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Synthesis of β-Keto Esters In-Flow and Rapid Access to Substituted Pyrimidines

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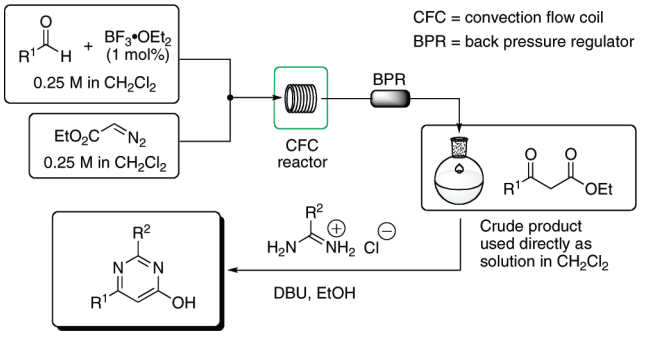

We have developed an in-flow process for the synthesis of β-keto esters via the $BF_3 \cdot OEt_2$-catalyzed formal C−H insertion of ethyl diazoacetate into aldehydes. The β-keto esters were then condensed with a range of amidines to give a variety of 2,6-substituted pyrimidin-4-ols.

β-Keto esters are versatile intermediates in organic synthesis, and have been extensively used in the construction of natural products and other biologically active heterocyclic molecules.[1] As the number of commercially available functionalized β-keto esters is limited, a number of methods have been developed for their preparation.[2] One of the simplest approaches involves an acid-catalyzed formal C−H insertion of ethyl diazoacetate into an aldehyde[3] and since the original report by Roskamp,[3a] various Lewis acids have been used ($SnCl_2$,[3] $TiCl_4$,[4a] $ZrCl_4$,[4a] $BF_3 \cdot OEt_2$,[4b] $NbCl_5$,[4c] Ag(TPA),[4d] [IPrAu(NCMe)]BF_4,[4e] MoO_2Cl_2,[4f] activated alumina,[4g] mesoporous silica,[4h] zeolites,[4i,j] clay[4k]) and the first asymmetric version has recently been reported[4l] using $Sc(OTf)_3$ and a bis-*N*-oxide chrial ligand.

Although this approach constitutes an elegant method for the synthesis of β-keto esters, the use of diazo compounds is potentially hazardous and this is particularly an issue when working on a larger scale. We considered that if it was possible to adapt this reaction for use "in-flow" this might offer several potential benefits over the "batch" process as exothermic processes, the release of gases, and the use of toxic or hazardous reagents are well tolerated.[5] To illustrate the synthetic utility of the in-flow process, we planned to use the resulting β-keto ester products to synthesize a range of substituted pyrimidines.

Our initial efforts focused upon selecting a suitable Lewis acid that could be used for catalyzing the addition of ethyl diazoacetate to aldehydes (the Roskamp reaction) under flow conditions. Roskamp originally reported that $SnCl_2$ was the catalyst of choice under batch conditions, but he also reported that $BF_3 \cdot OEt_2$ could be used, albeit with slightly diminished yields. As the $BF_3 \cdot OEt_2$-catalyzed reaction remains homogeneous throughout, we chose to use this as our basis for the development of an in-flow process. We began our studies by comparing the effectiveness of $BF_3 \cdot OEt_2$ and $SnCl_2$ as catalysts for the batch-wise addition of ethyl diazoacetate (**2**) to hydrocinnamaldehyde (**1**), in order to select an optimum catalyst loading for initial use under flow conditions (Table 1).

This preliminary study showed that $BF_3 \cdot OEt_2$ was an effective catalyst for the batch-wise production of the desired β-keto ester product **3** (76% yield at 10 mol % loading, entry 5), and this was comparable to the results obtained using either $SnCl_2$ (83% yield at 10 mol % loading, entry 1) or $SnCl_2 \cdot 2H_2O$ (81% yield at 10 mol % loading, entry 3). Furthermore, we found that the loading of $BF_3 \cdot OEt_2$ could be lowered to 1 mol % (entry 6) without affecting either yield or conversion. Lowering the loading of either $SnCl_2$ (entry 2) or $SnCl_2 \cdot 2H_2O$ (entry 4) to 1 mol % resulted in significant reductions in yield of the β-keto ester **3**.

