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## REVIEW ARTICLE

### Solvent-free reactivity in the undergraduate organic laboratory

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This review highlights progress made since 2000 in the development of solvent-free organic reactions for student use. It is directed at university instructors to illustrate the broad scope of solventless reactivity possible in undergraduate laboratories. Eliminating a reaction medium directly addresses the Twelve Principles of Green Chemistry and is a focal point of contemporary industrial research. Experimental conditions are straightforward to implement and include reactant grinding, room temperature stirring, microwave irradiation, and conventional heating. A wide range of functional group transformations is easily achievable. Solvent-free reactions are often complete in a matter of minutes and routinely require simplistic work-up and purification protocols. Procedures are compiled from educational resources (primarily pedagogical journals and laboratory manuals) and corollary green experimental elements emphasized where possible.

**Keywords:** solvent-free reactivity; Twelve Principles; organic synthesis; microwave reactivity; education

#### Introduction

When teaching organic reactivity principles to new chemistry undergraduates, instructors often discuss and rationalize types of solvent employed for different transformations. Examples of this include common use of dry ether for Grignard reactions (1) and acetonitrile for processes proceeding via an  $\text{Sn}2$  mechanism (2). Students quickly appreciate that solvents are an important component of organic reactions and eventually ponder “which solvent should I select?” when faced with designing conditions for their own chemistry. Sheldon has affirmed “the best solvent is no solvent” (3) with the last two decades seeing remarkable strides made in the field of solvent-free synthesis where reactions are conducted in the absence of auxiliary substances. Pioneering work by Tanaka and Toda has been reviewed (4,5) where solid reactants are often ground together to effect reactivity. This approach has spawned the technique of “grindstone chemistry” (6), which is adapted for large-scale production of pharmaceuticals. Much solventless reactivity is currently performed under microwave irradiation (7,8) either in a domestic microwave oven or a commercially available dedicated reactor. Microwave heating of reagent–reactant complexes is more consistent and expeditious to that achievable using conventional hot plates, oil/sand baths, and mantles. Since 2000, chemical educators have designed a wide range of

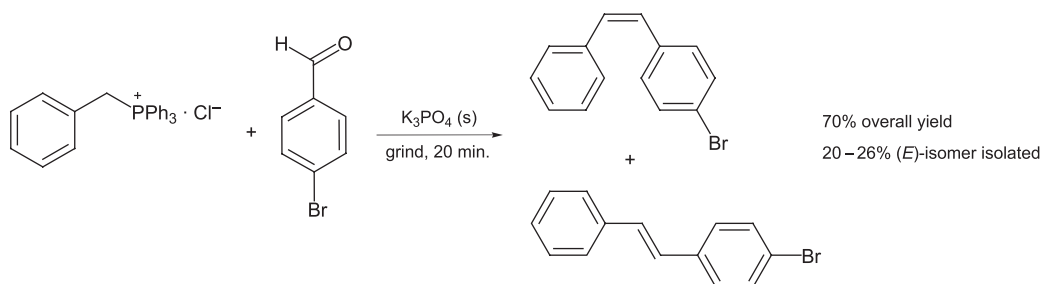
procedures facilitating application of solvent-free reactions in the undergraduate laboratory (9). This article compiles these experiments and is directed at college and university instructors with the aim of showcasing and promoting the principle of organic reactivity sans solvent.

Solventless reactivity has a number of advantages from the perspective of both teachers and students. Two of the Twelve Principles of Green Chemistry (10) are to “use safer solvents and reaction conditions” and to “prevent waste.” These axioms are both directly met by eliminating a reaction medium. A third principle is “increase energy efficiency” which is often addressed. Solvent-free processes regularly exhibit impressive rate accelerations due to increased reactant concentrations with some occurring under ambient conditions in the presence or absence of grinding. Microwave irradiation regularly affords a dramatic reduction in reaction time (often from hours to minutes) so that many procedures can be undertaken in a three or four-hour laboratory period. In addition, product work-up, isolation, and purification are straightforward for most reactions.

Reactions summarized here date from 2000 onward and are arranged according to the major experimental techniques employed in solventless reactivity. These are room temperature mechanical mixing (including reactant grinding and ambient stirring); microwave/visible light irradiation and

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Scheme 1. Wittig synthesis of diastereomeric (4-bromophenyl)styrenes via reactant grinding (11).

conventional heating. Each technique is sub-divided into reaction types where applicable: C–C bond-forming reactions, C–N bond-forming reactions, and transformations involving C–H and/or C–O bond formations. Experimental conditions, reaction times, and documented student yields (where known) are emphasized along with other green chemistry aspects and reactions of interest.

### Room temperature mechanical mixing

#### C–C bond formations

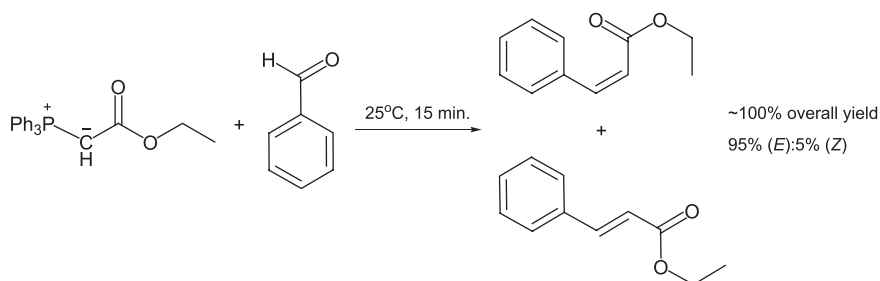
Many solvent-free pedagogical procedures feature C–C and C–N bond formation with the key mechanistic step being nucleophilic addition at an electron-deficient carbon atom. Leung and Angel (11) described preparation of (*Z*) and (*E*)-(4-bromophenyl)styrene by a solventless Wittig reaction. The reaction involves grinding 4-bromobenzaldehyde, benzyltriphenylphosphonium chloride, and tribasic potassium phosphate with a pestle and mortar for 20 minutes (Scheme 1). Washing the crude mixture with water and recrystallization from ethanol affords the pure (*E*)-isomer as the isolated product, engendering a green work-up procedure.

