CHEMCOMM Communication
www.rsc.org/chemcomm

Catalyst-free reactions under solvent-free conditions: microwave-assisted synthesis of heterocyclic hydrazones below the melting points of neat reactants†

Marjan Ješelnik,[a] Rajender S. Varma,*[b] Slovenko Polanc[a] and Marijan Kocevar*[a]

[a] *Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerceva 5, SI-1000 Ljubljana, Slovenia. E-mail: marijan.kocevar@Uni-Lj.si*

[b] *Clean Processes Branch, National Risk Management Research Laboratory, U.S. Environmental Protection Agency, MS 443, 26 W. Martin Luther King Drive, Cincinnati, OH 45268, USA. E-mail: varma.rajender@epa.gov*

Received (in Corvallis, OR, USA) 17th May 2001, Accepted 27th June 2001
First published as an Advance Article on the web 29th August 2001

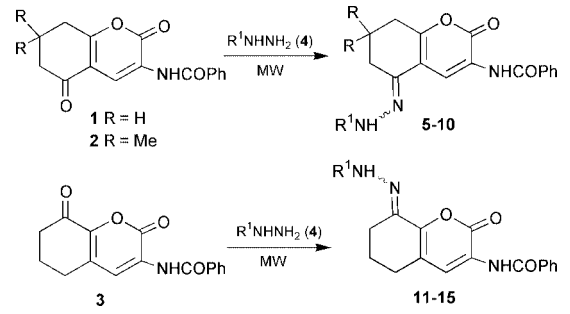
The reaction of neat 5- or 8-oxobenzopyran-2(1*H*)-ones, 1–3, with a variety of aromatic and heteroaromatic hydrazines, 4, is remarkably accelerated upon irradiation in a household microwave oven in the absence of any catalyst, solid support or solvent thus providing an environmentally friendly route to several heterocyclic hydrazones.

Microwave (MW) irradiation has been used for the rapid synthesis of a variety of compounds.[1] Chemical reactions can be accelerated because of selective absorption of microwave energy by polar molecules, non-polar being inert to the MW dielectric loss. Heterogeneous reactions facilitated by supported reagents on various inorganic surfaces have received special attention in recent years.[2] However, relatively little attention is paid to solventless reactions with neat reactants in the absence of a catalyst or solid support.

From the synthetic point of view hydrazones are important synthons for several transformations[3a–d] and their synthesis from various precursors is well documented.[3a,b] Recently, some hydrazones have been prepared from carbonyl compounds and hydrazine hydrate in ethylene glycol[4a] and toluene[4b] by the application of MW irradiation while some others are synthesized in the presence of silica gel and NaOH.[5]

We report here a general synthesis of several hydrazones **5–15**, which in some earlier preparations required relatively strenuous reaction conditions namely heating substrates for several hours in the presence of an acidic catalyst.[6] The synthetic efforts for these compounds have been previously directed for the selective design of the benzopyran-2-one ring at the positions 5 and 8 as well as for the new transformation into the corresponding quinoline derivatives. The conformational analysis has been accomplished for some of these derivatives by applying molecular modelling techniques based on experimentally determined NOE distance restraints in order to determine their structure in solution.[6a,d] These studies have been stimulated, in part, due to potentially significant biological activity associated with a variety of 2*H*-1-benzopyrans and quinolines.[6d] For the above reasons and in view of our general interest in the development of environmentally friendlier synthetic alternatives using microwaves,[2] we became interested in an expeditious synthesis of these compounds. In all the reactions reported in this paper we worked with neat starting materials, 1-benzopyran-2(2*H*)-ones **1**,[7a,b] **2**,[7a,b] **3**[7c] and hydrazines, **4**, wherein the reactions are completed within minutes and in high yields (61–98%, Scheme 1, Table 1)‡ using an unmodified household MW oven. Remarkably, reactions proceeded well even when both the starting reactants were solids and the reaction temperature was maintained below the melting points of both components; recently some comments have been made on the preparation of phthalimides starting from solid components, phthalic anhydride and amino compounds.[8a] In view of the unprecedented nature of this reaction, we examined the synthesis of the products **10** and **14** in detail. Since a conventional household MW oven is used with no accurate temperature control,§ we decided to measure the temperature of the alumina bath (used for housing the reaction vessel in the MW oven) with a calibrated thermometer immediately after completion of the reaction. In a controlled experiment, concurrently, we also heated the lower melting reactant in a second glass beaker to obtain visual information about the integrity of the solid materials upon exposure to microwaves.

