Tetrahedron Letters 49 (2008) 4505–4508

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted solid acid-catalyzed one-pot synthesis of isobenzofuran-1(3*H*)-ones

Shainaz M. Landge, Martin Berryman, Béla Török *

Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Blvd. Boston, MA, USA

ARTICLE INFO

Article history:
Received 18 April 2008
Revised 12 May 2008
Accepted 12 May 2008
Available online 16 May 2008

Keywords:
Condensation
Isobenzofuran-1(*3H*)-one
Microwave irradiation
Montmorillonite K-10

ABSTRACT

A new, solid acid-catalyzed microwave-assisted environmentally benign synthesis of isobenzofuran-1(3*H*)-ones is described. Montmorillonite K-10 appeared to be an excellent catalyst for the condensation and successive lactonization reactions. Reaction of phthalaldehydic acid (2-carboxybenzaldehyde) with methylaryl and cyclic ketones was initiated by microwave irradiation and occurred in one step. The reactions were complete in 10–30 minutes providing excellent yields (90–98%).

1. Introduction

Substituted phthalides (isobenzofuran-1(3*H*)-ones) represent an important class of natural products that posses significant biological properties.[1] In particular, 3-substituted phthalides are vital heterocyclic motifs in many bioactive compounds such as isocoumarins, anthraquinones, anthracyclines, and several alkaloids.[2] Their notable characteristics include anti-bacterial, anti-convulsant, anti-HIV, anti-asthmatic, anti-tumor, anti-platelet activities, anesthesia prolongation, and $PGF_{2\alpha}$ inhibitory properties.[3] 3-Alkylidene phthalide derivatives are known for their anti-spasmodic, herbicidal, and insecticidal properties and 3-styryl phthalides are used as color formers for heat and pressure sensitive recording materials.[4]

Due to the potential of phthalides, numerous methods have been developed for their synthesis. These methods include cyclization reactions catalyzed by strong acids such as trifluoroacetic acid[4] and trifluoromethanesulfonic acid.[5] Strong bases such as DBU,[2e,f] NaOH,[6] and KOH[3g] are also used in the synthesis of 3-phenacylphthalides. Gas phase reactions involving CO were also applied.[7] These methods involve the use of strong, corrosive and harmful acids and bases, and high temperatures. The importance of phthalides and the increasing awareness of the need for environmentally benign chemical production provide demand and potential for the development of sustainable green synthetic methods for these compounds.

Solid acid catalysis has become one of the most important tools of synthesis development for sustainable chemical production.[8] These catalysts are economic, active, and selective, while they are also safe, easy to use and handle, and produce no hazardous waste. The combination of solid acid catalysis with microwave irradiation[9] provides even more benign processes; the very short reaction times usually favor high product purity (selectivity) with no secondary reactions and very minimal energy consumption. K-10 montmorillonite is a very versatile solid acid catalyst, recently a number of K-10 catalyzed microwave-assisted approaches have been developed.[8a,b,e,10,11]

Continuing our efforts on the development of sustainable synthetic methods herein, we describe an efficient and expedient one-pot synthesis for the preparation of substituted isobenzofuran-1(3*H*)-ones.

Our new approach is based on the use of a solid acid (Montmorillonite K-10) catalyzed microwave-assisted cyclization of phthalaldehydic acid with substituted acetophenones and cyclic ketones that are all commercially available.

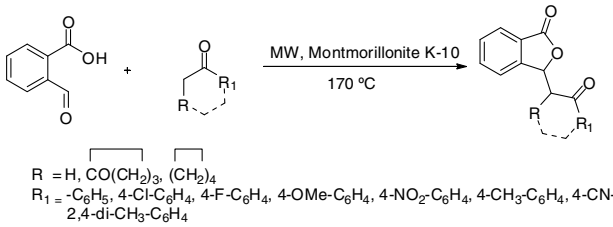
2. Results and discussion

The synthesis of the phthalides is based on the condensation and subsequent cyclization reactions of phthalaldehydic acid with substituted ketones. The approach is summarized in Scheme 1.