Nguyen and Weizman (12) recently developed a quantitative Wittig synthesis of diastereomeric ethyl cinnamate esters. This approach dispenses with dichloromethane as the usual reaction solvent as reactants are simply stirred at room temperature (Scheme 2). (*E*) and (*Z*)-isomers are both formed

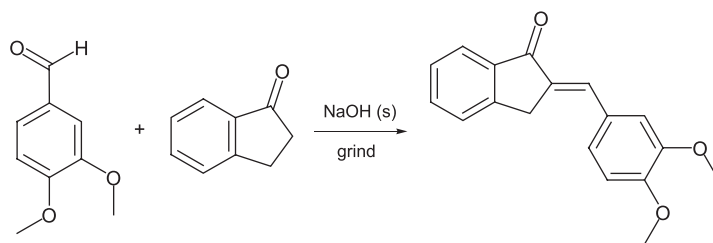
and isolated as oils after dilution with hexane and removal of insoluble triphenylphosphine oxide with a filtration pipette. Proton nuclear magnetic resonance (NMR) analysis reveals a typical 95% (*E*)-isomer:5% (*Z*)-isomer product ratio.

The aldol condensation between an aldehyde and ketone lends itself extremely well to grinding in the absence of solvent, and is a process with high atom economy (13). Such a reaction between 3,4-dimethoxybenzaldehyde and 1-indanone in the presence of catalytic sodium hydroxide has been reported [(14), Scheme 3]. Dehydration of the initial aldol product leads to a conjugated enone that is recrystallized from 9:1 ethanol:water. Although both carbonyl reactants are solids, their direct solventless mixing leads to melting so that condensation occurs in the liquid state. Presence of a liquid or melt phase has been discovered as essential for such aldol reactions (and related “solid–solid” or “solid-state” processes) to proceed (15). In keeping with these results, and employing both solid and liquid reactants, Palleros (16) demonstrated a range of chalcone products can be synthesized by a similar procedure in excellent yields (Scheme 4). These reactions are extremely rapid due to high reactant concentrations in a liquid yet solvent-free medium.

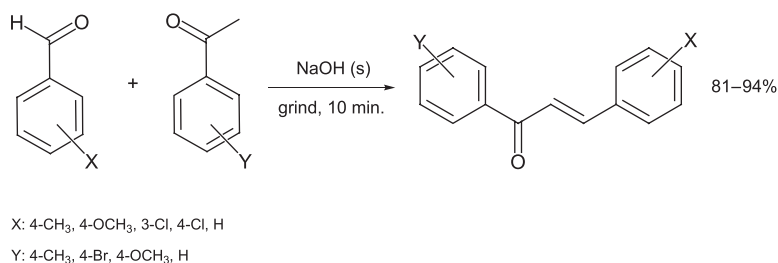
A sequential crossed-aldol condensation/Michael addition involving reactant grinding has been developed leading to a 1,5-diketone in 70–100% overall yield [(17), Scheme 5]. The chalcone intermediate can be isolated and characterized if desired, or directly



Scheme 2. Wittig synthesis of diastereomeric ethyl (3-phenyl)propenoate esters at room temperature (12).



Scheme 3. Crossed-aldol condensation of 3,4-dimethoxybenzaldehyde and 1-indanone (14).



Scheme 4. Substituted chalcone synthesis by a crossed-aldol condensation (16).

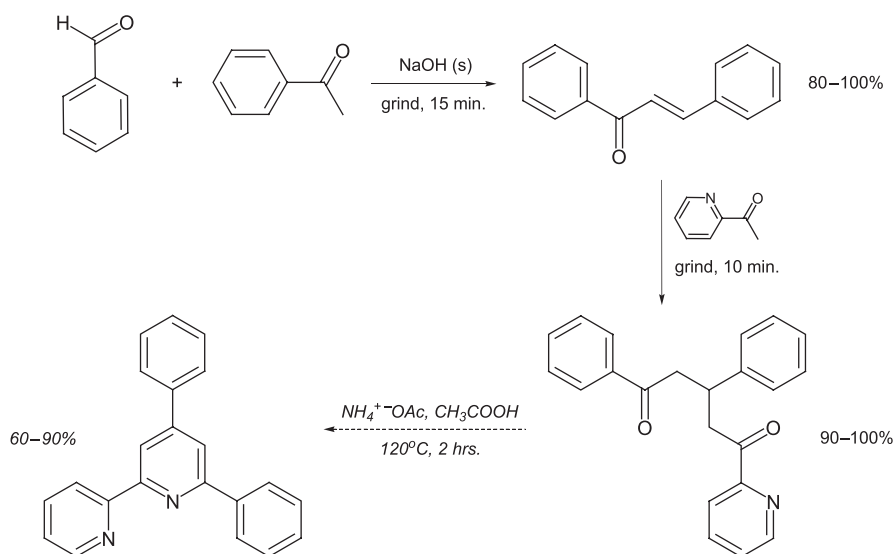
reacted further with 2-acetylpyridine to form the Michael adduct. The authors additionally describe subsequent reaction of the 1,5-diketone with ammonium acetate to generate a Kröhnke pyridine (18,19) utilizing acetic acid as a renewable solvent.

Electrophilic aromatic substitution of anisole can be achieved by solventless acylation with a mixed acid anhydride generated in situ [(20), Scheme 6]. Reaction of trifluoroacetic anhydride with acetic acid on acidic alumina generates ethanoic trifluoroethanoic anhydride, which reacts with anisole at room temperature to form 4-methoxyacetophenone. This procedure removes the requirement of aluminium trichloride as a Lewis acid catalyst and related

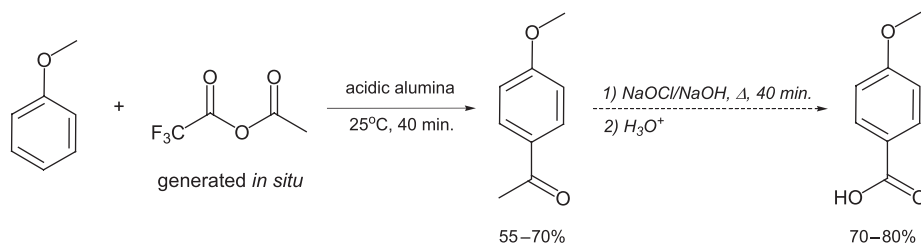
problematic work-up/product isolation procedures. The crude oil may be oxidized with aqueous sodium hypochlorite (commercial bleach) under basic conditions to synthesize 4-methoxybenzoic acid.