We next investigated adapting this batch reaction into a flow process (Scheme 1). We used a Vaportec R2+/R4 reactor

(1) (a) Hill, M. D.; Movassaghi, M. *Chem.—Eur. J.* **2008**, *14*, 6836. (b) Lagoja, I. M. *Chem. Biodiversity* **2005**, *2*, 1. (c) Jain, K. S.; Chitre, T. S.; Miniyar, P. B.; Kathiravan, M. K.; Bendre, V. S.; Veer, V. S.; Shahane, S. R.; Shishoo, C. J. *Curr. Sci. India* **2006**, *90*, 793.

(2) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065.

(3) (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258. (b) The formal C−H insertion of α-diazoketones into aldehydes has also been reported: Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297.

(4) (a) Nomura, K.; Iida, T.; Hori, K.; Yoshii, E. *J. Org. Chem.* **1994**, *59*, 488. (b) Dudley, M. E.; Morshed, M. M.; Brennan, C. L.; Islam, M. S.; Ahmad, M. S.; Atuu, M.-R.; Branstetter, B.; Hossain, M. M. *J. Org. Chem.* **2004**, *69*, 7599. (c) Yadav, J. S.; Subba Reddy, B. V.; Eeshwaraiah, B.; Reddy, P. N. *Tetrahedron* **2005**, *61*, 875. (d) Yadav, J. S.; Subba Reddy, B. V.; Purnima, K. V.; Jhansi, S.; Nagaiah, K.; Lingaiah, N. *Catal. Commun.* **2008**, *9*, 2361. (e) Fructos, M. R.; Díaz-Requejo, M.; Pérez, P. J. *Chem. Commun.* **2009**, 5153. (f) Jeyakumar, K.; Chand, D. K. *Synthesis* **2008**, *11*, 1685. (g) Dhavale, D. D.; Patil, P. N.; Mali, R. S. *J. Chem. Res., Synop.* **1994**, 152. (h) Murata, H.; Ishitani, H.; Iwamoto, M. *Tetrahedron Lett.* **2008**, *49*, 4788. (i) Sudrik, S. G.; Balaji, B. S.; Singh, A. P.; Mitra, R. B.; Sonawane, H. R. *Synlett* **1996**, 369. (j) Balaji, B. S.; Chanda, B. M. *Tetrahedron* **1998**, *54*, 13237. (k) Bandgar, B. P.; Pandit, S. S.; Sadavarte, V. S. *Green Chem.* **2001**, *3*, 247. (l) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532.

(5) (a) Baxendale, I. R.; Hayward, J. J.; Ley, S. V.; Tranmer, G. K. *ChemMedChem.* **2007**, *2*, 768. (b) Ley, S. V.; Baxendale, I. R. *Chimia* **2008**, *62*, 162. (c) Ley, S. V.; Baxendale, I. R. In *Systems Chemistry*, Proceedings of the Beilstein Bozen Symposium, Bozen, Italy, May 26−30th, 2008; pp 65−85. (d) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4017. (e) Wheeler, R. C.; Benali, O.; Deal, M.; Farrant, E.; MacDonald, S. J. F.; Warrington, B. H. *Org. Process Res. Dev.* **2007**, *11*, 704.

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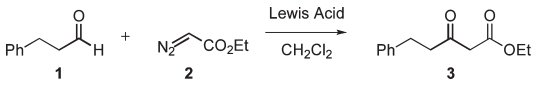
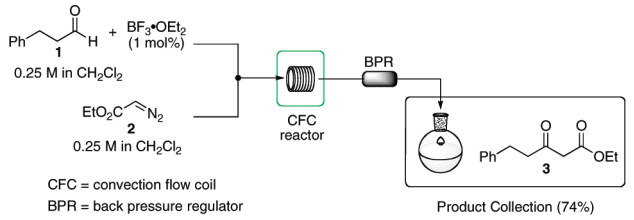
TABLE 1. Batch Optimization of Catalyst Loading[a]



entry	Lewis acid	mol %	yield (%)
1	$SnCl_2$	10	83
2	$SnCl_2$	1	32
3	$SnCl_2 \cdot 2H_2O$	10	81
4	$SnCl_2 \cdot 2H_2O$	1	35
5	$BF_3 \cdot OEt_2$	10	76
6	$BF_3 \cdot OEt_2$	1	83

[a]Reactions performed at 0.125 mM in CH_2Cl_2 at 23 °C.

