



Synthesis of quinolines, pyridine ligands and biological probes in green media†

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Nitrogen heterocycles are prepared using hot pressurized water under microwave and thermal conditions. Selective reduction, cyclodehydrations (Friedländer and Pfitzinger syntheses), Suzuki coupling, and ligand exchange have been effected in water or water-protic solvent media.

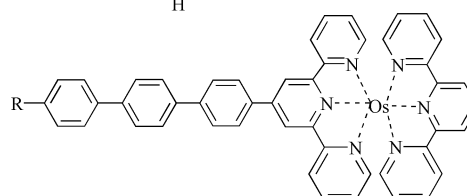
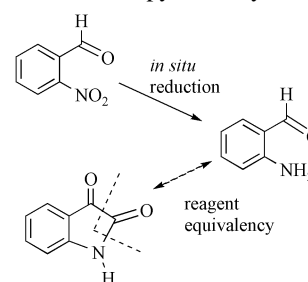
Introduction

Pyridines and quinolines of relevance to metal complexes and natural product, drug, and materials synthesis are generally readily prepared from condensation and cyclodehydration reactions. These preparations frequently employ environmentally unfavorable techniques such as acid catalyzed azeotropic removal of water using aromatic solvents. We have sought to address some typical organic preparations¹ and synthetic applications in water² or alternative environmentally friendly protic media, using pressure reactors and microwave techniques.

The cyclodehydration of *o*-aminobenzaldehyde and α -methylene ketones, the Friedländer synthesis, in organic media is

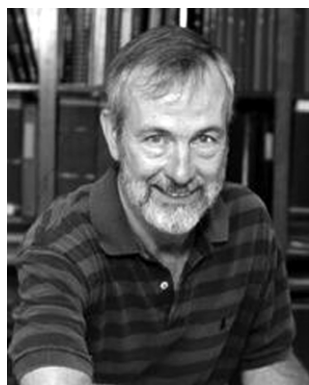
one such preparation.³ The use of this reaction has been limited because of the availability of *o*-aminocarbonyl compounds.⁴ Described is an *in situ* green preparation of *o*-aminobenzaldehyde.

Biological probe **1**⁵ has been assembled by following literature precedence for terpyridine synthesis⁶ and a Suzuki



1 R = H, acetyl, 1-hydroxyethyl

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Green Context

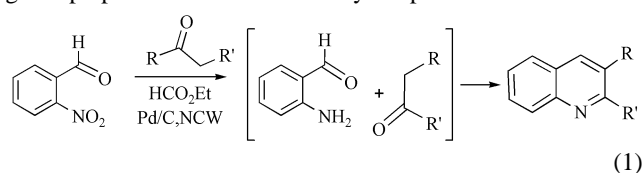
Water has many obvious attractions as a reaction solvent for organic synthesis but the poor solubility of many organic compounds in water restricts such applications under normal conditions. Water under high temperatures and pressures however, undergoes quite dramatic changes in its properties and it becomes a generally good solvent for organic compounds. While this has been exploited in remediation type processes it has been little used in synthesis. Here the use of near critical water as a medium for the organic synthesis of nitrogen heterocycles is demonstrated. The potential for solvent recycling is also demonstrated. The authors go on to use combined clean technologies—catalysis in near critical water, and microwave activated water systems to further demonstrate the clean synthesis potential for these interesting systems. **JHC**

coupling.⁷ However the terpyridine synthesis and the generally dependable Suzuki coupling, which can become problematic with high molecular weight materials, demonstrated to us the opportunities for improvements based on green chemistry.

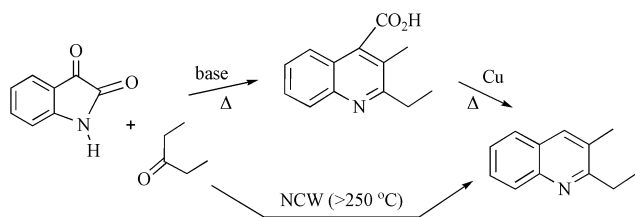
Disclosed is a greener preparation of biological probe **1** of possible interest for photoinjection⁵ studies.

