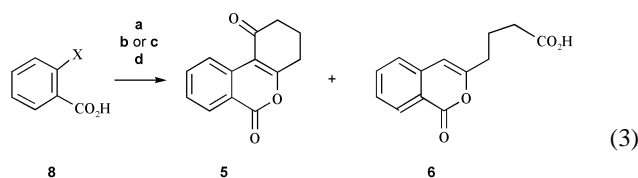


Table 1 Substitution techniques

Entry	Acid	Technique	Yield (%)	
			5	6
1	8, X = I or Br	Reflux/dioxane	60	Trace ^a
2	8, X = I	Parr/200 °C	Trace	55 ^b
3	8, X = I	Synthetic microwave/150 °C/80 psi	5 ^b	65
4	8, X = I	Commercial microwave/100 °C	60	8 ^b
5	8, X = Br	Parr/200 °C (CuBr cat.)	<5	50

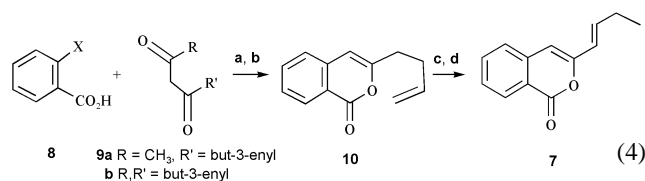
^a NaH as the base. ^b GC yield.

Similarly, β -ketoesters give the reflux product **3a** [steps a, c; eqn. (2)] or diacid **4** [steps b, c; eqn. (2)]¹¹ in NCW. What attracted attention was that 1,3-cyclohexanedione could afford either 3,4-dihydro-2*H*-benzo[*c*]chromen-1,6-dione (**5**) or 4-(1-oxo-1*H*-isochromen-3-yl)butyric acid (**6**) *in water* with the same reagents using different energy input [eqn. (3), Table 1]. Chromendione **5** has been investigated as a natural product and drug synthon and **6** has the same carbon skeleton as artemidin [**7**, eqn. (4)], an active natural product.¹² Structure **6** could be converted to artemidin and this is currently being pursued.¹³ However, a two-step proof of principle preparation of **7** has been completed to exploit the diversity of hot pressurized water in this substitution process.



a. 1,3-cyclohexanedione, base, CuX; b. dioxane/ Δ ; c. NCW; d. dil. HCl aq.

Synthesis of artemidin: *o*-Iodobenzoic acid (**8**), in a Parr or microwave pressure reactor, was treated with **9a** [step a then b; eqn. (4)] yielding a mixture of mainly **2** [eqn. (1), above] and minor amounts of desired structure **10**. It was errantly anticipated that the acyl group of **9a** would be more susceptible to *retro*-Claisen reaction than the pentenoyl group. To avoid this unfavorable cleavage symmetrical dione **9b** was used. The potassium salts of **9b** and acid **8** with cuprous iodide in water at 150 °C in a synthetic microwave pressure reactor^{8a} (80 psi) for an hour affords 3-but-3-enylisochromen-1-one (**10**) as a distillable oil.^{14–16}



a. KOH, Cu⁺, NCW; b. dil. HCl; c. m-NCW; d. m-NCW/ethylene glycol.

The terminal olefin of **10** is induced to migrate *via* irradiation (10 one minute bursts on full power)^{8b} in a commercial microwave with palladium on carbon in water–ethylene glycol, giving a mixture of isomeric structures, 45% of which is artemidin (**7**).¹⁷ Additional irradiation (15 one minute bursts on full power), drives isomerization to predominately artemidin with less than 10% of the isomers of **7** by GC.¹⁸

Water washing of organic reaction products is often the first step of purification and water–alcohol mixtures are frequently employed for crystallization of materials. Thus in addition to the role of being a green reaction media, water has the potential of being the first step of a greener purification protocol. The above NCW reaction [eqn. (4)] on cooling and neutralization gives an

oil [**6**, steps a, c, d; eqn. (4)] or solid [**5**, steps a, b, d; eqn. (4)] separable from the aqueous phase in larger scale preparations. Initial studies have employed classical organic (ethyl acetate) aqueous extractions and minimal chromatography.

Conclusion

The extreme changes in properties of water¹⁹ over a range of temperatures and pressures provide the potential to ‘tune’ reactions towards different outcomes. Formation of **1a** or **2b** by varying heating and pressure in water illustrates this potential. Further aspects of this process and the effects of catalyst efficiency are being investigated.

Acknowledgements

The University of South Carolina (The South Carolina EPA/EPSCoR Program, R826399-01-0), Wingate University, and SDR Pharmaceuticals are gratefully acknowledged for support of this work. J. J. S. is the 1998 Ken Hancock Memorial Green Chemistry Scholar.