In order to optimize the reaction parameters, we carried out several test reactions using phthalaldehydic acid and acetophenone. First, we investigated the effect of reactant ratios on the yield of the product (Table 1).

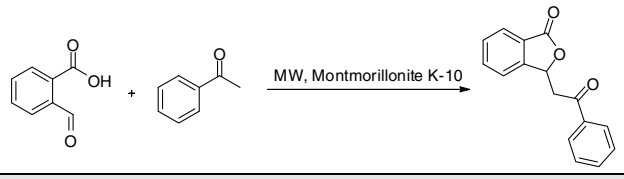
* Corresponding author. Tel.: +1 617 287 6159; fax: +1 617 287 6030.
E-mail address: bela.torok@umb.edu (B. Török).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.068



Scheme 1. Synthesis of substituted isobenzofuran-1(3*H*)-ones from phthalaldehydic acid and ketones.

Table 1
Effect of reactant molar ratio on the microwave-assisted (MW) K-10 catalyzed cyclization of phthalaldehydic acid (PAP) with acetophenone (AP)[a]



Entry	AP:PAP	Yield[b] (%)
1	1:0.5	76
2	1:0.8	85
3	1:0.9	62
4	1:1.0	75
5	1:1.2	60
6	1:1.5	60
7	1:2.0	53

[a] Reaction conditions: phthalaldehydic acid (0.8–2.0 mmol), acetophenone (1.0 mmol), K-10 (500 mg), 170 °C, 15 min, MW power = 250 W.
[b] GC yields, based on the limiting reagent.

The results indicated that 1:0.8 acetophenone/phthalaldehydic acid ratio was the optimum for the reaction. The increase in the amount of phthalaldehydic acid resulted in declining yields due to byproduct formation.

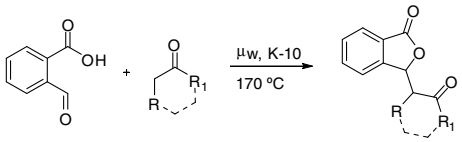
As a next step, we have optimized the reaction temperature and time. The results are summarized in Table 2. The data show that the reaction requires relatively high temperatures. At 110 °C, the yield was quite low (entry 1). At 130 °C and 150 °C the reaction proceeds with moderate yields (24–52%). At 170 °C and 190 °C, however, the cyclized product was formed in good yields (85%) and high selectivity. Accordingly, we selected 170 °C to study the effect of reaction times. We found 20 min to be the optimum reaction time. Shorter times gave lower yields due to lower conversion, while longer times resulted in a decrease in yield due to product decomposition and secondary reactions. For comparison, we have carried out the reaction under conventional conditions, using an external oil bath for heating (entry 11). The experiment was carried out in a closed pressure tube at the same temperature (170 °C). The 20-min reaction time gave multiple products and 45% yield for the target compound. It clearly indicates that the microwave heating initiated reaction conditions are more effective than the traditional setup. We have also tested the necessity of the solvent that was used prior to the reaction to ensure even adsorption of the reactants on the surface of the catalyst. Using a simple mechanical mixing of the catalyst and the reactants resulted in nearly the same yield (entry 10) as observed previously with the use of a solvent (entry 7). Thus, we concluded that no solvent is

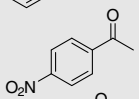
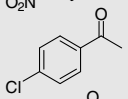
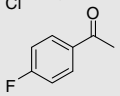
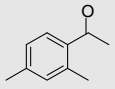
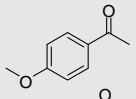
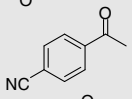
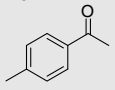
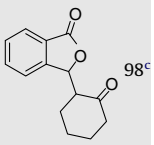
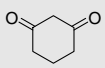
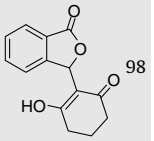
Table 2
Effect of temperature and reaction time on the microwave-assisted K-10 catalyzed cyclization reaction of phthalaldehydic acid with acetophenone[a]