For the synthesis of **10**, the starting benzopyran **2**[7a,b] (mp 179–179.5 °C) and 3-chloro-6-hydrazinopyridazine[9a] (mp 135–137 °C), were admixed in the ratio 1 : 2 (Table 1). When the reaction mixture was irradiated with MW for 5.5 min the highest temperature of the alumina recorded was 120–122 °C. The reaction mixture remained solid and no reaction was observed. After heating for 6 min, however, the temperature of the bath reached 130–132 °C and the reaction mixture was completely in



Scheme 1

Table 1 Solvent-free preparation of hydrazones, **5–15**, using microwaves

Starting benzopyran	Hydrazine **4** R¹=	(mmol)	React. time/ min	Product (yield, %)
1	Ph	(1.2)	6	**5** (83)
1	2,5-Difluorophenyl	(3.0)	8	**6** (69)
1	3-CF_3-C_6H_4	(1.5)	8	**7** (75)
2	Ph	(2.0)	8	**8** (61)
2	3-CF_3-C_6H_4	(3.0)	10	**9** (62)
2	6-Chloropyridazin-3-yl	(2.0)	6	**10** (85)
3	Ph	(3.0)	3	**11** (95)
3	3-CF_3-C_6H_4	(1.5)	8	**12** (92)
3	Pyridin-2-yl	(3.0)	5	**13** (65)
3	4-Nitrophenyl	(~2.6)[a]	9	**14** (98)
3	2,5-Difluorophenyl	(3.0)	8	**15** (96)

[a] Reagent contains 10–15% of water for stabilization.

† Dedicated with deep respect to Professor Miha Tišler, University of Ljubljana, Slovenia on the occasion of his 75th birthday.

 DOI: 10.1039/b104508n

liquefied form affording hydrazone **10** in 85% isolated yield (see Table 1). The 3-chloro-6-hydrazinopyridazine kept in the same bath barely melted (~5% as estimated visually) at that temperature. With the critical temperature information in hand, we embarked on a comparative study and heated the above reaction mixture in the same proportions using a preheated oil bath. Heating for 12 min at 133 °C gave a mixture (liquid with some suspended solid material). NMR analysis revealed that the molar ratio between hydrazone **10** and starting benzopyran **2** was approximately 3.3:1. Prolonged heating of the reaction mixture for 1 h at 133 °C resulted in the formation of the liquid with no suspended solids. The work-up (as in general procedure) and NMR analysis revealed that the ratio between **10** and **2** in the isolated product was 92:8. Obviously, the unreacted benzopyran derivative contaminated product **10**, while under MW conditions we observed complete conversion to a single product (Table 1).

For the synthesis of **14** starting from **3**[7c] (mp 248–250 °C) and 4-nitrophenylhydrazine[9b] (mp ~157 °C with decomp.) we performed an experiment with the reactants in the ratio 1:2.6 respectively. The commercially obtained hydrazine derivative, however, contained 10–15% of water for stabilization and as such slightly melted at 130 °C. Upon MW irradiation for 5.5 min the same temperature (120–122 °C) was attained and the reaction mixture was completely melted while the 4-nitrophenylhydrazine in the second beaker was only barely melted. NMR analysis of the crude mixture showed no presence of the benzopyran derivative **3**, and the work-up resulted in hydrazone **14** in 94% yield. On the other hand, heating the same reaction mixture for 1 h at 128 °C in an oil bath resulted in a mixture of product **14** and starting **3** in the ratio 4.3:1, as discerned from the ^{1}H NMR spectrum of the crude reaction mixture. It should be mentioned that in this case the reaction mixture at the end of the heating period remained solid but attained a brownish color presumably as a result of partial decomposition.

This comparative study of the reactions taking place in an oil bath in the absence of MW heating revealed a substantial rate enhancement for reactions conducted under MW irradiation conditions, presumably due to the increase in polarity after change from the solid to the liquid phase.[8a] Such bimolecular reactions[2d,e] will have polarity enhancement as a result of ensuing intermediate transition state and consequently may display a pronounced microwave effect.[8b] Further, the reactions could be visibly monitored since no reaction occurs without formation of a melt. This methodology allows for performing rapid syntheses of a variety of hydrazones¶ below melting points of starting materials used. This could be explained by the lowering of the melting point by the formation of the eutectic;[10] such methodology seems to be especially useful when starting from substrates, which decompose at the normal melting point.