### C–N bond formations

Touchette (21) outlined quantitative preparation of a bright orange imine on solventless reaction of ortho-vanillin (melting point, mp 40–42°C) and 4-toluidine (mp 41–46°C) (Scheme 7). This reaction can be easily undertaken in a beaker within one hour and includes an appealing color change. The process is considerably exothermic, aiding evaporation of the



Scheme 5. Consecutive solvent-free crossed-aldol and Michael addition reactions (17).



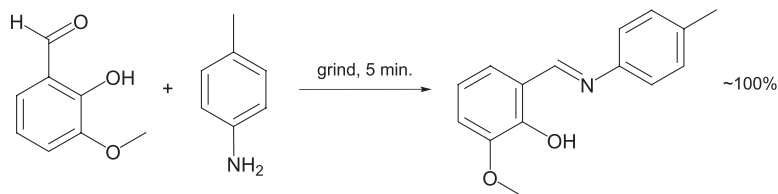
Scheme 6. Friedel-Crafts synthesis of 4-methoxyacetophenone (20).

water by-product. As with many effective aldol condensations, formation of a melt phase facilitates conversion. This provides a memorable example of an impurity causing a lowered melting point of a solid compound. Inexpensive para-vanillin may be used by large classes as an alternative reactant.

The contemporary practical technique of cocrystal controlled solid-state synthesis [abbreviated to  $C^3S^3$ , (22)] is amenable to implementation in the undergraduate laboratory. Cocrystals are composed of two or more solids crystallized together generating a novel lattice arrangement, which is different from those existing in the pure substances. Within the lattice are unique interactions (e.g. hydrogen bonds) that orient functional groups close enough for reaction to occur. The  $C^3S^3$  approach is in contrast to routine solid-state synthesis where compounds maintain their lattice structure and react in an amorphous environment. 1,4,5,8-Naphthalenetetracarboxylic dianhydride is ground together with 3-aminobenzoic acid [(23), Scheme 8] without any solvents to initially form a pale yellow cocrystal. On prolonged heating, the cocrystal generates a dark yellow diimide product which is isolated by washing with methanol and characterized by infrared spectroscopy (IR), NMR, X-ray diffraction (XRD), and differential scanning calorimetry (DSC). A variety of other anhydrides (e.g. phthalic anhydride) and amines (e.g. adamantylamine) can be reacted in the  $C^3S^3$  approach. The product of combining these two solids together [N-(1-adamantyl)phthalimide] is a potential anti-cancer pharmaceutical ingredient (24).

### *C-H and/or C-O bond-forming reactions*

The Cannizzaro disproportionation of 2-chlorobenzaldehyde can be performed under grinding conditions



Scheme 7. Imine formation from ortho-vanillin and 4-toluidine (21).

with solid potassium hydroxide acting as base [(25), Scheme 9]. The reactants are ground for 30 minutes before dilution with water. Solid 2-chlorobenzyl alcohol is isolated from the aqueous solution and 2-chlorobenzoic acid precipitated by acidification, so that organic solvents are not required during work-up. Both products are collected and analyzed as an unusual yet didactic feature of an undergraduate synthesis experiment.

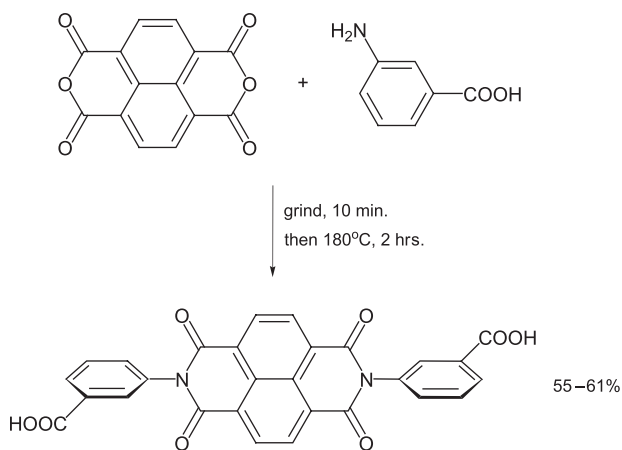
Esteb et al. (26) described the Baeyer-Villiger oxidation of 4-*t*-butylcyclohexanone with meta-chloroperoxybenzoic acid (mCPBA) under ambient conditions by stirring both reactants together for 30 minutes. An exothermic reaction leads to the caprolactone product, which is extracted into ether and isolated as a low melting point solid in good yield (Scheme 10).

### **Microwave heating and irradiation with visible light**

#### *C-C bond formations*

Martin and Kellen-Yuen (27) outlined solvent-free Wittig preparation of five  $\beta$ -methylstyrene derivatives by heating an aromatic aldehyde with ethyltriphenylphosphonium iodide in a domestic microwave oven (Scheme 11), rather than a laboratory-grade microwave reactor. Potassium carbonate is used as a weak, environmentally benign base. (*Z*) and (*E*)-alkenes are generally synthesized in almost equimolar amounts and may be separated from unreacted starting material by flash chromatography. Relative product ratios are readily determined by proton NMR and GC-MS techniques.

The facile solventless synthesis of methylenedioxypropocene, a naturally occurring insecticide (28,29) in a domestic microwave oven has been described

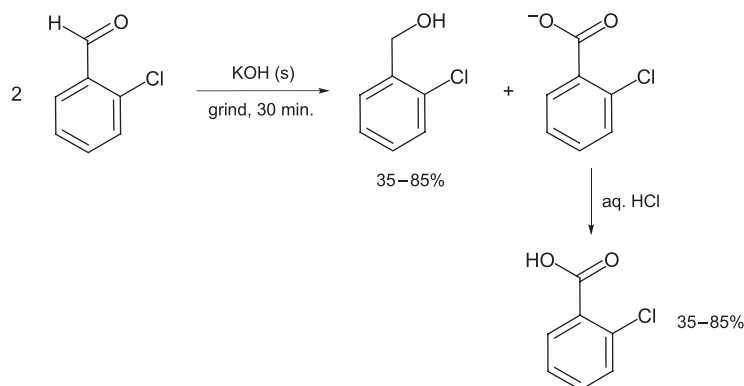


Scheme 8. Cocystal controlled solid-state imide synthesis (23).

