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Expedited Development through Parallel Reaction Screening: Application to PTC-Mediated Knoevenagel Condensation

John A. Corona, Roman D. Davis, Sandeep B. Kedia, and Mark B. Mitchell*

GlaxoSmithKline Research and Development, Five Moore Drive, Research Triangle Park, North Carolina 27709, U.S.A

Abstract:

Parallel microreactor screening enabled rapid identification of effective conditions for PTC-mediated Knoevenagel condensation between aldehyde (1) and thiazalone (2), affording a dramatic reduction in cycle time when compared to traditional conditions. Interesting facets of the reaction mechanism were revealed from kinetic profiling, specifically the operation of an extractive PTC mechanism with a pH optimum for the Knoevenagel condensation, a pK_a optimum for the elimination reaction and the requirement for crystallization of aldol tautomer (4) to drive the reaction to completion.

Introduction

A key step in the synthesis of one of our development compounds is classical base-mediated Knoevenagel condensation[1] between an aromatic aldehyde (**1**) and thiazalone (**2**) (Scheme 1). Although the Knoevenagel reaction has been applied widely in organic synthesis,[2] it is often problematic for active methylene compounds possessing only one activating group. This is the case for **2** where preliminary experiments found the reaction proceeded exceptionally slowly with piperidine in refluxing ethanol, typically taking 2−3 days to reach only 70% conversion. Elimination of intermediate aldol tautomers **3** and **4** was also sluggish, requiring addition of sulfuric acid in the latter stages of reaction to facilitate conversion through to olefin. Despite significant traditional optimization, the reaction at best furnished 84% conversion to product with a reaction time exceeding 30 h.

A number of modifications to the Knoevenagel reaction have been reported in recent years including the use of both phase transfer[3] (PTC) and Lewis acid[4] catalysis. From a process standpoint, we were particularly interested in the use of PTC conditions to effect the transformation using aqueous base. Additionally, we wanted to explore whether both PTC and Lewis acid catalysis could be applied synergistically.

Results and Discussion

Parallel reaction screening methodology was employed to rapidly examine the effect of solvent/base/PTC/Lewis acid upon the coupling of **1** and **2**. A D-Optimal experimental design,[5] comprising six solvents, five bases, three PTCs and three Lewis acids was utilized (Table 1), collecting and collating HPLC profile data using iChemExplorer[6] reaction system. Since reactions were performed under aqueous biphasic conditions, the Lewis acids selected for evaluation were restricted to water-tolerant transition metal triflates.

The efficacy of a PTC process is markedly dependent upon many factors,[7] notably the nature of the PTC (organophilic or accessible), the nature of the base (base strength, concentration, overall ionic strength) and the solvent. The factors were chosen to pragmatically evaluate various permutations of these parameters within the experimental design. The organophilic character for a given quaternary ammonium PTC is proportional to its carbon count (C#), while the electrostatic accessibility is best described by the Halpern number (q).[8] There is usually a compromise between organophilic and accessible character-PTCs at the extreme end of the spectrum are rarely the most effective catalysts-so for screening we typically use a few PTCs which are centrally tending with respect to both C# and q (Table 2). In addition the catalysts are selected to achieve a nonhomologous trend of C# and q with respect to the PTC, since this often provides useful information regarding the nature of the catalysis. Liquid−liquid PTC reactions commonly proceed by an extractive mechanism and will usually trend in line with C#. Alternatively an interfacial mechanism can sometimes prevail, and higher q values will now be favored.[7,8]

The screening data was visualized in Spotfire[9] (Figure 1) where a spread of results is apparent, ranging from negligible reaction to good conversion to aldol tautomer mixture **3** and **4** (∼68 combined LC area %). Elimination to olefin **5** was not facile with at best a 22 LC area % conversion being achieved.

A statistically significant fit was obtained for the data to a linear main effects model and the relative importance of each factor gauged from a Pareto view of the regression coefficients (Figure 2).

* Author to whom correspondence may be sent. E-mail: mark.b.mitchell@gsk.com.

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(5) The experimental design and data analysis were performed using the commercially available program *Modde*, ver. 6.0; Umetrics, Inc.: Kinnelon, NJ. http://www.umetrics.com.