References

- 1 Isochromen-1-one and isocoumarin refer to the same fused ring system.
- 2 For examples of organic reactions in water, see: A. R. Katritzky and S. M. Allin, *Acc. Chem. Res.*, 1996, **29**, 399–406; J. An, L. Bagnell, T. Cablewski, C. R. Strauss and R. W. Trainor, *J. Org. Chem.*, 1997, **62**, 2505–11; P. E. Savage, *Chem. Rev.*, 1999, **99**, 603–21; M. Siskin and A. R. Katritzky, *Chem. Rev.*, 2001, **101**, 825–835; N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725–2750.
- 3 The general range of temperatures and pressures used in pressure reactors: 100–275 °C and 40–800 psi.
- 4 F. Bellina, D. Ciucci, P. Vergamini and R. Rossi, *Tetrahedron*, 2000, **56**, 2533–2545(a) R. D. Barry, *Chem. Rev.*, 1964, **64**, 229–259; (b) F. Bohlmann and C. Zdero, *Chem. Ber.*, 1970, **103**, 2856–2859; (c) F. Bohlmann and C. Zdero, *Phytochemistry*, 1976, **15**, 1318–1319; (d) G. Qabaja, E. M. Perchellet, J.-P. Perchellet and G. B. Jones, *Tetrahedron Lett.*, 2000, **41**, 3007–3010; (e) W. B. Turner, *Fungal Metabolites*, Academic Press, London, 1971, ch. 5; (f) R. A. Hill, *Progress in the Chemistry of Organic Natural Products*, Wein-Springer-Verlag, New York, 1986, vol. 49; (g) S. Ohta, Y. Kamata, T. Inagaki, Y. Masuda, S. Yamamoto, M. Yamashita and I. Kawasaki, *Chem. Pharm. Bull.*, 1993, **41**, 1188–1190.
- 5 Base generally refers to KOH. For convenience alkoxides were also used to form salts of carboxylic acids and β -dicarbonyl compounds.
- 6 Examples: A. McKillop and D. P. Rao, *Synthesis*, 1977, 759–760; A. McKillop and D. P. Rao, *Synthesis*, 1977, 760–761; A. Bruggink and A. McKillop, *Tetrahedron*, 1975, **31**, 2607–2619; G. Chang, seminar USC, 2001, MTP inhibitor made by the analogous *o*-haloacid substitution and converted to a tetrahydroisoquinoline.

- 7 p-NCW refers to near critical water generated in a Parr pressure reactor; m-NCW refers to near critical water generated with microwaves.
- 8 (a) MARS5 synthetic microwave (b) Goldstar 300 watt microwave oven.
- 9 Without acidification isochromenone formation is incomplete.
- 10 Retro-Claisen reaction (*e.g.* formation of **2**) must occur before isochromenone formation; treating isochromenone **1** with NCW (Parr, 200–250 °C) affords no **2** with good recovery of **1**.
- 11 Isochromenone **3b** is a minor product from organic solvent reflux or near critical water procedures.
- 12 Synthesis of artemidin: G. Batu and R. Stevenson, *J. Org. Chem.*, 1980, **45**, 1532–1534.
- 13 As of the present we have no green way of reducing acid **6** to an alcohol.
- 14 (a) Synthon **10**: (110–130 °C, 0.02 mm, bulb-to-bulb), IR (cm⁻¹): 1731, 1658; ¹H NMR (ppm): signals of isochromen-1-one plus 5.77 (m, 1H), 5.04 (m, 2H), 2.55 (m, 2H), 2.40 (m, 2H); MS (*m/z*): 200 (M), 159 (M – 41 (allyl)), 131 (B) (b) artemidin (**7**): IR (cm⁻¹): 1728, 1606; ¹H NMR (ppm): signals of isochromen-1-one plus 6.68 (dt, 1H), 6.01 (dt, 1H), 2.25 (m, 2H), 1.09 (t, 3H); MS (*m/z*): 200 (M, B).
- 15 For convenience the preformed potassium salts of acid **8** and the β-dicarbonyl or β-ketoester were prepared and mixed together.
- 16 For this study dione **9b** was prepared by dianion alkylation of acetylacetone and allyl bromide (2×); 4-pentenyl chloride is commercially available for a malonic ester synthesis of **9b**. 4-Pentenoic acid is recovered from the reaction of **8** and **9b**.
- 17 Ethylene glycol is added to enhance energy absorption. A heat sink of water was used around a glass pressure reactor. The glass pressure reactor was briefly air-cooled by shaking between bursts. See: B. Hayes, *Microwave Synthesis, Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, USA, 2002, ch. 2, p. 70.
- 18 The minor components consist mainly of the *cis* isomer of **7**. Long-term commercial microwave irradiation of **10** at very low power settings led to only minor amounts of olefin isomerization to **7** and 3-(but-2-enyl)isochromen-1-one.
- 19 As the temperature and pressure increase, the dielectric constant and hydrogen bonding decrease, and the water ionization and organic solubility increases.