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Green chemistry approaches to the Knoevenagel condensation: comparison of ethanol, water and solvent free (dry grind) approaches

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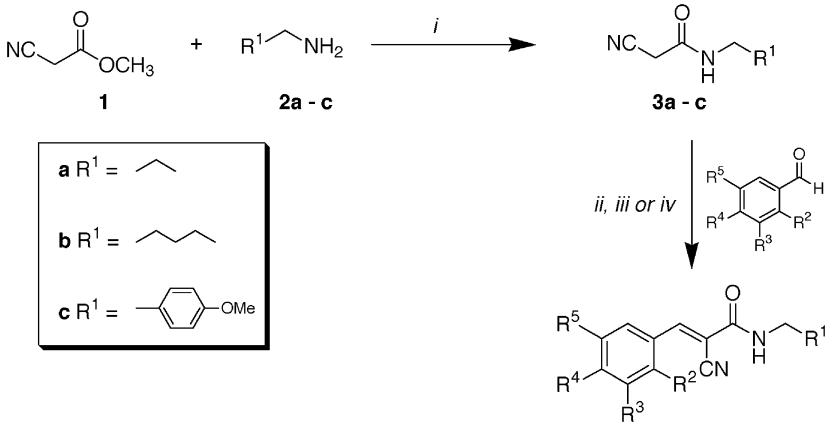
Abstract—We report a comparative study of the Knoevenagel condensation with a variety of substituted benzaldehydes (17 examples) and cyanoamides (3 examples), using three different methodologies: (a) traditional ethanol reflux; (b) water reflux; and (c) solvent free conditions. Almost without exception these reactions proceeded faster, more cleanly and in higher yields when the reactions were conducted in a solvent-free fashion. Additionally, our solvent free approach allowed the use of nitrobenzaldehydes, which failed to yield the desired products under traditional and water based approaches.

1. Introduction

At the commencement of the new century, a shift in emphasis in chemistry is apparent with the desire to develop more environmentally friendly routes to a myriad of materials. This shift is most apparent in the growth of Green Chemistry.[1–3] Green chemistry approaches not only hold out significant potential for reduction of by-products, a reduction in the waste produced and lowering of energy costs, but also in the development of new methodologies towards previously unobtainable materials, using existing technologies.[4]

Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large waste:product ratio,[5] are perhaps the most ripe for greening. However, in these fields, particularly during lead compound development, the end product is of



Scheme 1. *Reagents and conditions*: (i) mix at rt; (ii) EtOH reflux for 2 h overnight, piperidine (cat.); (iii) water reflux for 2 h overnight, piperidine (cat.); (iv) grind gently, piperidine (cat.).

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paramount importance and the route taken is often viewed as largely irrelevant. The introduction of combinatorial chemistry, which has become almost universally linked with lead compound development, appears in many applications to be contrary to the principles of green chemistry as, once again, focus is on the desired product with little concern for the overall efficiency of the process with regards transforming reactants into products with the least possible production of waste. As a result, one of the questions that our group is exploring is:

Are green chemistry and medicinal chemistry mutually exclusive?

Within our group we are actively investigating potential drug intervention strategies for control of signal transduction pathways. In doing so we typically design small

Table 1. Reaction of functionalised benzaldehydes with cyanoamides **3a–c**

Entry	Benzaldehyde	R^1	EtOH reflux (%)	H_2O (%)	Solvent-free (%)
1	Benzaldehyde	CH_2CH_3	42	46	68
2	3-OH-		49	56	99
3	4-OH-		30	52	94
4	3,4-di-OH-		53	40	>99
5	2,4-di-OH-		46	24	58
6	3,4-di-OCH_3-		48	64	69
7	2-OH-		40	64	74
8	2-Cl-		42	53	68
9	4-OCH_3-		45	61	64
10	3-Br-		45	40	97
11	4-Cl-		25	35	94
12	3-NO_2-		17	46	74
13	3-OCH_3-		26	40	87
14	4-NO_2-		0	80	>99
15	4-CO_2H-		58	37	97
16	3-OH, 4-OCH_3-		65	88	67
17	4-$N(CH_3)_2$-		63	40	99
18	Benzaldehyde	$(CH_2)_4CH_3$	37	55	>99
19	3-OH-		57	58	>99
20	4-OH-		50	53	89
21	3,4-di-OH-		57	66	>99
22	2,4-di-OH-		11	46	>99
23	3,4-di-OCH_3-		45	44	97
24	2-OH-		38	44	>99
25	2-Cl-		13	61	81
26	4-OCH_3-		65	11	79
27	3-Br-		19	44	43
28	4-Cl-		66	45	97
29	3-NO_2-		0	33	96
30	3-OCH_3-		30	28	58
31	4-NO_2-		0	27	12
32	4-CO_2H-		83	60	48
33	3-OH, 4-OCH_3-		97	40	>99
34	4-$N(CH_3)_2$-		81	74	44
35	Benzaldehyde	*p*-MeO-$PhCH_2$	10	50	96
36	3-OH-		35	47	95
37	4-OH-		39	50	93
38	3,4-di-OH-		36	54	85
39	2,4-di-OH-		39	40	71
40	3,4-di-OCH_3-		58	34	>99
41	2-OH-		52	37	98
42	2-Cl-		39	48	49
43	4-OCH_3-		42	16	68
44	3-Br-		45	17	38
45	4-Cl-		34	32	96
46	3-NO_2-		9	37	69
47	3-OCH_3-		24	31	99
48	4-NO_2-		0	22	51
49	4-CO_2H-		22	34	58
50	3-OH, 4-OCH_3-		45	43	69
51	4-$N(CH_3)_2$-		55	55	99

