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Pot, atom and step economic (PASE) synthesis of highly functionalized piperidines: a five-component condensation

Paul A. Clarke,* Andrey V. Zaytzev and Adrian C. Whitwood†

Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK

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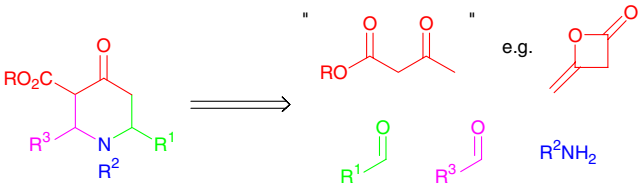
Abstract—The diastereoselective pot, atom and step economic (PASE) synthesis of highly functionalized piperidines has been realized. The procedure simply involves mixing methyl acetoacetate, 2 equiv of aldehyde and 2 equiv of aniline together in the presence of $InCl_3$. In most cases the piperidine precipitates out of solution.

Functionalized piperidines occur with great regularity in the natural product arena and as important units in pharmaceuticals. Consequently, a huge amount of effort has been directed towards developing ever more efficient methods to synthesize them.[1] For example, over the last ten years thousands of piperidine-containing compounds have been entered into preclinical and clinical trials.[2] We have recently become interested in the development of 'Greener' methods for the synthesis of organic molecules of medium complexity, and have reported the pot, atom and step economic (PASE) synthesis of highly substituted tetrahydropyran-4-ones.[3] Pot, atom[4] and step[5] economy aims to combine as many transformations as possible into a single reaction vessel, without the need for work-up and isolation of intermediate compounds. Ideally, all the reagents should also be incorporated into the final product. This should lead to a reduction in the amount of waste generated by a synthetic route due to the minimization of by-products, reaction and extraction solvents, silica gel for chromatographic purification of intermediate compounds and alike. Process chemists in industry have long been applying these criteria to synthetic routes and during our discussions with them we became aware of a need to extend our PASE synthesis of THPs to the synthesis of functionalized piperidines. This Letter reports our success at developing a *five-component*, pot, atom and step economic, diastereoselective synthesis of highly functionalized piperidines.

Our initial strategy was similar to the one we had developed for our synthesis of THPs,[3,6] that is, disconnection of the target piperidine to a β-ketoester derivative and two aldehyde derived reaction partners (Scheme 1). In this instance we envisaged using an imine as one of the reaction partners and an aldehyde as the other, giving us the potential for diversification at the greatest number of positions around the piperidine ring.

We initially considered using diketene as the β-ketoester derivative, however, problems with supply and the hazards associated with its use prompted us to consider other alternatives. One interesting possibility was to use a β-ketoester itself and to increase the nucleophilicity of its α-carbon by formation of the enamine derivative. We rationalized that it may then be possible to develop a multi-component reaction which coupled the in situ formation of the enamine of the β-ketoester, with formation of an imine and the sequential condensation of the enamine to the aldehyde and then the imine,



Scheme 1.

Keywords: Piperidines; PASE; One-pot; Multi-component.
* Corresponding author. Tel.: +44 01904 432614; e-mail: pac507@york.ac.uk
† Corresponding author for information concerning X-ray crystallography.

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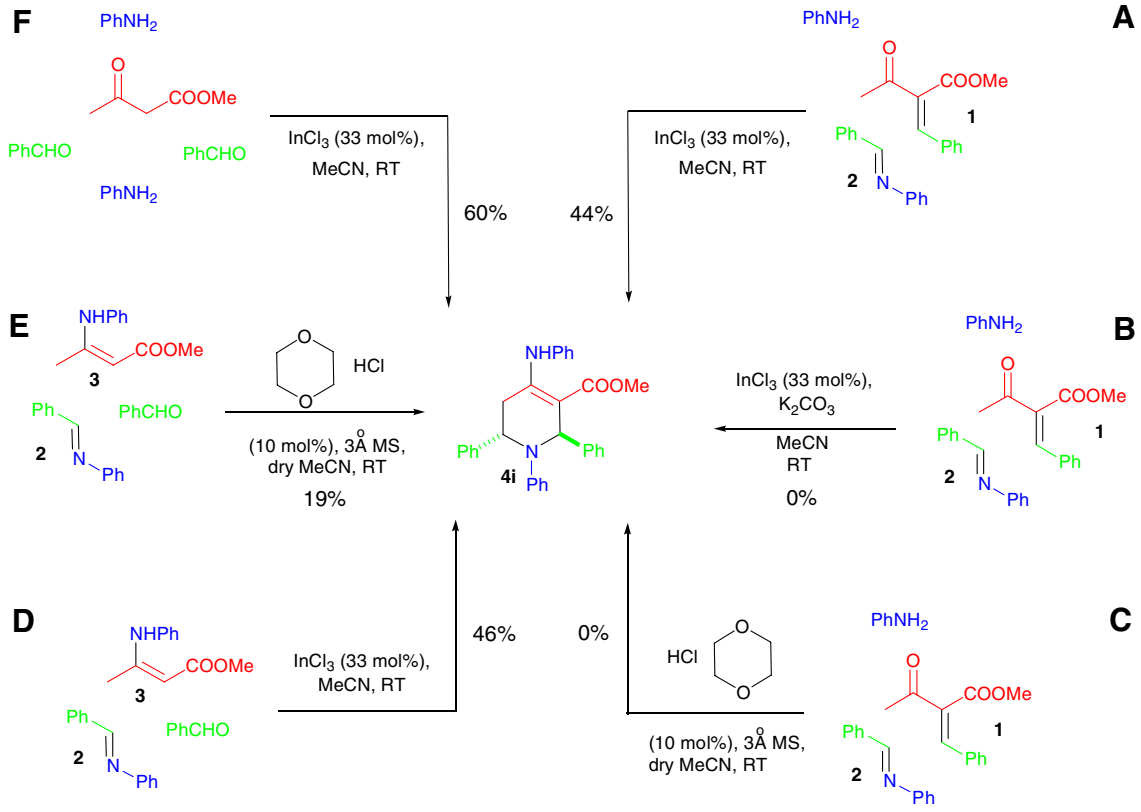