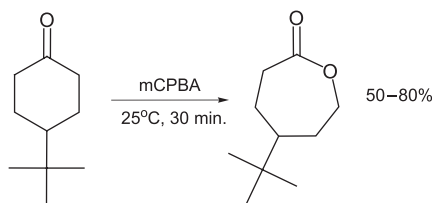
[(30), Scheme 12]. The transformation occurs in three steps: initial electrophilic addition of 3-methyl-2-butenal to sesamol followed by loss of water and finally an intramolecular hetero-Diels–Alder reaction to form the isolated product. The process features inexpensive, readily available Montmorillonite K10 clay in a basic form as a solid catalyst and a heating time of just eight minutes. Methylene dioxy precocene is separated from basic Montmorillonite K10 by ethyl acetate extraction and both clay and solvent recycled, incorporating other green aspects to the experiment.

Microwave chemistry has been applied to synthesis of porphyrin derivatives (31) which are essential compounds for life to exist. In humans, porphyrins containing iron (hemes) ions are necessary for hemoglobin to act as an oxygen carrier within blood whereas in plants, structurally similar compounds form the basis of chlorophyll and facilitate photosynthetic pathways. The original report has been adapted for implementation in the undergraduate organic laboratory (32). Benzaldehyde and pyrrole are mixed neat, added to silica gel as a solid support, and irradiated in a domestic microwave oven for 10 minutes (Scheme 13). Extraction with ethyl acetate and column chromatography leads to 5,10,15,20-tetraphenylporphyrin of about 85% purity that is quantifiable by UV/visible spectroscopy. Typical product yields are around 5% after purification.

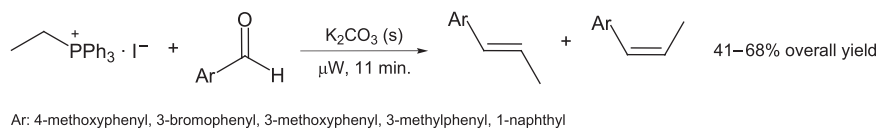
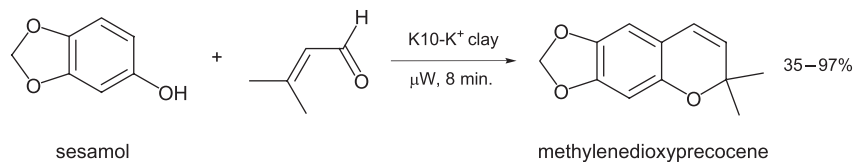
Photochemical alkene pericyclic reactions are capable of occurring in the solid-state in the absence of solvents (33,34). When (*E*)-cinnamic acid is irradiated with visible light for one week a photochemical [2+2] cycloaddition occurs to regioselectively and stereoselectively form only one truxillic acid stereoisomer [(35), Scheme 14]. Truxillic acid is known as a “head-to-tail” dimer in this reaction. This notable transformation proceeds at the exclusion of forming any of 10 other potential products, and with an intrinsic atom economy of 100%. Both truxillic acid and truxinic acid



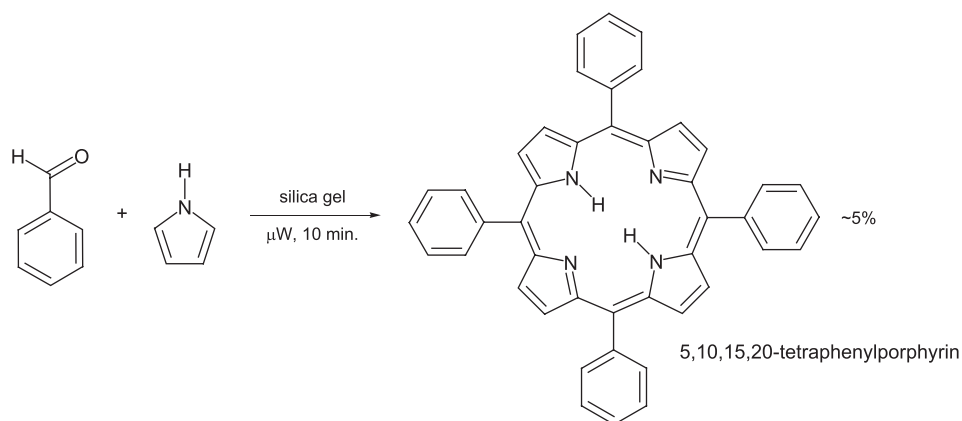
Scheme 9. Cannizzaro disproportionation of 2-chlorobenzaldehyde (25).



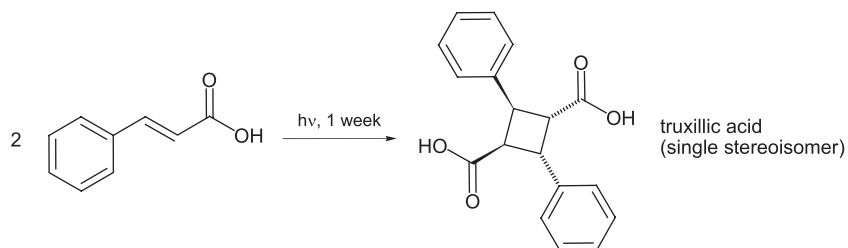
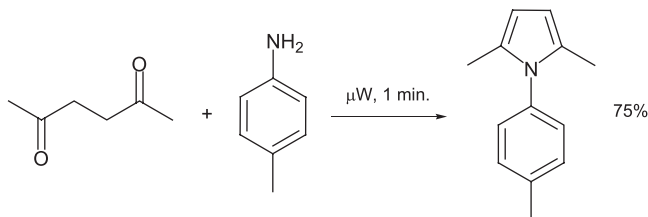
Scheme 10. Baeyer–Villiger oxidation of 4-t-butylcyclohexanone with mCPBA (26).

Scheme 11. Wittig synthesis of  $\beta$ -methylstyrene derivatives via microwave heating (27).

Scheme 12. Preparation of methylenedioxyprococene on Montmorillonite K10 clay (30).



Scheme 13. Porphyrin synthesis via microwave irradiation of benzaldehyde and pyrrole (32).