In conclusion, we have shown an expeditious, easy-to-handle and environmentally friendlier approach to the synthesis of a variety of non-easily-available hydrazones using MW irradiation that can be extended to other systems.

The authors wish to thank the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support (P0-0503-103). Dr B. Kralj and Dr D. Žigon ('Jožef Stefan' Institute, Ljubljana) are acknowledged for mass spectra.

Notes and references

‡ The starting benzopyran-2(2*H*)-ones, **1**–**3**, and 3-chloro-6-hydrazinopyridazine were prepared as described in the literature.[7,9a] A household microwave oven operating at 2450 MHz was used at its full power, 650 W, for all the experiments.

*General procedure for the synthesis of hydrazones **5**–**15***: a neat mixture of benzopyran derivative **1**–**3** (1 mmol) and hydrazine **4** (1.2–3 mmol; see Table 1) in a 10 mL glass beaker was thoroughly mixed for about 5 min, then it was placed in an alumina bath inside the household microwave oven and irradiated. Maximum temperature reached in the alumina after 10 min was about 150 °C. After cooling, methanol (~4 mL) was added to the mixture and the separated solid was filtered off and washed with a small amount of methanol. Reaction conditions and yields are given in Table 1 for products, **5**–**15**, which conform to the NMR and elemental analyses.

§ There are commercial microwave devices available that provide adequate mixing and control of reaction parameters such as temperature, pressure.

¶ *N*-(5,6,7,8-Tetrahydro-2-oxo-5-phenylhydrazono-2*H*-1-benzopyran-3-yl)benzamide (**5**): mp 213–216 °C (DMF–MeOH); lit.[6c] 216–220 °C.

N-[5-(2,5-Difluorophenyl)hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl]benzamide (**6**): mp 248–249 °C, decomp. (DMF–MeOH).

N-[5,6,7,8-Tetrahydro-2-oxo-5-(3-trifluoromethyl)phenylhydrazono-2*H*-1-benzopyran-3-yl]benzamide (**7**): mp 222–223 °C (DMF–MeOH).

N-(5,6,7,8-Tetrahydro-7,7-dimethyl-2-oxo-5-phenylhydrazono-2*H*-1-benzopyran-3-yl)benzamide (**8**): mp 223–226 °C (DMF–MeOH); lit.[6c] 223–226 °C.

N-[5,6,7,8-Tetrahydro-7,7-dimethyl-2-oxo-5-(3-trifluoromethyl)phenylhydrazono-2*H*-1-benzopyran-3-yl]benzamide (**9**): mp 221–223 °C (DMF).

N-[5,6,7,8-Tetrahydro-7,7-dimethyl-2-oxo-5-(6-chloropyridazin-3-yl)-hydrazono-2*H*-1-benzopyran-3-yl]benzamide (**10**): mp 259–261 °C (DMF–MeOH); lit.[6a] 260–263 °C.

N-(5,6,7,8-Tetrahydro-2-oxo-8-phenylhydrazono-2*H*-1-benzopyran-3-yl)benzamide (**11**): mp 258–262 °C (DMF–MeOH); lit.[6f] 257–260 °C.

N-[5,6,7,8-Tetrahydro-2-oxo-8-(3-trifluoromethyl)phenylhydrazono-2*H*-1-benzopyran-3-yl]benzamide (**12**): mp 113–114.5 °C (DMF–MeOH).

N-[5,6,7,8-Tetrahydro-2-oxo-8-(pyridin-2-yl)hydrazono-2*H*-1-benzopyran-3-yl]benzamide (**13**): mp 226–229 °C (DMF–MeOH).

N-[5,6,7,8-Tetrahydro-2-oxo-8-(4-nitrophenyl)hydrazono-2*H*-1-benzopyran-3-yl]benzamide (**14**): mp 290 °C (DMSO).

N-[5,6,7,8-Tetrahydro-2-oxo-8-(2,5-difluorophenyl)hydrazono-2*H*-1-benzopyran-3-yl]benzamide (**15**): mp 238–239 °C (DMSO).