Results and discussion

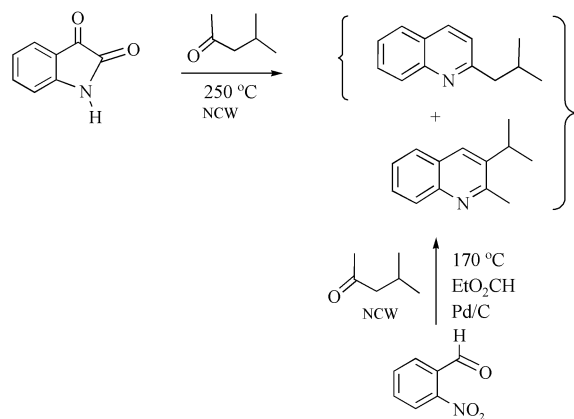
Quinoline chemistry. One of the most used preparations of *o*-aminobenzaldehyde is the ferrous sulfate reduction of *o*-nitrobenzaldehyde which is done in water but is waste prone in reducing reagent and energy.⁸ Other excellent preparations of *o*-aminobenzaldehyde are not environmentally benign.⁹ An alternative is to reduce the nitro group *in situ* for imine formation with carbonyl compounds using ethyl formate and palladium on carbon in near critical water (NCW) as illustrated in eqn. (1). Ethyl formate in hot pressurized water has been shown to be an effective green reducing system for olefins, acetylenes and aldehydes.¹⁰ However the nitro group can be selectively reduced in the presence of aldehydes and ketones in a pressure reactor at 170–200 °C yielding the Friedländer quinoline product in good to modest yields (Table 1, method A).^{11,12} The yields of this combined one-step quinoline preparation is generally close to the overall yield of a two-step procedure from *o*-nitrobenzaldehyde.¹³ The equivalents of formate, carbonyl substrate, reaction time and temperature have not been varied. These variables will be reviewed to optimize a green preparation of these heterocyclic products.



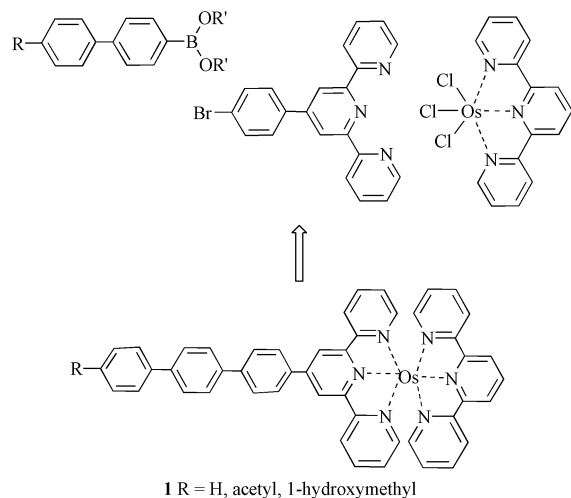
The use of isatin is a classical alternative to the *o*-aminobenzaldehyde-Friedländer synthesis. Isatin in heated aqueous base, opens and condenses on methylene ketones, to give quinoline carboxylic acids.¹⁴ Although these acids are troublesome to isolate, they do decarboxylate under forcing conditions to 2- or 2,3-substituted quinolines. The same carbonyl compounds with isatin in NCW (> 250 °C, 1 h) form the substituted quinoline systems with *in situ* decarboxylation (Table 1, method B). Hot pressurized water (NCW) is more ionized and it is a dehydrating media well suited for isatin opening, condensation and cyclodehydration with carbonyls.^{15,16} 4-Quinoline carboxylic acids can be found for reaction temperatures below 250 °C and these acids decarboxylate on cycling with a higher temperature (> 250 °C) water treatment. In the few comparative reactions the yields of quinolines from isatin are generally about the same as using *o*-nitrobenzaldehyde (*e.g.* entries 3 and 4, Table 1) but in the case of methyl isopropyl ketone with isatin, no regioisomer is formed (entries 6 and 7, Table 1). This is presumably due to steric hindrance at C-3 of the forming quinoline carboxylic acid.



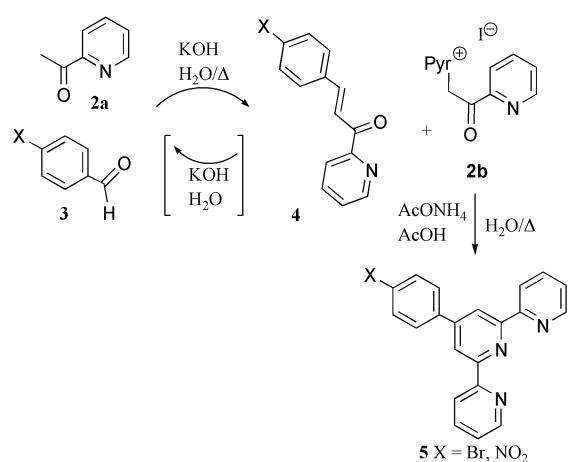
Pyridine-ligand chemistry. Biphenylboronic acids (or esters), bromophenylterpyridine and a suitable osmium complex



are the rational building blocks for biological probe **1**. However without microwave assistance **1** could not have been prepared for potential use as a biological probe.