Scheme 2.

forming the desired piperidine in a pot, atom and step economic fashion. To assess the feasibility of this approach, we conducted a few investigative studies on the reactivity of the potential reacting partners (Scheme 2).

We elected to use $InCl_3$ as a Lewis acid promoter as it had been used previously to catalyze Knoevenagel reactions,[7] Mannich-like reactions and imine formation[8] and Michael reactions.[9] Initially we pre-formed Knoevenagel adduct **1** and imine **2** and mixed them with aniline in the presence of $InCl_3$ and we were pleased that the desired piperidine was formed in a reasonable yield (**A**). However, when this reaction was repeated in the presence of anhydrous potassium carbonate no reaction took place (**B**). This led us to speculate that the reaction was actually promoted by trace amounts of HCl present in the $InCl_3$, although when we ran the reaction using a solution of HCl in 1,4-dioxane no product was formed (**C**). We next examined the reaction of pre-formed enamine **3** with benzaldehyde and imine **2** in the presence of $InCl_3$. In this case the desired piperidine **4** was again formed in a moderate yield (**D**). The Brønsted acid promoted reaction was also investigated, and in this instance a 19% yield of piperidine **4i** was recovered from the reaction (**E**). Given the success of routes **A** and **D**, we investigated the in situ formation of both the enamine and the imine and their condensation/cyclization reactions, which is in effect a *five-component condensation reaction*. We were delighted to find that not only did this reaction yield piperidine **4i**, but it did so in an increased yield of 60% (**F**). The relative stereochemistry of the 2,6-phenyl groups in **4i** was confirmed as trans- by single crystal X-ray analysis (Fig. 1). These studies provided proof of concept that a *five-component condensation reaction* was indeed a viable approach to the PASE synthesis of highly functionalized piperidine rings.

We suggest that a plausible mechanism for the formation of piperidine **4i** involves the Lewis acid promoted

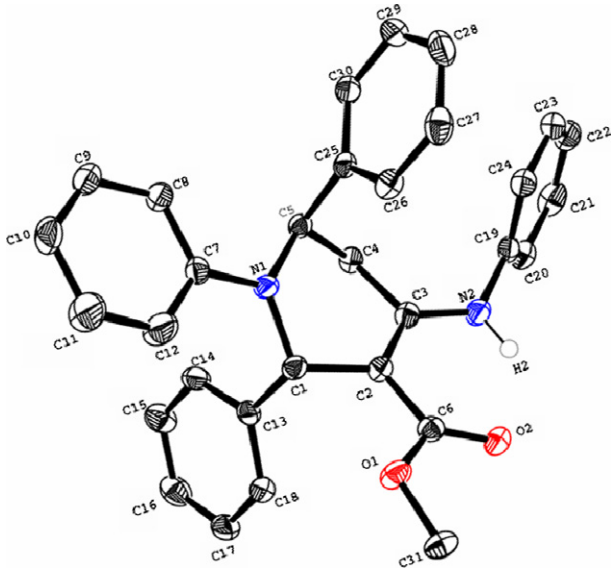
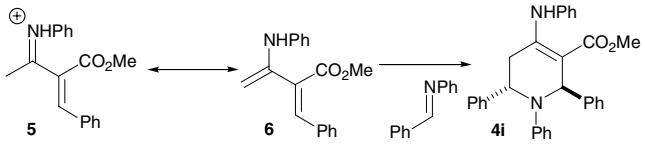


Figure 1. ORTEP diagram of the X-ray crystal structure of **4i** (ADP shown at 50%).

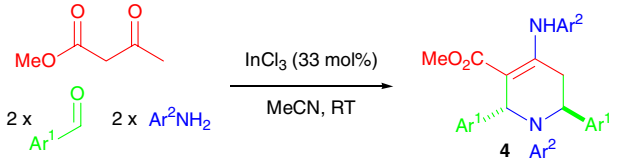


Scheme 3.

formation of imine **2** and enamine **3**, enamine **3** can then undergo a 'Knoevenagel-like' condensation with benzaldehyde to form the iminium ion–Knoevenagel product **5**. Loss of a proton and tautomerisation of the imine to the enamine generates a diene **6**, which can undergo either an aza-Diels–Alder cyclization or a tandem Mannich–Michael reaction to furnish piperidine **4** (Scheme 3).