(6) All screening was performed in HPLC vial microreactors using the *iChemExplorer system*; Reaction Analytics Inc.: Wilmington, DE. http://www.ichemexplorer.com.

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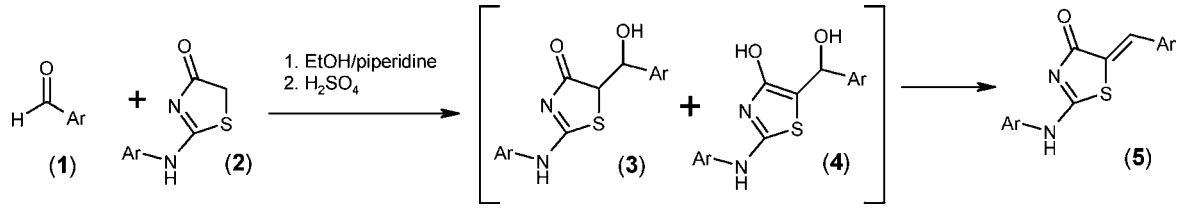
Scheme 1. **Knoevenagel condensation to prepare key intermediate 5**



This indicated that the use of either aqueous potassium carbonate or bicarbonate was central to achieving good conversion to aldol intermediate. The regression coefficients for the PTCs trended in line with C# supporting the anticipated operation of an extractive mechanism. The significant positive regression coefficient for $Yb(OTf)_3$ implied this was beneficial for conversion to aldol, while iPrOAc, 2- MeTHF, and 2-BuOH were the most favorable solvents. This prompted further investigation, paying particular attention to the effect of pH upon reaction progress (Table 3).

Examination of reaction progress for these experiments was most instructive and shed light on a number of aspects to the reaction. Key findings from these experiments were:

• Reaction completion was driven by crystallization of aldol tautomer **4** (Figure 3).

• A pH optimum of around 11.5 for fast conversion to **3** and **4** (Figure 4).

• Slow and incomplete conversion < pH 9.5

The first point is illustrated in Figure 3, where the profile for experiment 8 (Table 3) is depicted. There is initial reaction to an equilibrium mixture of aldol tautomers **3**/**4** and unreacted starting materials. After a brief period tautomer **4** crystallizes dragging the equilibrium over. Similar behavior was observed with both iPrOAc and 2-BuOH as solvent.

The observed pH optimum makes sense since at pH < 9.0 the base strength is too weak to effectively deprotonate **2**, while at high pH the anion of **2** is fully formed and precipitates from the aqueous base. At pH 11.5 substantial deprotonation of **2** does not occur in the aqueous layer since precipitation of the anion of **2** is not observed. However, hydroxide anion extracted by PTC is clearly able to deprotonate **2** in the organic layer as signaled by facile reaction and in accord with the known enhanced basicity of the organically extracted hydroxide.[7] Added $Yb(OTf)_3$ had negligible effect for experiments run with buffer mixture close to optimal pH, but had a marked effect for experiments run at high pH (Table 3, exp 11 cf. exp 12). Interestingly, added $Yb(OTf)_3$ was if anything detrimental for reactions using buffer of suboptimal pH (Figure 4). This trend suggests the main function of $Yb(OTf)_3$ was to simply lower the effective pH of the buffer solution.[10]

The use of 2-MeTHF, 1:1 $KHCO_{3(sat)}/K_2CO_{3(sat)}$ and Aliquat 336 was selected for scale-up, furnishing complete formation to aldol **4** in <3 h. We had seen earlier that elimination of aldols **3**/**4** to olefin **5** under basic conditions was not facile, and so attention focused upon use of acidic conditions. A number of acids were evaluated (sulfuric, acetic, TFA, TCA, DCA, oxalic, dodecylbenzenesulfonic) in various solvents (2-MeTHF, 2-BuOH, water, AcOH), and it was found that an optimal acid pK_a existed for the elimination. Use of acids with too low a pK_a resulted in substantial retro-aldol reaction (e.g., dodecylbenzenesulfonic, H_2SO_4), while at too high a pK_a reaction was sluggish (e.g., AcOH). Use of acid with a pK_a in the range of 0−1.5 was ideal—ultimately a solution of trichloracetic acid in AcOH was selected for the elimination. Aldol **4** was smoothly converted to olefin **5** in less than 2 h under these conditions. The complete transformation (condensation and subsequent elimination) was demonstrated at practical scale to furnish product olefin **5** in 92% overall yield and with a total batch time of <6 h.