SCHEME 1. In-Flow Preparation of β-Keto Ester 3



controlled by Vaportec Flow Commander software in order to allow optimization of the process. Hydrocinnamaldehyde was once again used as our test substrate, employing 1 mol % of $BF_3 \cdot OEt_2$ catalyst, and we systematically varied reaction parameters including temperature, flow rate, and back pressure in order to find optimum conditions.

During optimization, we found that a back pressure of 390 psi was required on the system in order to minimize outgassing of the N_2 generated inside the coil reactor. Under these conditions 30 °C was found to be the optimum reactor temperature (with 39 °C being the maximum) to ensure efficient conversion without exceeding the system pressure limit. A residence time of 7.2 min (equating to a flow rate of 0.139 mL/min from each of the two pumps) was found to be optimal (>99% conversion at steady state), with shorter residence times (i.e., ca. 5 min) leading to poorer conversions, and longer residence times (i.e., 10 min) offering no further advantage in conversion or isolated yield. This optimized procedure gave high conversion and produced the desired product **3** in good yield (74%) (Scheme 1), and furthermore it could be applied to a wider range of aldehydes (Table 2).

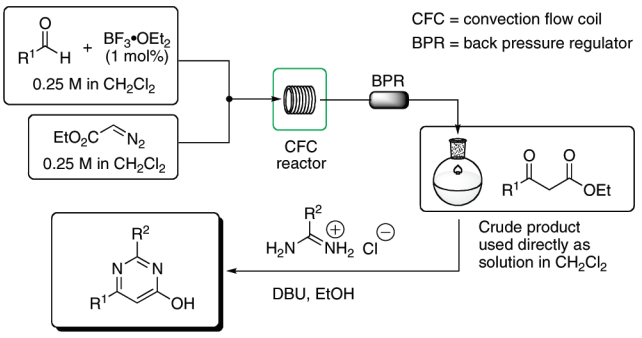
Analysis of the crude reaction mixture by ^1H NMR spectroscopy indicated that the β-keto ester was sufficiently pure to be used in subsequent transformations without purification. To demonstrate this, we treated the crude reaction mixture with acetamidine hydrochloride[6] (DBU, EtOH), which provided the corresponding pyrimidin-4-ol[7] **5a** in excellent yield (70%, 2 steps) (Scheme 2). The 70% yield obtained over the two steps compares favorably with the individual yields obtained when the two separate steps were carried out on purified material (Table 1, entry 6 and Scheme 2).

As the pyrimidine heterocycle is an important core structure in a range of biologically active molecules,[1] we next

(6) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 2381.

(7) For the in-flow synthesis of a pyrimidine from an yne-one see: Baxendale, I. R.; Schou, S. C.; Sedelmeier, J.; Ley, S. V. *Chem.—Eur. J.* **2010**, *16*, 89.

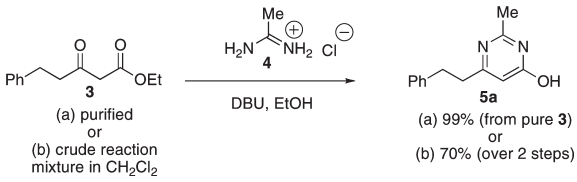
TABLE 2. In-Flow β-Keto Ester Synthesis and Subsequent Pyrimidine Formation



entry	R^1	R^2	product	yield (%)
1	CH_2CH_2Ph	Me	**5a**	70[a]
2		*c*-Pr	**5b**	67[a]
3		Ph	**5c**	33[a,c]
4		SH	**5d**	63[a,d]
5		H	**5e**	30[a]
6	CH_2Ph	Me	**5f**	54[a]
7		*c*-Pr	**5g**	54[a]
8	$(CH_2)_5CH_3$	Me	**5h**	62[a]
9		*c*-Pr	**5i**	67[b]
10		Ph	**5j**	51[b,c]
11		H	**5k**	33[b]
12	C_6H_{11}	Me	**5l**	78[b]
13		*c*-Pr	**5m**	60[a]
14	$CH(CH_3)CH_2CH_2CH_3$	Me	**5n**	62[b]
15		Ph	**5o**	50[b,c]
16	CH_2OBn	Me	**5p**	70[b]
17	CH_2CH_2OBn	Me	**5q**	52[a,e]
18	$(CH_2)_3C{\equiv}CH$	Me	**5r**	63[b]
19	$CH_2CH(CH_3)CH_2CH_2CHC(CH_3)_2$	Me	**5s**	35[b,f]

[a]1.05 equiv of amidine·HCl and 2.0 equiv of DBU. [b]2.1 equiv of amidine·HCl and 4.0 equiv of DBU. [c]Reaction refluxed for 18 h. [d]NaOEt and thiourea. [e]10 mol % of $BF_3 \cdot OEt_2$ used. [f]Modified flow procedure, see main text.