Scheme 14. Stereoselective formation of truxillic acid by irradiation of (*E*)-cinnamic acid with visible light (35).

Scheme 15. Paal-Knorr pyrrole preparation (38).

(the “head-to-head” dimer), are found within plant cell walls and considered contributors to the polymeric nature of these structures (36).

### C–N bond formations

Solvent-free synthesis of a wide variety of heterocyclic compounds under microwave heating has recently been the subject of a comprehensive review (37). Katritzky et al. reported preparation of an N-substituted 2,5-dimethylpyrrole derivative in good yield by a classical Paal–Knorr synthesis [(38), Scheme 15]. This remarkably fast conversion requires one minute of heating reactants sans solvent in a commercially available single-mode BenchMate microwave system (39,40). As a comparison, 2,5-hexanedione was reacted with 4-toluidine/Montmorillonite KSF clay in dichloromethane at ambient temperature for 10–25 hours to achieve comparable product yields. Solventless synthesis of heterocyclic benzimidazole, phthalimide, and 2,3-diphenylquinoxaline has been described using a similar microwave system (41). Generation of benzimidazole involves reactant adsorption on alumina which acts as a carrier surface (Scheme 16). Products are generally recrystallized from water or ethanol after short heating times.

### C–H and/or C–O bond-forming reactions

Reduction of an aldehyde or ketone with sodium borohydride is a reaction routinely discussed in introductory organic lectures and performed in many laboratory curricula. White and Kittredge

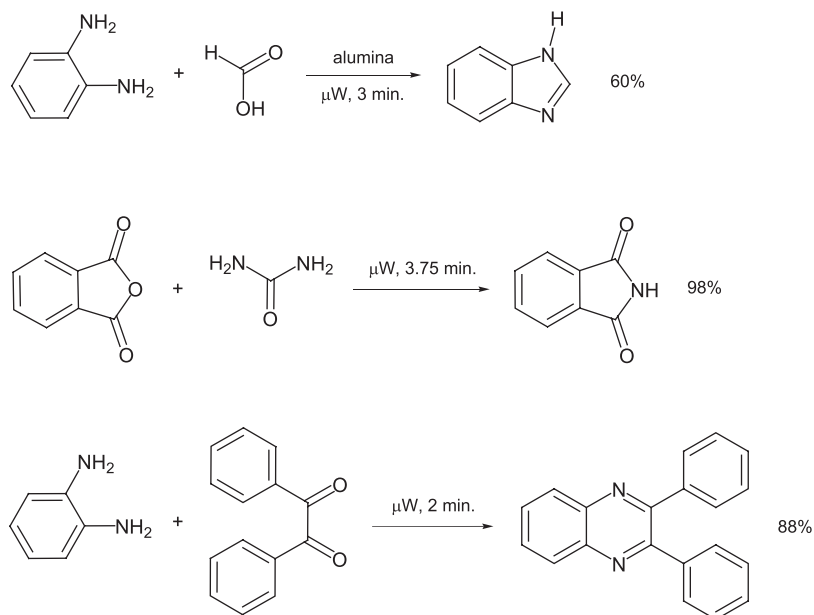
(42) devised a cyclohexanone reduction protocol where  $\text{NaBH}_4$  is initially ground with and supported on a silica gel matrix (Scheme 17). Microwave irradiation in a commercial reactor for three minutes leads to cyclohexanol formation in excellent yield after work-up. Although borohydride reductions are commonly undertaken in biodegradable solvents such as ethanol (43), this procedure serves to minimize solvent media and drastically reduce reaction times.

Benzaldehyde can be purified by reaction with sodium bisulfite to form an  $\alpha$ -hydroxysulfonate and subsequent solvent-free microwave irradiation [(44), Scheme 18]. A recyclable clay (Montmorillonite KSF) is employed on a silica gel support, in place of corrosive acidic or basic conditions. An ethyl acetate extraction facilitates isolation of regenerated pure benzaldehyde. This approach provides an alternative to other aldehyde purification techniques such as column chromatography and distillation.

### Conventional heating

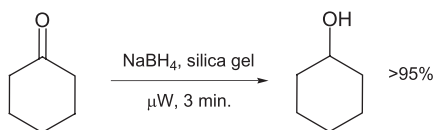
#### C–C bond formations

A Wittig reaction has recently been implemented in student laboratories involving conjugated ester synthesis in the absence of solvent (12). Conventional (hot plate/sand bath) heating of 9-anthraldehyde with a commercially available stabilized Wittig reagent [(carbethoxymethylene)triphenylphosphorane] negates the requirement of basic conditions (Scheme 19). At  $110^\circ\text{C}$ , the aldehyde has melted (mp  $103\text{--}105^\circ\text{C}$ ) but the Wittig reagent is still a solid

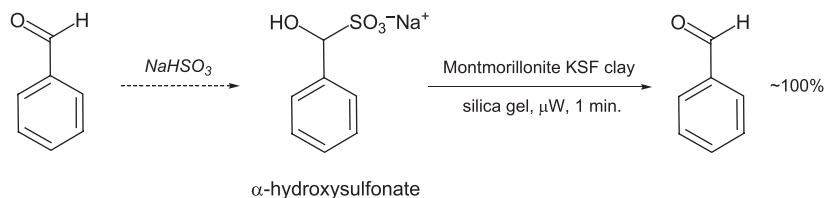


Scheme 16. Microwave-assisted benzimidazole, phthalimide and 2,3-diphenylquinoxaline synthesis (41).





Scheme 17. Borohydride reduction of cyclohexanone (42).

Scheme 18. Purification of benzaldehyde by microwave treatment of an  $\alpha$ -hydroxysulfonate (44).

(mp 128–130°C). The crude product contains 5% of the minor (*Z*)-isomer, which is easily removed on recrystallization with methanol.

Solventless synthesis of ethyl 3-oxo-2,4-diphenylbutanoate as the product of a self-Claisen condensation has been devised [(45), Scheme 20]. Heating ethyl (2-phenyl)ethanoate, an inexpensive and non-toxic reactant, with potassium *t*-butoxide for 30 minutes generates the solid  $\beta$ -ketoester in good yield. Performing a Claisen condensation under these conditions means the common concern of alkoxy group exchange between solvent, ester reactant, and base becomes moot.