The published procedures for making terpyridines are quite good, but the preparation of the necessary terpyridine **5** was reformulated to greener techniques without a reduction in yield.



General procedure. Acetylpyridine (**2a**) and *para*-substituted benzaldehydes (**3** (X = Br, NO₂)¹⁷ with one equivalent of KOH in water were heated using 10 min low power bursts (total of 50 min) over a 3 h period with a commercial microwave oven, resulting in the formation of azachalcone **4**. As the organics begin to solidify, the solid was removed by filtration and, in the case of bromide **4**, the aqueous base was recharged

Table 1 Quinolines from *in situ* formation of *o*-aminobenzaldehyde (A) or isatin (B)

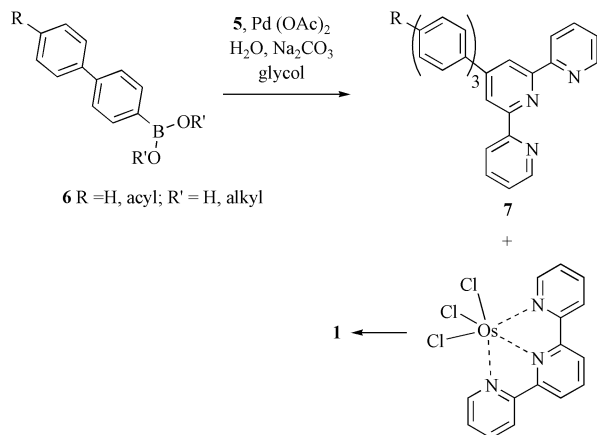
Entry	Method	Carbonyl	Product(s)	Yield (%)
1	A	Diethyl ketone	2-Ethyl-3-methylquinoline	60
2	B	Diethyl ketone	2-Ethyl-3-methylquinoline	43
3	A	Cyclohexanone	1,2,3,4-Tetrahydroacridine	45
4	B	Cyclohexanone	1,2,3,4-Tetrahydroacridine	45
5	A	Valeraldehyde	3-Propylquinoline	55
6	A	4-Methyl-2-pentanone	2-Isobutyl- and 3-isopropyl-2-methylquinoline	46 (4/1)
7	B	4-Methyl-2-pentanone	2-Isobutylquinoline	48
8	A	Dipropyl ketone	3-Ethyl-2-propylquinoline	25
9	B	Dipropyl ketone	3-Ethyl-2-propylquinoline	40
10	A	1-Indanone	11 <i>H</i> -Indeno[1,2- <i>b</i>]quinoline	20
11	B	1-Indanone	11 <i>H</i> -Indeno[1,2- <i>b</i>]quinoline	22
12	B	5-Benzyloxyvaleraldehyde	3-(3-Benzyloxypropyl)quinoline	30 ^a

^a Ether cleavage reduced yields of 3-benzyloxypropylquinoline.

with benzaldehyde (**3**, X = Br) and acetylpyridine (**2**) for additional preparation of the azachalcone **4**.¹⁸ After a couple of cycles the aqueous layer began to color but the yield of azachalcone (**4**, X = Br) remained nearly quantitative.

The azachalcone **4** (X = Br) was recrystallized from ethanol¹⁹ and mixed with ammonium acetate and iodopyridylacetylpyridine (**2b**) in water-acetic acid (25:75). The heterogeneous mixture was irradiated²⁰ in a commercial microwave oven, affording bromophenylterpyridine **5**. Alternatively the same reaction mixture in a stainless steel pressure reactor (filled to less than 30% capacity) was heated between 140–190 °C for 2 h yielding terpyridine **5** (X = Br).

Normal Suzuki coupling of **5** to biphenylboronic acids **6** was confirmed by mass spectra but only in low yield and long periods of heating under reflux in high boiling solvents.⁷



Based on literature precedence²¹ intense microwave radiation (200 °C, 200 psi max, 1 h) rapidly forms the desired terpyridine ligand **7** in high yield after an acid–base extractive purification. Similarly a sluggish ligand exchange **7** to **1** (R = H)²² is best accomplished using microwave assistance (200 °C, 75 psi max, 1 h).²³ The PF₆ salt of **1** is separated from a mixture of two other osmium compounds on Al₂O₃ in acetonitrile–sat. aq. KNO₃–water (14:2:1).²⁴

Conclusion

Preliminary results further demonstrate the potential of near critical water as a green medium for heterocyclic synthesis and in some procedures water with reaction catalyst can be easily recycled. Microwave techniques and pressure vessels can alter long-term low yielding processes to short term, more efficient reactions. The combination of these techniques yields green preparation of quinolines and photoinjection tools.