SCHEME 2. Synthesis of Pyrimidin-4-ol 5a from β-Keto Ester 3



investigated the two-step formation of a wider variety of pyrimidinols from in-flow generated β-keto esters. Thus, a range of aldehydes were converted in-flow into the corresponding β-keto esters. To the output from the flow was added the desired amidine hydrochloride and DBU in EtOH in a modification of a literature procedure.[6] The resulting solution was stirred under Ar at rt for 18 h (formamidine, acetamidine, and cyclopropylcarbamidine hydrochlorides) or heated to reflux for 18 h (benzamidine hydrochloride). The solvent was then removed in vacuo and the crude material purified by column chromatography to give a range of novel pyrimidinols in moderate to good yields over two steps from the starting aldehydes (Table 2, Figure 1).

Once again, the yields obtained for the two-step process (using acetamidine·HCl) were in general comparable to the yields of the intermediate β-keto esters when isolated and

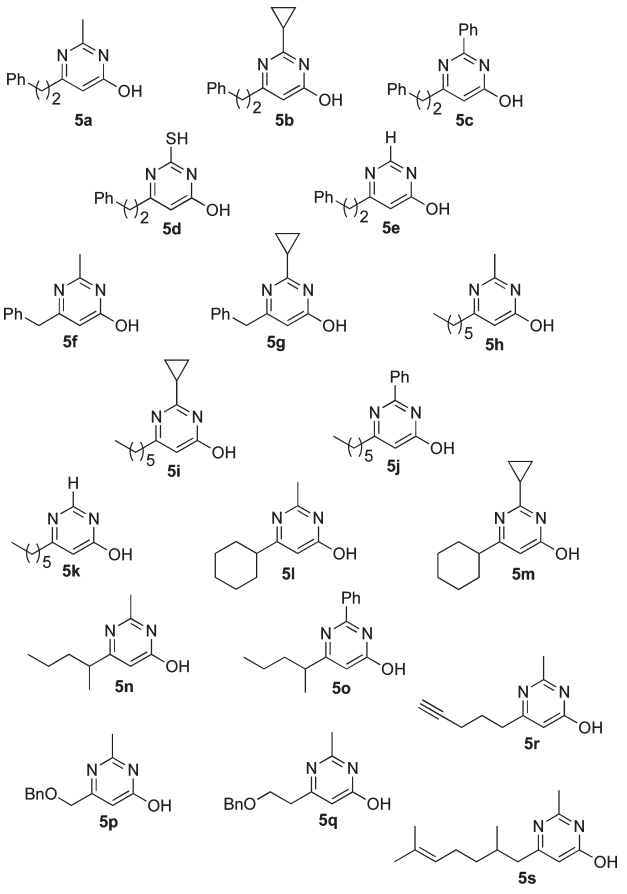


FIGURE 1. Structures of pyrimidin-4-ol products.

therefore the yield over two steps for these derivatives gives an indication of the efficiency of the β-keto ester formation.

Primary and secondary aldehydes were well tolerated by this two-step procedure and gave reasonable yields of a variety of pyrimidinols (entries 1−15). Pleasingly the procedure was compatible with the presence of oxygen functionality in the side chain of the aldehyde (entries 16 and 17). The flow process also tolerated the presence of an alkyne moiety (entry 18) or alkene (entry 19). Although the yield for the reaction with citronellal (entry 19) is relatively low, it is an encouraging result given the propensity for the aldehyde to undergo a cyclization in the presence of acid.[8] For this example we utilized a modified flow procedure, which involved delivery of the aldehyde and ethyl diazoacetate (as a solution in CH_2Cl_2) from one R2+ injection loop, and delivery of 10 mol % $BF_3 \cdot OEt_2$ (in CH_2Cl_2) from the other.[9] This procedure avoided exposing citronellal to the Lewis acid prior to combination with ethyl diazoacetate, and led to isolation of the pyrimidinol **5s** in 35% yield (entry 19) after the heterocycle formation step. In general, good yields were obtained over the two steps for the 2-methyl- and 2-cyclopropyl-derived pyridimidinols (e.g., entries 8 and 9). Reaction with benzamidine required harsher conditions (reflux, 18 h) but gave reasonable yields of the phenyl-substituted pyrimidinols (e.g., entry 10). In addition to forming C2-alkyl- and aryl-substituted pyrimidines, it was also possible to synthesize a sulfur analogue (entry 4) in good yield by reacting thiourea (NaOEt in EtOH) with an in-flow-generated β-keto ester. When β-keto ester formation was attempted with a range of aromatic aldehydes (e.g., benzaldehyde, *p*-anisaldehyde, *p*-NO_2-benzaldehyde, 2-furaldehyde, 2-pyridine carboxaldehyde) a mixture of products was obtained. This is perhaps not surprising given that previous reports in the literature have found that use of $BF_3 \cdot OEt_2$ as a catalyst for this transformation gives low yields of the desired β-keto esters in addition to significant amounts of 2-aryl-3-hydroxy-2-acrylic esters.[4b]