Preparation of 5,10,15,20-tetraphenylporphyrin can be achieved not only under microwave irradiation [(32), Scheme 13], but also via more conventional heating methods. Adaptation of a novel synthetic approach (46) facilitates porphyrin synthesis in the gas phase (47). Heating benzaldehyde in a sand bath (170°C) followed by addition of pyrrole at 180°C and subsequent heating at 250°C for 15 minutes leads to product formation and isolation after column chromatography (Scheme 21).

### *C–N bond formations*

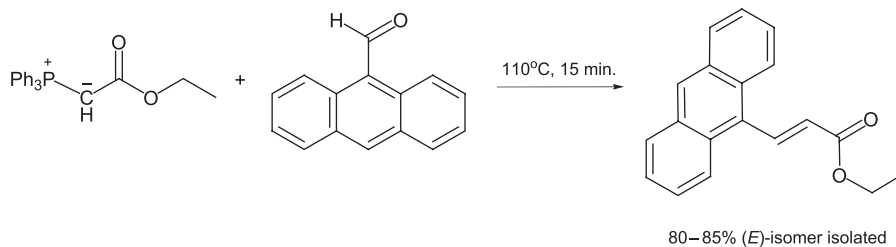
Bennett (48) has developed a protocol for green polymerization of an amino acid to form poly(succinimide), a precursor for sodium poly(aspartate), without use of organic solvents (Scheme 22). This approach represents

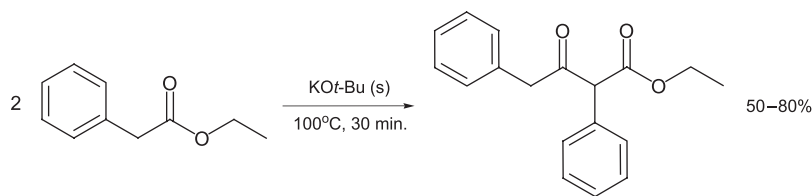
modification of a Presidential Green Chemistry Challenge Award winning project from 1996 (49). *L*-Aspartic acid is simply heated in beaker at 250°C for two hours followed by several aqueous basic and acidic washes. After oven-drying the water-insoluble poly(succinimide) generated is hydrolyzed with 0.1M aqueous NaOH to form sodium poly(aspartate). Both *L*-aspartic acid and sodium poly(aspartate) are examples of biodegradable materials. The latter therefore finds use as an environmentally friendly alternative to sodium poly(acrylate) as an anti-scaling compound (50) and chelating agent.

A “dry-laboratory” approach to teaching green chemistry principles of process optimization with concomitant waste reduction has been proposed (51). Students analyze (but do not actually perform) solvent-free synthesis of 3-acetyl-5-methylisoxazole from 2,5-hexadione and ethyl nitrite under acid-catalyzed conditions (Scheme 23). They consider how improvements can be made to the reaction environmental profile (e.g. elimination or diminution of work-up solvents, usage of a recyclable solid phase acid catalyst) to gain appreciation of green chemical metrics.

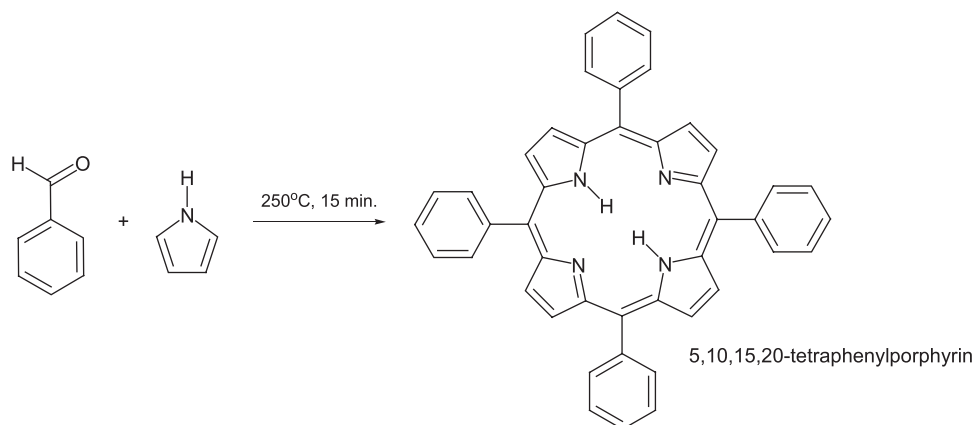
### *C–H and/or C–O bond-forming reactions*

Significant efforts have recently been made to improve the “greenness” of alcohol oxidation reactions (52,53). One strategy from a pedagogical perspective

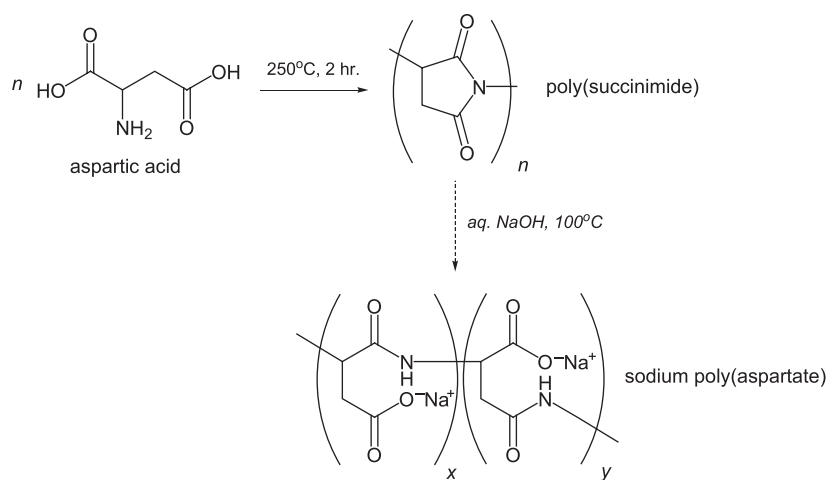
Scheme 19. Wittig synthesis of (*E*)-ethyl 3-(9-anthracenyl)propenoate by conventional heating (12).