Entry	Conditions[b]	Temperature (°C)	Time (min)	Yield[c] (%)
1	MW	110	15	15
2	MW	130	15	24
3	MW	150	15	52
4	MW	170	5	56
5	MW	170	10	79
6	MW	170	15	85
7	MW	170	20	90
8	MW	170	30	86
9	MW	170	40	88
10	MW[d]	170	20	88
11	CH[e]	170	20	45
12	MW	190	15	84

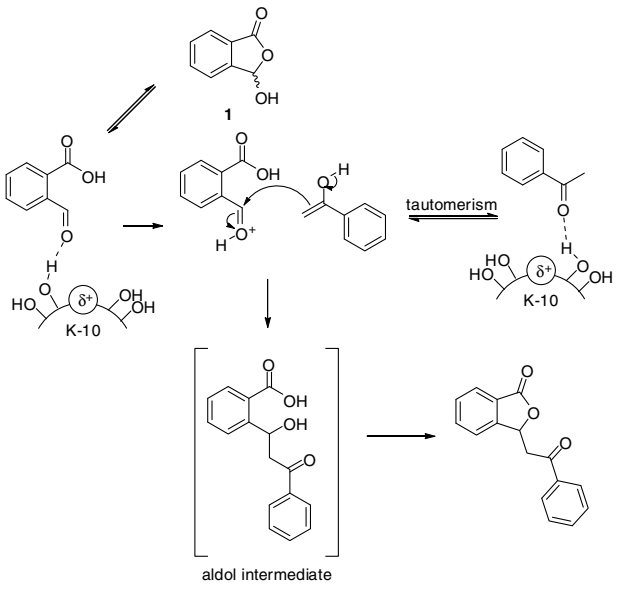
[a] Reaction conditions: phthalaldehydic acid (0.8 mmol), acetophenone (1.0 mmol), K-10 (500 mg), MW power = 250 W.
[b] MW—microwave, CH—conventional heating.
[c] GC yields, based on phthalaldehydic acid.
[d] The reactants were mixed with K-10 without any solvent.
[e] Conventional heating, pressure tube, toluene was used as a solvent.

Table 3
Synthesis of substituted isobenzofuran-1(3*H*)-ones by microwave-assisted K-10 montmorillonite catalyzed cyclization of phthalaldehydic acid with ketones at 170 °C and 250 W[a]



Entry	Ketone	Time (min)	Yield[b] (%)
a		20	90
b		30	92
c		30	90
d		20	91
e		30	92
f		30	98
g		10	98
h		10	98
i		20	 98[c]
j		30	 98

[a] Reaction conditions: phthalaldehydic acid (0.80 mmol), acetophenone (1.0 mmol), K-10 (500 mg), 170 °C, MW power = 250 W.
[b] GC yields, based on phthalaldehydic acid.
[c] Enol/ketone ratio = 1:1.



Scheme 2. Proposed mechanism for the synthesis of 3-phenacylphthalides via microwave-assisted montmorillonite K-10 catalyzed cyclizations.

necessary during the preparation of the reaction mixtures that makes the process even greener.

Based on the above studies, we found that the reaction took place in high yields with excellent selectivities under optimized conditions, although time may vary in reactions of different reactants (ketones). To explore the scope of our methodology, a wide variety of ketones were selected to synthesize substituted isobenzofuran-1(3*H*)-ones. The results are summarized in Table 3.

As the data indicated, all ketones gave excellent yields (>90%). The yields were not affected by the substituents, as neither electronic nor steric effects were predominant. The cyclization appeared to be a generally applicable process for the synthesis of a wide range of the target compounds.