1 (*a*) S. Caddick, *Tetrahedron*, 1995, **51**, 10 403; (*b*) R. S. Varma, *Green Chem*., 1999, **1**, 43; (*c*) R. S. Varma, *J. Heterocycl. Chem*., 1999, **36**, 1565; (*d*) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis*, 1998, 1213; (*e*) A. de la Hoz, A. Díaz-Ortis, A. Moreno and F. Langa, *Eur. J. Org. Chem*., 2000, 3659.

2 (*a*) R. S. Varma, in *ACS Symposium Series No. 767/ Green Chemical Syntheses and Processes*, ed. P. T. Anastas, L. Heine and T. Williamson, American Chemical Society, Washington DC, 2000, Chapter 23, pp. 292–313; (*b*) R. S. Varma, in *Green Chemistry: Challenging Perspectives*, ed. P. Tundo and P. T. Anastas, Oxford University Press, Oxford, 2000, pp. 221–244; (*c*) R. S. Varma, *Pure Appl. Chem*., 2001, **73**, 193; (*d*) R. S. Varma, R. Dahiya and S. Kumar, *Tetrahedron Lett*., 1997, **38**, 2039; (*e*) A. Vass, J. Dudas and R. S. Varma, *Tetrahedron Lett*., 1999, **40**, 4951; (*f*) R. S. Varma, *Clean Products and Processes*, 1999, **1**, 132.

3 (*a*) J. S. Clark, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon, Oxford, 1995, Vol. 3, pp. 443–490; (*b*) D. E. Bergbreiter and M. Momongan, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, Vol. 2, pp. 503–526; (*c*) W. Sucrow, *Org. Prep. Proced. Int*., 1982, **14**, 93; (*d*) R. Fusco and F. Sannicolo, *Tetrahedron*, 1980, **36**, 161.

4 (*a*) B. K. Banik, K. J. Barakat, W. R. Wagle, M. S. Manhas and A. K. Bose, *J. Org. Chem*., 1999, **64**, 5746; (*b*) S. Gadhwal, M. Baruah and J. S. Sandhu, *Synlett*, 1999, 1573.

5 A. R. Hajipour, I. Mohammadpoor-Baltork and M. Bigdeli, *J. Chem. Res., (S)*, 1999, 570.

6 (*a*) P. Trebše, S. Polanc, M. Kocevar, T. Šolmajer and S. Golic Grdadolnik, *Tetrahedron*, 1997, **53**, 1383; (*b*) P. Trebše, B. Recelj, M. Kocevar and S. Polanc, *J. Heterocycl. Chem*., 1997, **34**, 1247; (*c*) P. Trebše, B. Recelj, T. Lukanc, S. Golic Grdadolnik, A. Petric, B. Vercek, T. Šolmajer, S. Polanc and M. Kocevar, *Synth. Commun*., 1997, **27**, 2637; (*d*) S. Golic Grdadolnik, P. Trebše, M. Kocevar and T. Šolmajer, *J. Chem. Inf. Comput. Sci*., 1997, **37**, 489; (*e*) M. Kocevar, *Chem. Listy*, 1997, **91**, 610; (*f*) P. Trebše, L. Vranicar, I. Mušic, S. Polanc, W. C. Stevens and M. Kocevar, *Heterocycles*, 2000, **53**, 1111.

7 (*a*) M. Kocevar, S. Polanc, M. Tišler and B. Vercek, *Synth. Commun*., 1989, **19**, 1713; (*b*) V. Kepe, M. Kocevar, S. Polanc, B. Vercek and M. Tišler, *Tetrahedron*, 1990, **46**, 2081; (*c*) V. Kepe, M. Kocevar, A. Petric, S. Polanc and B. Vercek, *Heterocycles*, 1992, **33**, 843.

8 (*a*) T. Vidal, A. Petit, A. Loupy and R. N. Gedye, *Tetrahedron*, 2000, **56**, 5473; (*b*) S. Paul, M. Gupta, R. Gupta and A. Loupy, *Tetrahedron Lett*., 2001, **42**, 3827.

9 (*a*) N. Takahayashi, *J. Pharm. Soc. Jpn*., 1955, **75**, 778; *Chem. Abstr*., 1956, **50**, 4970c; (*b*) The Merck Index, 12th edn., Merck & Co., Inc., Whitehouse Station, 1996, p. 1138 (Monograph number 6721).

10 C. F. Most, *Experimental Organic Chemistry*, J. Wiley & Sons, New York, 1988, pp. 53–62.