Table 1. **Factors for D-Optimal PTC-base−solvent−Lewis acid screen**

factor	type	unit	levels
1	constant	mmol	0.19
2	constant	mmol	0.19
solvent	controlled		2-BuOH, toluene, MeTHF, MIBK, iPrOAc, DEE
base	controlled		50% NaOH, 2 N NaOH, 2 N NaOH−brine, 50% K_2CO_3, 25% $KHCO_3$
solvent volume	constant	μL	750
base volume	constant	μL	300
$Ln(OTf)_3$	controlled		none, $Sc(OTf)_3$, $Y(OTf)_3$, $Yb(OTf)_3$
$Ln(OTf)_3$ Amount	constant	mmol	0.02
PTC	controlled		Aliquat 336, TBAHS, BnTEACl
PTC amount	constant	mmol	0.02
temp	constant	°C	60

Table 2. **PTC C# and *q* values**

PTC	C#	*q*
BnTEACl	13	1.64
TBAHS	16	1
Aliquat 336	22	1.42

Conclusion

The application of statistical experimental design and reaction profiling allowed rapid delineation of conditions to effect facile PTC mediated Knoevenagal condensation between **1** and **2**. Screening was performed in microreactors allowing conditions to be determined both rapidly (within 2 weeks) and with minimal material (~3 g). Interesting facets of the reaction mechanism were revealed from kinetic profiling, specifically the operation of an extractive PTC mechanism with a pH optimum for the Knoevenagel condensation, a pK_a optimum

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(9) Spotfire decision suite available from TIBCO Software, Sommerville, MA; http://spotfire.tibco.com. For a discussion on the use of Spotfire in data visualization and mining, see: Higginson, P. D.; Sach, N. W. *Org. Process Res. Dev.* **2004**, *8*, 1009.
(10) It is possible that a wider screen of traditional Lewis acids under nonaqueous conditions may have identified suitable conditions to effect this Knoevenagel condensation in one-pot; however, this was not evaluated as part of this investigation.