Phthalaldehydic acid is often represented in two forms, 2-formylbenzoic acid and 3-hydroxyphthalide (**1**), which are in equilibrium with each other. The reaction proceeds in two steps; an aldol condensation and the subsequent cyclization. The first reaction follows the regular mechanism of acid-catalyzed condensation reactions and results in an aldol intermediate that immediately undergoes lactonization. It is known that K-10 montmorillonite possesses both Lewis and Brønsted acid centers on its surface and depending on the conditions, one or the other takes a leading role in catalysis.[8a,b,e,11] We suggest that in the present case, the reaction is driven by the Brønsted acid centers via the open form of the formyl benzoic acid. The existence of the cyclic hydroxyphthalide form is not favored by the strongly acidic and extremely polar conditions. The proposed mechanism is illustrated in Scheme 2.

3. Conclusion

A new, solid acid-catalyzed, effective, economic, and environmentally benign one-pot synthesis of 3-substituted phthalides has been developed. The products were obtained in excellent yields and exclusive selectivities in short reaction times. This simple, sustainable synthesis is a novel method for the preparation of the target compounds. Due to the importance of the products, our approach may contribute to widening pharmaceutical and biomedical applications of phthalide derivatives.

4. General procedure

Phthalaldehydic acid, ketones, and K-10 montmorillonite were purchased from Aldrich and used without further purification. The reactions were carried out at constant temperatures (usually 170 °C) in a Discover Benchmate microwave reactor, with continuous stirring. The temperature was measured and controlled by a built-in infrared detector. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained on a 300 MHz Varian NMR spectrometer in $CDCl_3$. Tetramethylsilane, $CFCl_3$ (for ^{19}F NMR), or the residual solvent signal were used as reference. The MS identification of the products was carried out with an Agilent 6850 GC–5973 MS system (70 eV electron-impact ionization) using a 30 m long DB-5 column (J&W Scientific). The melting points are uncorrected and were recorded on a MEL-TEMP apparatus.

4.1. One-pot microwave-assisted synthesis of isobenzofuran-1(3*H*)-ones—general procedure

In a typical reaction, phthalaldehydic acid (0.8 mmol) and a ketone (1 mmol) were dissolved in 9 ml of methylene chloride and 1 ml of methanol. Five hundred milligrams of K-10 montmorillonite were added to the mixture, which was stirred for 2 min. Then the solvent was evaporated in vacuo. The dry mixture was transferred into a reaction tube and irradiated in a microwave reactor under continuous stirring (CEM Discover Benchmate) in an open system under atmospheric pressure. During optimization, the progress of the reaction was monitored by GC–MS. When the reaction was completed the product was dissolved in CH_2Cl_2, separated from the catalyst by filtration and the solvent was removed in vacuo. The crude product was purified by flash chromatography.

Excluding two compounds (entries i and j), all products synthesized in this study are known and their spectral characterization showed satisfactory agreement with literature data. Here, the spectral data are listed only for the new compounds.

4.1.1. 3-(2-(4-Cyanophenyl)-2-oxoethyl)isobenzofuran-1(3*H*)-one (Table 3; entry j)

Yield: 98%; mp 165–167 °C (hexane/ethylacetate 80:20) ^{1}H NMR (300 MHz, $CDCl_3$); 8.03 (d, 2H, J = 8.7 Hz, Ar-H), 7.91 (d, 1H, J = 7.8 Hz, Ar-H), 7.78 (d, 2H, J = 8.7 Hz, Ar-H), 7.66 (qd, 1H, J = 7.5, 1.2 Hz, Ar-H), 7.50–7.61 (m, 2H, Ar-H), 6.13 (t, 1H, J = 6.3 Hz, CH), 3.73 (dd, 1H, J = 18.0, 6.3 Hz, CH), 3.40 (dd, 1H, J = 17.7, 6.6 Hz, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$); 194.7, 174.2, 149.2, 147.6, 139.8, 134.4, 132.7, 129.6, 128.5, 125.9, 122.5, 116.6, 116.2, 76.7, 43.9; MS-$C_{17}H_{11}NO_3$ (277), m/z (%): 277 (M^+, 10), 232 (12), 207 (10), 147 (100), 130 (82), 102 (68), 77 (44).