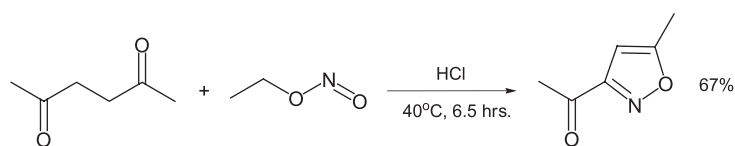
Scheme 20. Self-Claisen condensation of ethyl (2-phenyl)ethanoate (45).



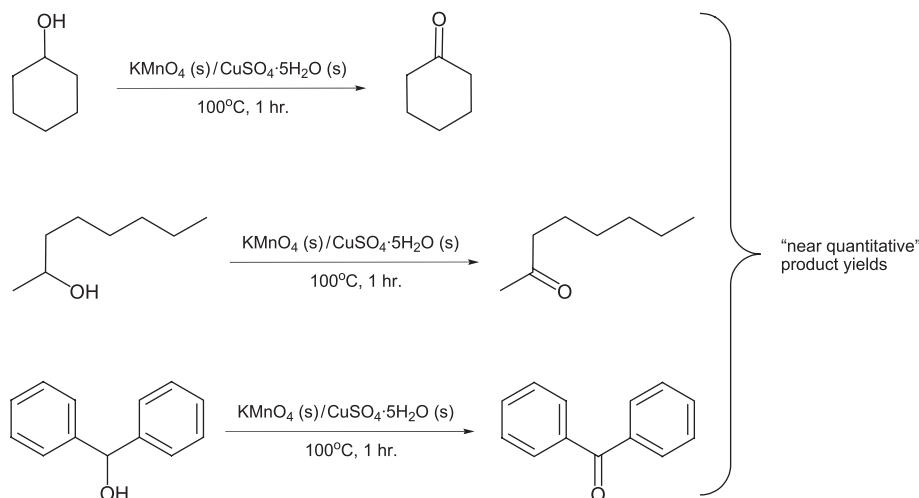
Scheme 21. Porphyrin synthesis via conventional heating of benzaldehyde and pyrrole (47).



Scheme 22. Preparation of poly(succinimide) by polymerization of aspartic acid (48).



Scheme 23. "Dry-laboratory" synthesis of 3-acetyl-5-methylisoxazole (51).

Scheme 24. Oxidation of secondary alcohols to ketones with  $\text{KMnO}_4/\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (55).

is to oxidize secondary alcohols with aqueous hydrogen peroxide in the absence of organic solvents (54). Esteb et al. (55) have employed an equimolar ground mixture of potassium permanganate and copper (II) sulfate pentahydrate as the oxidant for a range of secondary alcohols (Scheme 24). Each ketone is formed in “near quantitative yield” on heating for one hour by a noticeably exothermic reaction under solvent-free conditions. This method can be slightly adapted for preparation of pentanoic acid from 1-pentanol, albeit in lower isolated yields [(56), Scheme 25].

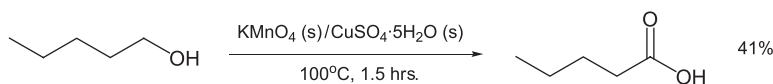
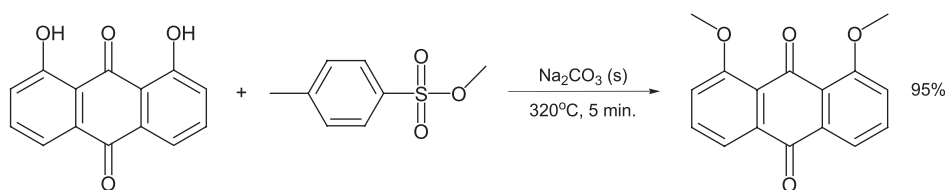
Dimethylation (dietherification) of 1,8-dihydroxy-9,10-anthracenedione has been reported at high temperatures using methyl tosylate as the alkylating agent and sodium carbonate as an environmentally benign base [(57), Scheme 26]. The reaction takes five minutes and forms 1,8-dimethoxy-9,10-anthracenedione in excellent yield that is purified by sublimation after washing with water. Interestingly, reflux of the same reactants in tetraglyme solvent leads to exclusive monomethylation of 1,8-dihydroxy-9,10-anthra-

enedione, facilitating discussion of chemoselectivity principles.

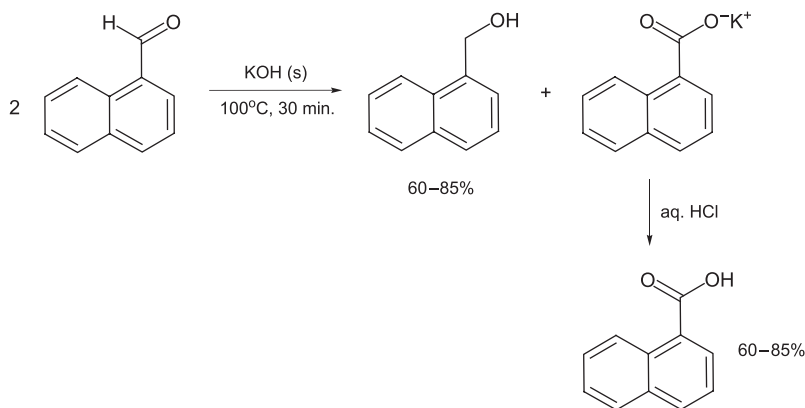
1-Naphthaldehyde can be subjected to a Cannizzaro reaction under basic solventless conditions utilizing KOH [(58), Scheme 27]. The aldehyde and base are combined and heated for 30 minutes before cooling and aqueous dilution. 1-Naphthalenemethanol is isolated as a solid via ether extraction and 1-naphthoic acid precipitated by acidification.

## Conclusions

It is clear that the last decade has produced a diverse range of solvent-free transformations for the undergraduate organic teaching laboratory. Procedures can be completed using minimal and unsophisticated apparatus within short timeframes. The current versatility of reactions without formal solvents is exemplified by the Wittig alkene synthesis. Traditionally performed in organic media (ether or tetrahydrofuran, THF) and in the presence of a strong base (e.g. *n*-butyllithium) (59), students may now

Scheme 25. Oxidation of 1-pentanol to pentanoic acid with  $\text{KMnO}_4/\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (56).

Scheme 26. Synthesis of 1,8-dimethoxy-9,10-anthracenedione from 1,8-dihydroxy-9,10-anthracenedione (57).