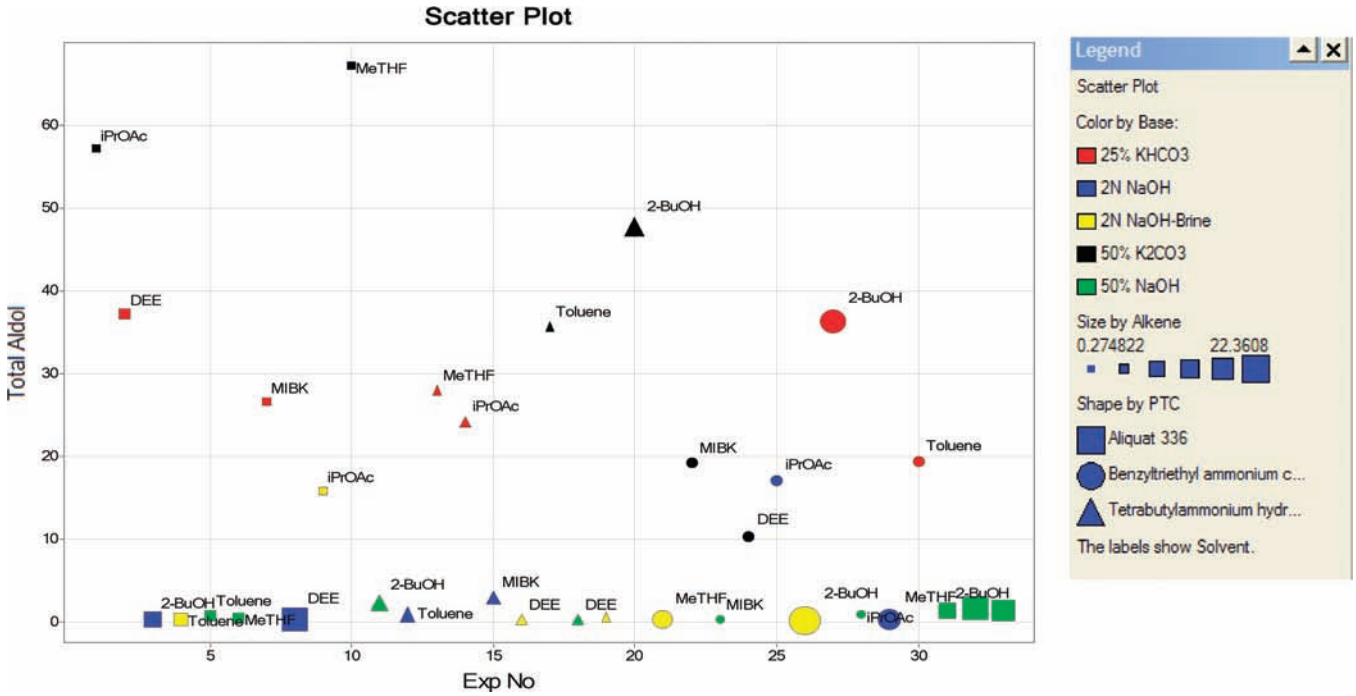

Figure 1. **Spotfire overview of screening data.**

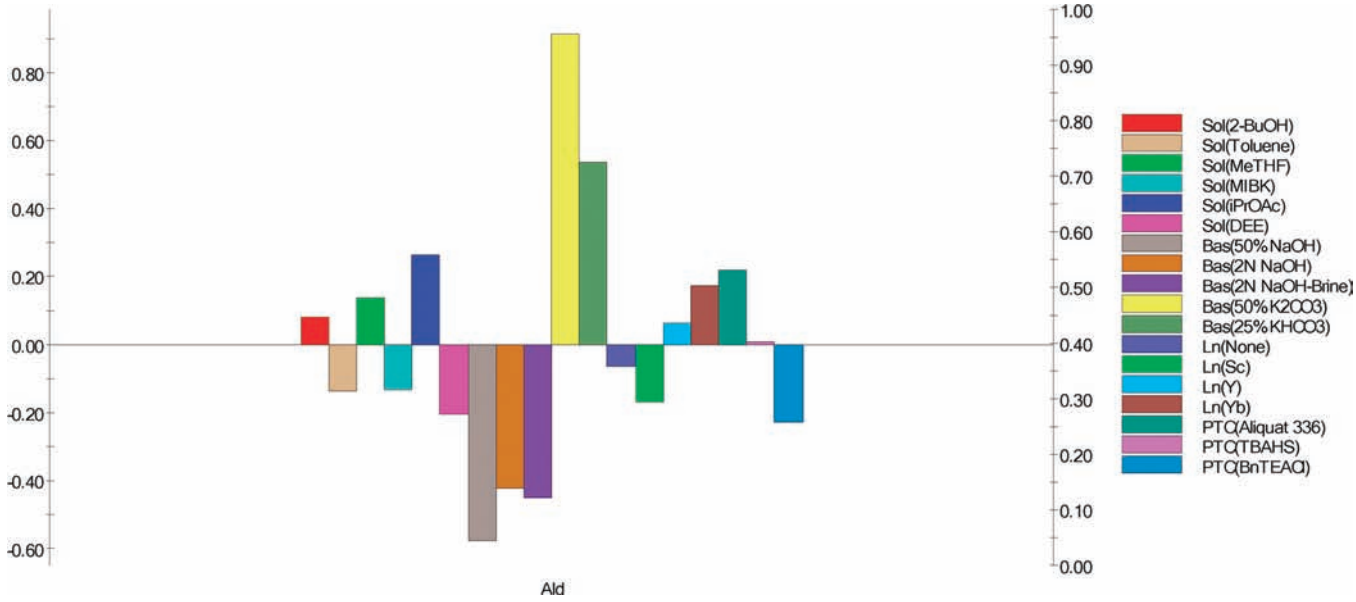

Figure 2. **Pareto view of regression coefficients.**

Table 3. **Experiments for full reaction profiling**

exp	**1** (mg)	**2** (mg)	solvent	solvent (vols)	base (vols)	Aliquat 336 (μL)	$KHCO_{3(sat)}$:$K_2CO_{3(sat)}$	buffer pH	$Yb(OTf)_3$ (mg)	time for **4** >85 LC area % (min)
1	30	50	MeTHF	15	6	20	1:1	10.6	13.4	185
2	30	50	MeTHF	15	6	20	1:2	11.3	13.4	129
3	30	50	MeTHF	15	6	20	1:3	11.7	13.4	134
4	30	50	MeTHF	15	6	20	1:1	10.6	0	139
5	30	50	MeTHF	15	6	20	1:2	11.3	0	144
6	30	50	MeTHF	15	6	20	1:3	11.7	0	118
7	30	50	MeTHF	15	6	20	1:0	8.1	13.4	incomplete
8	30	50	MeTHF	15	6	20	1:1	10.6	13.4	253
9	30	50	MeTHF	15	6	20	2:1	9.9	13.4	238
10	30	50	MeTHF	15	6	20	3:1	9.5	13.4	incomplete
11	30	50	MeTHF	15	6	20	0:1	13.3	13.4	130
12	30	50	MeTHF	15	6	20	0:1	13.3	0	540
13	30	50	IPAC	15	6	20	0:1	13.3	0	840
14	30	50	2-BuOH	15	6	20	1:1	10.6	13.4	600

for the elimination reaction and the requirement for crystallization of tautomer **4** to drive the condensation to completion. The process was demonstrated at practical scale furnishing the desired intermediate **5** in over 92% yield and with a cycle time