4.1.2. 3-(2-Oxocyclohexyl)isobenzofuran-1(3*H*)-one and 3-(2-hydroxycyclohex-1-enyl)isobenzofuran-1(3*H*)-one (Table 3; entry i)

Yield: 98%; oil; 1:1 mixture of tautomers ^{1}H (300 MHz, $CDCl_3$); 8.07 (d, 1H, J = 7.5 Hz, Ar-H, keto), 7.89 (d, 1H, J = 7.5 Hz, Ar-H, enol), 7.61–7.68 (m, 2H, Ar-H, keto/enol), 7.49–7.53 (m, 2H, Ar-H, keto/enol), 7.36 (t, 1H, Ar-H, keto/enol), 7.23 (t, 1H, Ar-H, keto/enol), 6.11 (d, 1H, J = 3.0 Hz, CH, enol), 5.98 (d, 1H, J = 6.0 Hz, CH, keto), 3.20 (m, 1H, keto), 1.51–2.76 (m, 17H, 8CH_2, keto/enol); ^{13}C (75.5 MHz, $CDCl_3$); 199.6, 174.1, 172.4, 166.0, 150.8, 134.0, 133.9, 129.1, 125.53, 125.51, 124.1, 122.7, 116.6, 79.7, 79.0, 53.2, 42.1, 34.2, 28.5, 27.6, 26.9, 26.5, 24.2, 20.9; MS-$C_{14}H_{14}O_3$ (230), enol: m/z (%): 230 (M^+, 40), 212 (93), 201 (58), 133 (100), 105 (25), 77 (28); keto: m/z (%): 230 (M^+, 47), 212 (98), 201 (55), 133 (100), 105 (27), 77 (22).

Acknowledgments

Financial support provided by University of Massachusetts Boston and NIH (R-15 AG025777-02) is gratefully acknowledged.