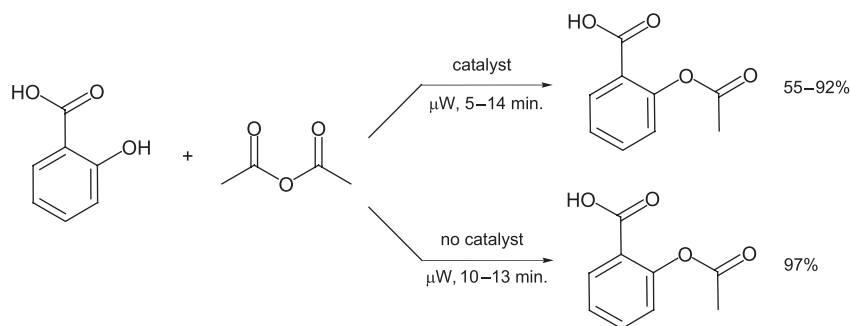
Scheme 27. Cannizzaro disproportionation of 1-naphthaldehyde (58).

undertake solventless Wittig reactions by one of four approaches. These include grinding solid reactants together, microwave heating, conventional heating, or simple stirring at room temperature (11,12,27). Practical exposure to these approaches within the framework of a high-profile reaction could provide immeasurable pedagogical benefit. Nonetheless, performing a reaction without solvent does not necessarily mean the process adheres to every green chemistry principle (10). A cursory analysis of the aforementioned Wittig reactions reveals each takes place with very poor intrinsic atom economy. Cann and Dickneider (60) calculated the atom economy for Wittig synthesis of methylenecyclohexane from cyclohexanone to be only 18%, largely due to formation of triphenylphosphine oxide ( $M_r = 278.3$ ) as waste. The majority of reviewed reactions still require an organic solvent during work-up or for chromatographic purposes, although a few products are recrystallized from alcohol (11,12,41) or alcohol-water mixtures (14). Some reactions require elevated temperatures for long periods of time (48,55,56).

Debate has taken place over what actually constitutes a solvent-free reaction. Welton has asserted

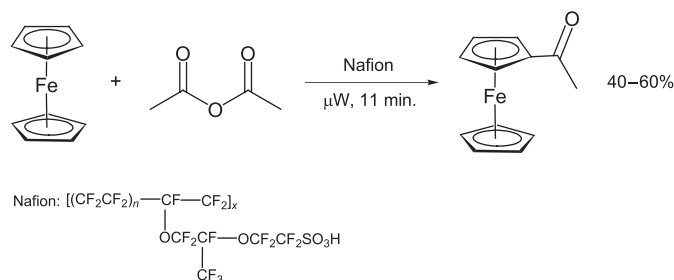
“a dry solid phase reaction is solvent-free, also a reaction where there is a liquid present, but it is not acting as a solvent (i.e. nothing is dissolved in it) is also solvent-free” (61). These two situations were presented as the only possible examples of solventless reactivity. It has been noted that many reactions declared as solvent-free in fact have a surplus of one liquid reagent present – this substance therefore behaves as both reactant and solvent (62). Montes et al. outlined microwave synthesis of aspirin under catalytic and non-catalytic conditions by acetylation of salicylic acid (5 mmol) with acetic anhydride (15 mmol) [(63,64), Scheme 28]. This protocol represents an efficient method of aspirin preparation but excess acetic anhydride means solvent is in fact present during all reactions. A similar position exists during a recent microwave ferrocene acetylation experiment [(65), Scheme 29], where the authors acknowledged that acetic anhydride acts as reagent and solvent.

Pereira and Afonso (66) utilized urea (75 mmol) as an excess reagent during preparation of a chiral auxiliary from (–)-ephedrine hydrochloride (25 mmol) (Scheme 30). On heating to 200°C, the urea melts and additionally acts a liquid solvent. Although

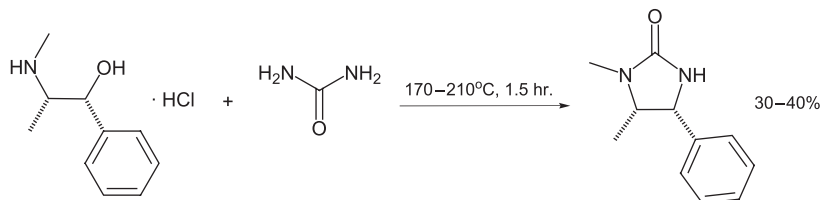


Catalysts:  $H_2SO_4$ ,  $H_3PO_4$ ,  $MgBr_2 \cdot OEt_2$ ,  $AlCl_3$ ,  $CaCO_3$ ,  $NaOAc$ ,  $NEt_3$ , 4-*N,N*-dimethylaminopyridine

Scheme 28. Aspirin (acetylsalicylic acid) preparation under “solvent-free” conditions (63).



Scheme 29. Microwave-assisted ferrocene acylation (65).



Scheme 30. Chiral auxiliary synthesis from (–)-ephedrine hydrochloride and urea (66).

promoted as a solventless reaction, it is more correctly stated as one (amongst others) where no *additional* solvent is required beyond the reactants. Instructors and students should exercise care and consider reaction conditions/stoichiometries when interpreting processes as being “solvent-free.”

Eliminating a reaction medium furnishes occasion to discuss with undergraduates why solvents have historically been employed in organic reactivity. Beyond principles surrounding solubility and reaction homogeneity lies the concept of solvents acting as heat sinks. Many solventless reactions (including some reviewed here) are vigorously exothermic (21,26,55,56) and research into calorimetric aspects of this chemistry is ongoing (67). Exothermic reactions provide significant challenges when subject to scale-up in an industrial venue. Thermal “runaways” (when the rate of heat removal from a process does not correlate with the rate of heat production) can lead to catastrophic results. Improvements in solvent-free reactor design are being made at the chemical/chemical engineering interface, particularly in fields of microwave reactivity (68,69) and photochemistry (70). Microreactors (where reactants combine in narrow pathways with diameters of 10  $\mu\text{m}$ ) are additionally now employed to deal with rapid temperature increase from solventless reactions (71). In conclusion, advantages to implementing solvent-free reactions into introductory and advanced organic courses are multiple and intimately linked with green chemistry principles. Drawbacks do, however, still exist and their reflection with students represents an important teaching opportunity.

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