In conclusion, we have synthesized a variety of novel 2,6-substituted pyrimidin-4-ols utilizing a two-step procedure involving preparation of intermediate β-keto esters in flow, followed by subsequent condensation reactions with a range of amidines.

Experimental Section

Representative Procedure for the Synthesis of Pyrimidin-4-ols. A solution of hydrocinnamaldehyde (**1**) (0.500 mmol, 0.25 M) and $BF_3 \cdot OEt_2$ (1 mol %) in CH_2Cl_2 (2 mL) was injected into one of the sample loops of the R2+ unit. The other sample loop was loaded with a solution of ethyldiazoacetate (**2**) (0.505 mmol) in CH_2Cl_2 (2 mL). The valves of the loop were set to load and the reagents pumped through the system using CH_2Cl_2 as a system solvent at a flow rate of 0.139 mL/min per pump. The reagents combined in a T-piece before entering a 2 mL coil reactor (inside diameter = 1 mm, length = 2.9 m) (PFA), which was maintained at 30 °C by the R4 unit. A back pressure regulator (390 Psi) was added in line after the reactor to ensure the nitrogen produced during the reaction stayed in solution. The output (8 mL total volume) was collected directly into a round-bottomed flask. To the output from the flow reaction (crude β-ketoester **3** in 8 mL of CH_2Cl_2) was added EtOH (8 mL), acetamidine hydrochloride (52 mg, 1.10 equiv), and DBU (150 μL, 2.00 equiv). The resulting solution was stirred under Ar at rt for 48 h, after which time the solvent was removed in vacuo and the crude material purified by column chromatography (2% MeOH/CH_2Cl_2) to give the pyrimidinol **5a** (74 mg, 70%) as colorless needles, mp 126−127 °C (lit.[10] mp 125−127 °C); found C 72.7, H 6.6, N 13.1, $C_{13}H_{14}N_2O$ requires C 72.9, H 6.6, N 13.1; R_f 0.6 (10% MeOH/CH_2Cl_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3011, 2865, 2760, 1663, 1606, 1562, 1497, 1455, 1383, 1304, 1184, 967, and 856; δ_H (400 MHz; $CDCl_3$) 13.13 (1H, br s), 7.31−7.26 (2H, m), 7.22−7.17 (3H, m), 6.12 (1H, s), 3.02−2.96 (2H, m), 2.86−2.81 (2H, m), 2.48 (3H, s); δ_C (100 MHz; $CDCl_3$) 169.5, 166.0, 158.7, 140.8, 128.5, 128.4, 126.3, 109.6, 39.4, 34.1, 21.7; *m*/*z* (ESI) found 237.1001 (M + Na $C_{13}H_{14}N_2NaO$ requires 237.0998).[11]

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Supporting Information Available: Detailed experimental procedures, spectroscopic data, and copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) Clark, B. C., Jr.; Chamblee, T. S.; Iacobucci, G. A. *J. Org. Chem.* **1984**, *49*, 4557.

(9) This procedure could be used in any situation where the aldehyde is sensitive to being in contact with a Lewis acid for prolonged periods of time, but it offers no advantage to the standard protocol described in Scheme 1 and Table 2 for examples where the aldehyde and Lewis acid are compatible.

(10) Murray, T. P.; Hay, J. V.; Portlock, D. E.; Wolfe, J. F. *J. Org. Chem.* **1974**, *39*, 595.

(11) Sakamoto, T.; Yoshizawa, H.; Yamanaka, H. *Chem. Pharm. Bull.* **1984**, *32*, 2005.