References and notes

1. (a) Pedrosa, R.; Sayalero, S.; Vicente, M. *Tetrahedron* **2006**, *62*, 10400; (b) Zhu, X. Z.; Li, X.-Y.; Liu, J. *Eur. J. Pharmacol.* **2004**, *500*, 221; (c) Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, S.-L. Chemistry and Biological Action of Naturally Occurring Phthalides. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2005; Vol. 32, p 611; (d) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; (e) Barton, D. H. R.; de Varies, J. X. *J. Chem. Soc.* **1963**, 1916; (f) Bayer, E.; Hayat, S.; Atta-ur-Rahman; Choudhary, M. I.; Khan, K. M.; Shah, S. T. A.; Imran-ul-Haq, M.; Anwar, M. U.; Voelter, W. *Arzneim.-Forsch./Drug Res.* **2005**, *55*, 588.
2. (a) Paradkar, M. V.; Ranade, A. A.; Kulkarni, M. S.; Godbole, H. M.; Joseph, A. R. *J. Chem. Res.* **1998**, 332; (b) Narsimhan, N. S.; Mali, R. S. *Synthesis* **1975**, 797; (c) Baldwin, J. E.; Bair, K. W. *Tetrahedron Lett.* **1978**, *19*, 2559; (d) Kim, K. S.; Spatz, M. W.; Johnson, F. *Tetrahedron Lett.* **1979**, *20*, 331; (e) Pahari, P.; Senapati, B.; Mal, D. *Tetrahedron Lett.* **2004**, *45*, 5109; (f) Mal, D.; Pahari, P.; De, S. R. *Tetrahedron* **2007**, *63*, 11781.
3. (a) Safari, J.; Naeimi, H.; Khakpour, A. A.; Jondani, R. S.; Khalili, S. D. *J. Mol. Catal. A* **2007**, *270*, 236; (b) Brady, S. F.; Wagenaar, M. M.; Sing, M. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043; (c) Yoganathan, K.; Rossant, C.; Ng, S.; Huang, Y.; Butler, M. S.; Buss, A. D. *J. Nat. Prod.* **2003**, *66*, 1116; (d) Veeraraghavan, P. R.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205; (e) Yang, H.; Hu, G.-Y.; Chen, J.; Wang, Y.; Wang, Z.-H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5210; (f) Mor, S.; Dhavan, S. N.; Kapoor, M.; Kumar, D. *Tetrahedron* **2007**, *63*, 594; (g) Bousquet, E. W.; Moran, M. D.; Harmon, J.; Johnson, A. L.; Summers, J. C. *J. Org. Chem.* **1975**, *40*, 2208.
4. Paradkar, M. V.; Gadre, S. Y.; Pujari, T. A.; Khandekar, P. P.; Kumbhar, V. B. *Synth. Commun.* **2005**, *35*, 471.
5. Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Klumpp, D. A. *J. Org. Chem.* **2004**, *69*, 2340.
6. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2003**, *4*, 747.
7. Lee, D. Y.; Cho, C. S.; Jiang, L. H.; Wu, X.; Shim, S. C.; Oh, D. H. *Synth. Commun.* **1997**, *27*, 3449.
8. (a) Benesi, H. A.; Winquest, B. H. C. *Adv. Catal.* **1978**, *27*, 97; (b) Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays*; Springer: Berlin, 1993; (c) Smith, G. V.; Notheisz, F. *Heterogeneous Catalysis in Organic Chemistry*; Academic Press: San Diego, 1999; (d) Clark, J. H. *Acc. Chem. Res.* **2002**, *35*, 791; (e) Gates, B. C. Catalysis by Solid Acids. In *Encyclopedia of Catalysis*; Horvath, I. T., Ed.; Wiley: New York, 2003; Vol. 1, p 104; (f) Dasgupta, S.; Török, B. *Org. Prep. Proced. Int.* **2008**, *40*, 1; (g) Dasgupta, S.; Török, B. *Curr. Org. Synth.*, in press.
9. (a) Loupy, A. *Microwaves in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2005; (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005; (c) Tierney, J. P.; Lidstrom, P. *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, 2005.
10. (a) Abid, M.; Török, B. *Adv. Synth. Catal.* **2005**, *37*, 1797; (b) Abid, M.; Landge, S. M.; Török, B. *Org. Prep. Proced. Int.* **2006**, *38*, 495; (c) Abid, M.; Spaeth, A.; Török, B. *Adv. Synth. Catal.* **2006**, *348*, 2191; (d) Landge, S. M.; Schmidt, A.; Outerbridge, V.; Török, B. *Synlett* **2007**, 1600; (e) Landge, S. M.; Atanassova, V.; Thimmaiah, M.; Török, B. *Tetrahedron Lett.* **2007**, *48*, 5161; (f) Abid, M.; Savolainen, M.; Landge, S. M.; Hu, J.; Prakash, G. K. S.; Olah, G. A.; Török, B. *J. Fluorine Chem.* **2007**, *128*, 587; (g) Abid, M.; De Paolis, O.; Török, B. *Synlett* **2008**, 410; (h) Landge, S. M.; Török, B. *Catal. Lett.* **2008**, *122*, 338.
11. (a) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039; (b) Nikalje, M. D.; Phukan, P.; Sudalai, A. *Org. Prep. Proced. Int.* **2000**, *32*, 1; (c) Varma, R. S. *Tetrahedron* **2002**, *58*, 1235; (d) Ju, Y. H.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135.