focused drug libraries of ca. 25–50 compounds. Although subtle variations in synthetic methodology will occur depending upon the choice of target, the drug design process is typically an iterative one. Thus, the development of a targeted library provides the ideal opportunity to examine the broad applicability of a synthetic approach, examining a wide range of functionality.

In this particular instance we required a facile route to libraries of highly functionalised cyanoamido benzaldehyde derivatives. After examination of the available options Knoevenagel condensation chemistry was deemed to be the most expedient approach. Accordingly we set about examining methodologies amenable to solution-phase synthesis approaches.

As can be seem from Scheme 1, our approach is elegantly simple: commencing from methyl cyanoacetate (**1**) and a variety of substituted amines (**2a**–**c**) allows for the generation of substituted cyano amides (**3a**–**c**) in excellent yields (data not shown). This reaction proceeds in the absence of solvent or heating.[6]

The base (piperidine) catalysed reactions of preformed **3a**–**c** with substituted benzaldehydes (see Table 1 for details of ring substituents) were subsequently examined under three different sets of reaction conditions: (i) traditional ethanol reflux overnight; (ii) dry grind in a mortar and pestle; and (iii) overnight reflux in water. Product yields are shown in Table 1.[7]

Traditional Knoevenagel conditions (Table 1, ethanol reflux) afford poor (0%, Table 1 entries 14, 29, 31 and 48) to excellent yields (97%, Table 1 entry 33) of the anticipated condensation products. Typically, however, the isolated product yields are moderate at best (40–60%) and require significant purification. A more serious limitation is the $-NO_2$ group sensitivity with poor yields being observed via the traditional route (17, 0, 0, 0, 9 and 0%, Table 1 entries 12, 14, 29, 31 46 and 48, respectively).

Similar examination of the Knoevenagel condensations using water as a solvent showed a slight improvement upon the isolated product yields ranging from 11 (Table 1 entry 26) to 88% (Table 1 entry 16). Although we also note that the typical yield is in the order of 40–70%. Additionally, difficulties were still encountered in the use of $-NO_2$-substituted benzaldehydes (46, 80, 33, 27, 37 and 22, Table 1 entries 12, 14, 29, 31 46 and 48, respectively). However, these reactions were confounded, from the green perspective, by the requirement for extractive isolation followed by