Acknowledgements

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References

- 1 A number of organic transformations have been effected in water.² This group's long range goal is to effect multistep synthesis replacing various organic solvents and exotic or environmentally unfriendly reagents with water and green catalysts and reagents.
- 2 For examples of organic reactions done in water, see: A. R. Katritzky and S. M. Allin, *Acc. Chem. Res.*, 1996, **29**, 399–406; P. E. Savage, *Chem. Rev.*, 1999, **99**, 603–621; J. An, L. Bagnell, T. Cablewski, C. R. Strauss and R. W. Trainor, *J. Org. Chem.*, 1997, **62**, 2505–2511.
- 3 C.-C. Cheng and Y.-S. Yan, *Org. React.*, 1982, **28**, 37–201.
- 4 B. Mundy and M. Eller, *Name Reactions and Reagents in Organic Synthesis*, Wiley, New York, 1988, p. 86–87.
- 5 I. J. Dmochowski, J. R. Winkler and H. B. Gray, *J. Inorg. Biochem.*, 2000, **81**, 221–228.
- 6 P. Korall, A. Borje, P. Norrby and B. Akermark, *Acta Chem. Scand.*, 1997, **51**, 760–766.
- 7 A. Suzuki, *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich and P.J. Stang, Wiley-VCH, Weinheim, Germany, 1998, ch. 2.
- 8 L. I. Smith and J. W. Opie, *Org. Synth.*, 1948, **28**, 11; this procedure produces good quality product but requires a laborious steam distillation limiting the amounts of *o*-aminobenzaldehyde and the scope of *ortho*-amino carbonyl compounds that can be prepared by this reduction; *ortho*-amino carbonyl compounds do not store well due to intermolecular imine formation.
- 9 S. Murata, M. Miura and M. Nomura, *Chem. Lett.*, 1998, **2**, 361–362.
- 10 J. M. Jennings, T. A. Bryson and J. M. Gibson, *Green Chem.*, 2000, 87–88; T. A. Bryson, J. M. Jennings and J. M. Gibson, *Tetrahedron Lett.*, 2000, **41**, 3523–3526.
- 11 *General procedure*: the amounts of liquid (primarily water) and solids used were adjusted to less than 40% of the reactor volume. A stainless steel pressure reactor containing a mix of degassed water, ethyl formate (3 to 4 eq.), Pd/C (~0.02 eq. of Pd), *o*-nitrobenzaldehyde (1 eq.) and reagent ketone or aldehyde (1.5+ eq) was heated at 170–200 °C for 2 h; the quinoline product was isolated using acid–base chemistry.
- 12 Mixed formate systems (ethyl formate/formic acid and ethyl formate/sodium formate) also afford the same quinolines adding to the variables that must be reviewed to optimize a green preparation of these heterocyclic products.
- 13 Using the best yield for ferrous sulfate reduction of *o*-nitrobenzaldehyde, the two-step conversion to 2-ethyl-3-methylquinoline is 61%.
- 14 For a typical example of an isatin-Pfitzinger synthesis, see: C. Koelsch, *J. Org. Chem.*, 1951, **16**, 1362.
- 15 C. Eckert, *Chem. Eng. News*, 2000, **3**, 26–27.
- 16 *General procedure*: isatin (1 eq.), ketone or aldehyde (>1 eq.), degassed water (total volume less than 40% of the pressure reactor)

- were brought to 250–275 °C for 0.5 h. The product was purified using minimal ether extraction or acid–base chemistry.
- 17 The nitrobenzaldehyde substrate was used to provide an alternate (diazonium ion) coupling route.
 - 18 The nitro azachalcone **4** formed in excellent yield but both the product and aqueous layer were highly colored. This aqueous layer was not recycled.
 - 19 Recrystallization was done for aesthetics and is not necessary.
 - 20 Irradiation: in a glass pressure reactor with a water heat sink, 7–10 min bursts were administered on low power in a commercial microwave totaling approximately 1 h of irradiation. Each burst was followed by a cooling period of from 5 to 35 min.
 - 21 G. C. Blettner, W. A. König, W. Stenzel and T. Schotten, *J. Org. Chem.*, 1999, **64**, 3885–3890; general reference: B. Hayes, *Microwave Synthesis, Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, USA, 2002, ch. 4 (MARS5 system was used for this coupling).
 - 22 E. C. Constable and A. M. Cargill Thompson, *J. Chem. Soc., Dalton Trans.*, 1995, 1615–1627.
 - 23 T. Matsumura-Inoue, M. Tanabe, T. Minami and T. Ohashi, *Chem. Lett.*, 1994, 2443–2446.
 - 24 The mass spectra of the complex has a predominant 443 double charged ion. The remarkable chromatographic separation of **1** is the procedure of Constable and Cargill Thompson, ref. 22.