**2d**	**3s**	14.3 min. 0.1M	 **1ds**	95

[a] All reactions in 10 mL sealed tubes containing 2 mL of dry toluene at a power of 300W with a maximum run time of 3 min. (eventually repeated), a maximum internal pressure of 17 bar, and a maximal temperature of 180 °C. The microwave irradiation was automatically stopped when one of these three conditions was met. [b] Yields are given for the crude clean product obtained by concentration of the reaction mixture followed by high vacuum removal of all volatiles. [c] dr = 1:1. [d] The crude product was purified by flash chromatography on silica gel.

than ever corroborated with its conciseness and its sustainable aspects. In the synthetic work delineated above, we have placed a strong emphasis on eco-compatibility[12] which resulted in a protocol where (1) no excess of substrate and no additive is used, (2) only nitrogen gas is evolved, (3) no purification is required in most cases, (4) the reaction time is very short, and (5) the sequence requires a minimum of energy.

In summary, the microwave-assisted Wolff rearrangement of cyclic 2-diazo-1,3-diketones generates a very reactive ring-contracted α-oxoketene which can be trapped with a variety of nucleophiles to give efficiently the corresponding α-carbonylated cycloalkanones under eco-compatible conditions.

Experimental Section

General Procedure. All reactions under microwave irradiation were performed at 300 W in a CEM Discover 1-300W system equipped with build-in pressure measurement sensor and a vertically focused IR sensor (mode discover power time). A solution of 2-diazo-1,3-cycloalkandione **2** (1.0 mmol) and nucleophile **3** (1.0 mmol) in dry toluene (2 mL) in a 10 mL sealed tube equipped with a Teflon-coated stirring bar was microwave irradiated (ν = 2.45 GHz) at 300 W until the temperature reached 180 °C, or the pressure reached 17 bar, or for a maximum time of 3 min (repeated in a few cases), whereupon the reaction mixture was cooled to 40 °C with an air flow. Concentration of the reaction mixture followed by high vaccum removal of volatiles afforded the clean crude product **1** without a need for purification in most cases. For **1aa**: 96% (117 mg) colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (tdd, J = 5.6, 10.4, 17.2 Hz, 1H), 5.34−5.18 (m, 2H), 4.6 (m, 2H), 3.37 (dd, J = 8.8, 11.1 Hz, 1H), 2.40−2.02 (m, 4H), 1.19 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2 (C), 169.0 (C), 131.6 (CH), 118.3 (CH_2), 65.7 (CH_2), 54.1 (CH), 52.9 (CH_2), 40.7 (CH_2), 34.4 (C), 28.8 (CH_3), 27.5 (CH_3); HRMS (ESI+) $[M + H]^+$ calcd for $C_{11}H_{17}O_3$ 197.1172, found 197.1176.

Acknowledgment. We thank Dr. Jean-Luc Parrain and Pr. Jean-Marc Pons for their interest in our work, and M.P. thanks the ENS Cachan for a fellowship award. Financial support from the French Research Ministry, the Université Paul Cézanne, the CNRS (UMR 6263), and the Conseil Général des Bouches du Rhône is also gratefully acknowledged.

Supporting Information Available: Full characterization data and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8021567