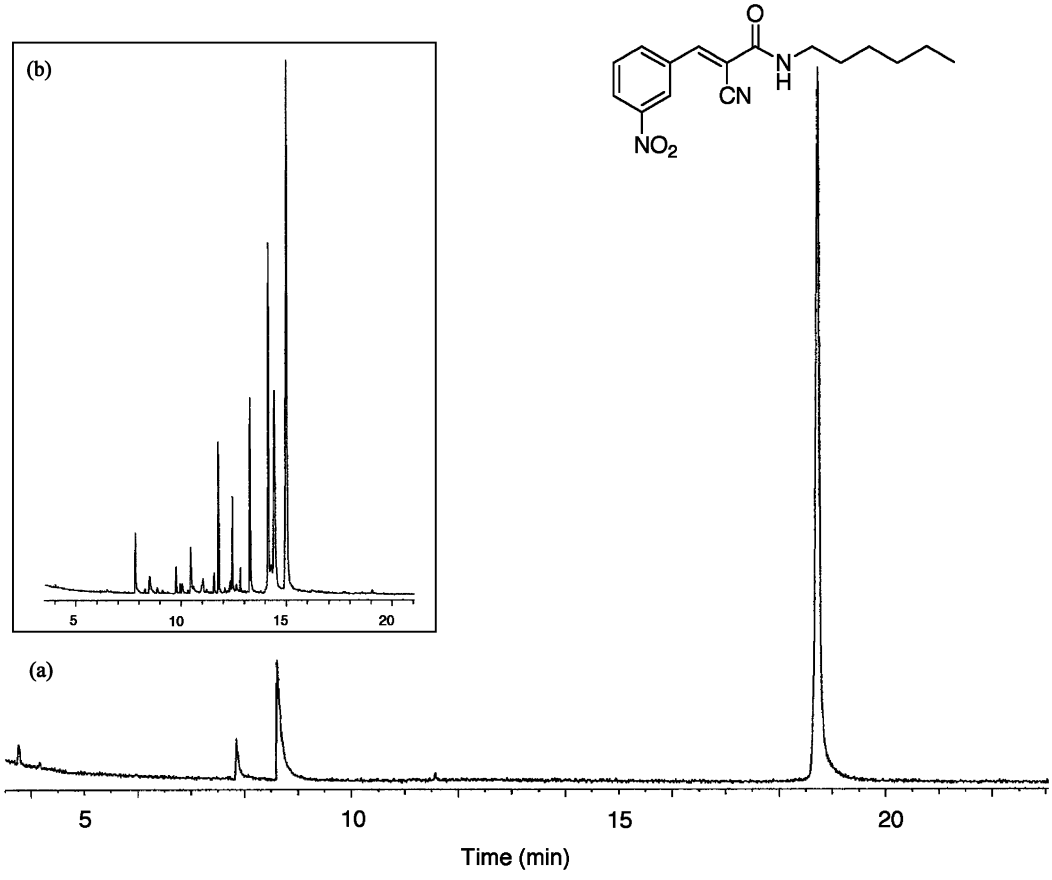

Figure 1. (a) GC trace obtained for the reaction of 3-nitrobenzaldehyde with cyanoamide **3b**. The main image shows the results of solvent-free reaction with the expected product at ca. 18 min and traces of 3-nitrobenzaldehyde at 8 min and cyanoamide **3b** at 9 min. (b) The insert shows the equivalent GC-trace obtained via the traditional EtOH reflux methodology. In this latter case no trace of the Knoevenagel product is observed.

recrystallisation to afford material of a suitable quality for biological examination.

In our final series of experiments we set out to examine the equivalent solvent-free reaction. Simple mixing (gentle grinding) of the cyanoamides (**3**) and benzaldehydes in the presence of a single drop of piperidine rapidly afforded the anticipated Knoevenagel product in a typically excellent yield (up to >99%), with the notable exception of the reaction with 4-nitrobenzaldehyde and **3b** (12%, Table 1 entry 31). The solvent-free approach afforded excellent yields of most other nitrobenzaldehydes examined during the course of this study (74, >99, 96, 69 and 51%, Table 1 entries 12, 14, 29, 46 and 48, respectively). In the majority of instances our solvent-free approaches generated materials of sufficient purity for subsequent biological testing. This is in sharp contrast to the outcomes of the solution or aqueous suspension based methodologies, where, when conversion to product is poor, a plethora of by-products are detected. Fig. 1 highlights a typical GC-trace obtained after a solvent-free synthesis protocol with essentially a single product observed, whereas in the more traditional approaches (ethanol reflux) no condensation product was observed (Fig. 1 insert) and the reaction mixture is significantly more complex.

The search for more environmentally acceptable routes to Knoevenagel products is by no means new with Davis et al. recently reporting the combined use of [6-mim]PF_6 and supercritical CO_2 as a green alternative in the synthesis of Knoevenagel products.[8] However, this approach still requires access to novel solvents, and equipment. Specialised equipment is required too for microwave mediated Knoevenagel condensations.[9,10]

In conclusion, we have shown, in this instance, it is possible to apply the tenets of green chemistry to a medicinal setting in the development of solvent-free approaches to the generation of biologically interesting molecules using Knoevenagel chemistry. Our approach can be adapted towards the use of semi-automated synthesis protocols.

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7. **Representative procedure for the preparation of 2-cyano-3-(3-hydroxy-phenyl)-*N*-propyl-acrylamide** (Table 1 entry 2). **Ethanol reflux**: 3-Hydroxybenzaldehyde (122 mg, 1 mmol) was dissolved in ethanol (10 mL) containing 2-cyano-*N*-propyl-acetamide (**3a**) (126 mg, 1 mmol) and piperidine (5 mg, cat.) and the mixture refluxed for 2 h. After cooling the precipitated material was collected and the ethanol removed in vacuo. Both materials were combined and recrystallised from ethanol/water to yield 96.7 mg (49%) of the title compound. Spectral and physical data obtained are in agreement with those obtained previously.
   Water reflux: 3-Hydroxybenzaldehyde (122 mg, 1 mmol) was suspended in water (10 mL) along with 2-cyano-*N*-propyl-acetamide (**3a**) (126 mg, 1 mmol) and piperidine (5 mg, cat.) and the heterogeneous mixture was stirred rapidly and refluxed for 2 h. After cooling the product was extracted with dichloromethane (2×10 mL), dried over $MgSO_4$, the solvent removed in vacuo and the residue recrystallised from ethanol water to yield 128.9 mg (56%) of the title compound.
   Solvent free: 3-Hydroxybenzaldehyde (122 mg, 1 mmol) was placed in a mortar followed by 2-cyano-*N*-propyl-acetamide (**3a**) (126 mg, 1 mmol) to which was added one drop of piperidine. These materials were then mixed using a pestle for ca. 5 min during which time a colour change occurred (the change is typically colourless to yellow or orange). The mixture was then allowed to stand at room temperature until it solidified, transferred to a round-bottomed flask and dried under high vacuum (which facilitates the removal of water and residual piperidine) to afford 227.9 mg (99%) of the title compound, identical to that prepared via ethanol reflux.
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