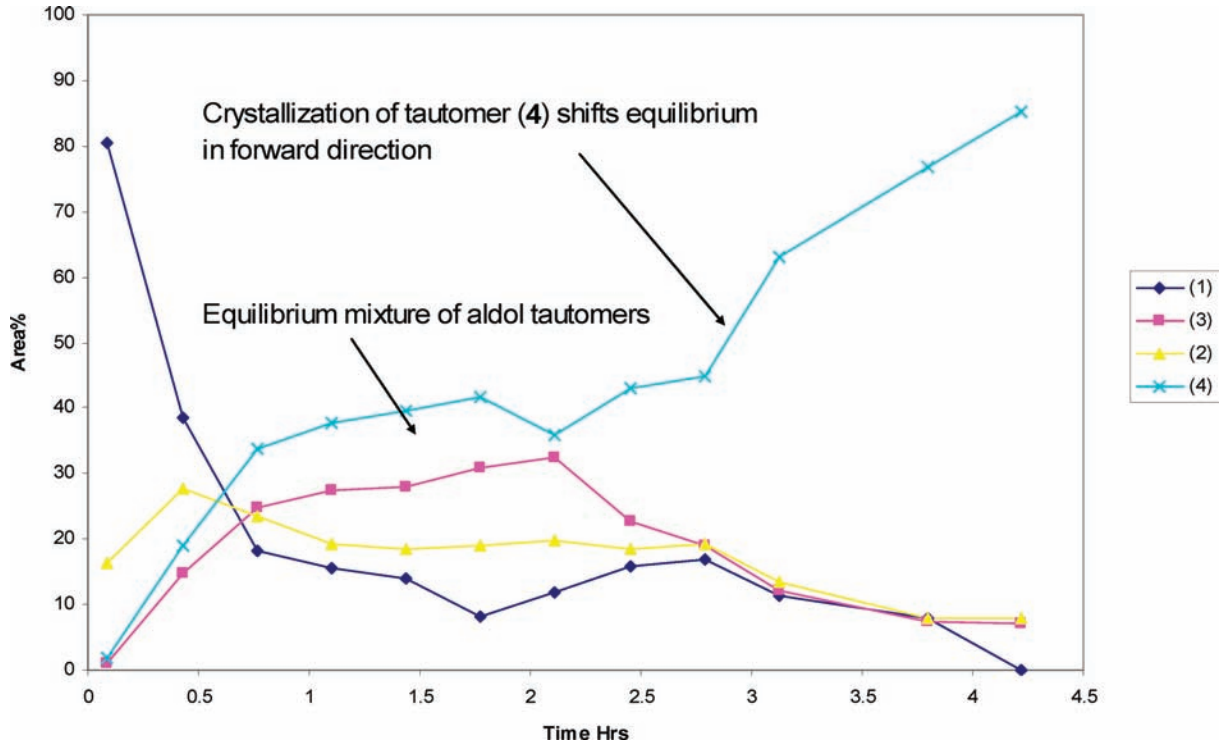

Figure 3. **Crystallization of aldol tautomer 4 shifts the equilibrium.**

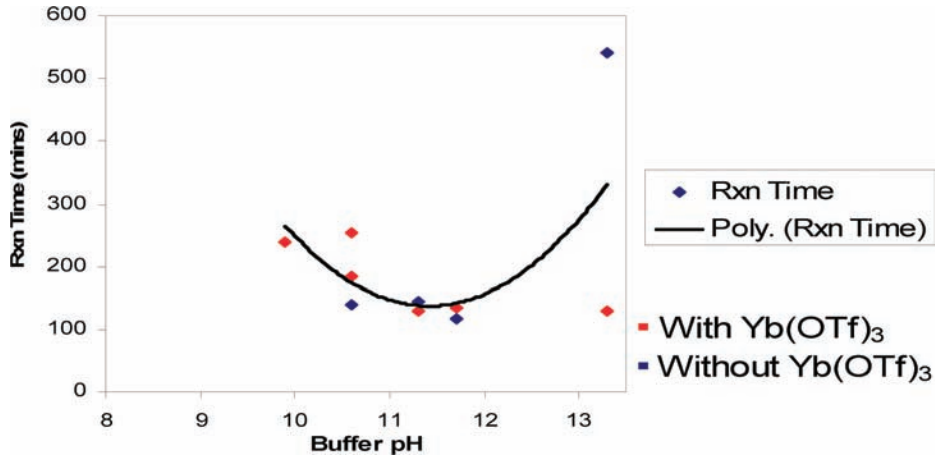

Figure 4. **Reaction time versus pH with 2-MeTHF as solvent.**

of less than 6 h, greatly reduced from >30 h when using traditional conditions.

Experimental Section

General. HPLC data was collected using an Agilent 1200 LC system. Analytical HPLC conditions were the following: Agilent ZORBAX SB-C18 RRHT, 1.8 μm, 3.0 mm × 50 mm, flow rate 1.5 mL/min, gradient (acetonitrile/water with 0.05% TFA): 100% water to 95% acetonitrile/5% water ramp over 2.5 min, then hold for 0.5 min. Compounds were observed by UV detection at 240 nm. Retention times under these conditions were as follows: **1** 1.52 min, **2** 1.94 min, **3** 1.90 min, **4** 1.98 min, **5** 2.35 min.

Representative Preparation of 5 by PTC-Mediated Knoevenagel Condensation. To a stirred solution of **1** (15 g, 0.057 mol) and **2** (9.1 g, 0.057 mol) in 2-MeTHF (105 mL) were added Aliquat 336 (2.3 g, 0.006 mol), 50% w/w aqueous K_2CO_3 (25 mL) and 25% w/w aqueous $KHCO_3$ (25 mL). The reaction mixture was heated at 70 °C for 2.5 h during which time precipitation of aldol **4** was observed. HPLC analysis of the reaction mixture showed >98% **4** with <1% **3**. The mixture was cooled to 25 °C and aldol **4** collected by filtration, washing the cake with 2-MeTHF (15 mL). The damp cake was dissolved in acetic acid (225 mL) and trichloroacetic acid added (62.9 g, 0.38 mol). The solution was heated at 80 °C for 1.5 h. HPLC analysis indicated >90% conversion to **5**. The reaction mixture was cooled to 25 °C, and product was precipitated by addition of water (200 mL), collected by filtration, and dried *in vacuo*. This furnished 22.2 g **5** (92%), which was analytically identical (HPLC, NMR, MS) to a reference sample.[11]

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