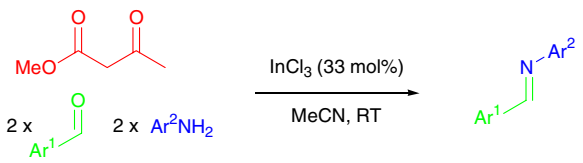
Given the success of these preliminary studies, we decided to investigate the scope of the reaction and the results are displayed in Table 1.[10] Some interesting observations were made during these studies. *p*-Anisidine reacted faster than aniline, and in general reactions were complete within 24 h rather than 48 h. While 4-chloroaniline reacted very slowly and took 7 days to generate a 52% yield of the piperidine product, *p*-nitroaniline did not react at all. This is undoubtedly due to the reduced nucleophilicity of these anilines compared to *p*-anisidine and aniline. A wide range of aromatic aldehydes could be used in the reaction. Yields were found to be lower when 2-substituted aldehydes were employed and this is probably due to steric effects. In the cases of aniline/4-methylbenzaldehyde **4g** and aniline/benzaldehyde **4i**, hydrolysis of the final enamine-piperidine occurred to some extent yielding the enol-piperidines in 3% and 11%, respectively. It was also found that certain aldehyde–aniline combinations did not form any piperidine, as the reaction stopped due to the precipitation of an insoluble imine (Table 2).

Table 1.



	Ar^1CHO	Ar^2NH_2	Yield (%)
a	$4\text{-}CH_3C_6H_4$	$4\text{-}MeOC_6H_4$	45
b	$3\text{-}CH_3C_6H_4$	$4\text{-}MeOC_6H_4$	48
c	Ph	$4\text{-}MeOC_6H_4$	74
d	$2\text{-}CH_3C_6H_4$	$4\text{-}MeOC_6H_4$	27
e	$3\text{-}CF_3C_6H_4$	$4\text{-}MeOC_6H_4$	57
f	$4\text{-}MeOC_6H_4$	Ph	52
g	$4\text{-}CH_3C_6H_4$	Ph	50
h	$3\text{-}CH_3C_6H_4$	Ph	64
i	Ph	Ph	60
j	$4\text{-}NO_2C_6H_4$	Ph	52
k	$2\text{-}CH_3C_6H_4$	Ph	16
l	$4\text{-}MeO_2CC_6H_4$	Ph	24
m	$4\text{-}MeOC_6H_4$	$4\text{-}ClC_6H_4$	52

Table 2.



Ar^1CHO	Ar^2NH_2	Yield (%)
$4\text{-}CH_3OC_6H_4$	$4\text{-}MeOC_6H_4$	59
$4\text{-}NO_2C_6H_4$	$4\text{-}MeOC_6H_4$	42
2-Naphth	$4\text{-}MeOC_6H_4$	58
$4\text{-}MeO_2CC_6H_4$	$4\text{-}MeOC_6H_4$	83

We next investigated the use of the aliphatic aldehydes, benzyloxyacetaldehyde, butanal and *iso*-butyl aldehyde with both aniline and *p*-anisidine, but in all cases multiple products arose. This can be attributed to a number of reasons: (i) the propensity for aliphatic aldehydes to favour enamine formation rather than imine formation and, (ii) the enamines of the aliphatic aldehydes forming preferentially to the enamine of the β-ketoester and then condensing with any remaining aldehyde before the desired reaction occurs. Additionally, we investigated the use of benzylamine instead of aniline; however, only the HCl salt of the amine was isolated, presumably due to the more basic nature of aliphatic amines compared to anilines.

In summary, we have developed a five-component condensation reaction for the formation of highly substituted piperidines, which is pot, atom and step economic. In general the yields are good and the piperidine product precipitates from the reaction allowing for easy isolation. Work is underway to extend the procedure to the synthesis of piperidines using different aldehyde and imine components in order to form piperidines with different 2,6-substituents and also to the asymmetric synthesis of such compounds. These studies will be reported in due course.

Acknowledgements

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References and notes

1. For recent reviews on the synthesis of piperidines see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781; Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953; Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
2. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.
3. Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438.
4. (a) Trost, B. M. *Science* **1991**, *254*, 1471; (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
5. (a) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25; (b) Wender, P.

A.; Handy, S. T.; Wright, D. L. *Chem. Ind. (London)* **1997**, 765; (c) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, 1993; Vol. 2, pp 27–66.
6. Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Chem. Commun.* **2005**, 1061; Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Org. Biomol. Chem.* **2005**, *3*, 3551.
7. Prajapati, D.; Gohain, M. *Beilstein J. Org. Chem.* **2006**, *2*, 11.
8. Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323.
9. Loh, T.-P.; Wei, L.-L. *Synlett* **1998**, 975.
10. General procedure for the PASE synthesis of piperidines: Methyl acetoacetate (2 mmol), aldehyde (4 mmol) and aniline (4 mmol) were dissolved in acetonitrile (4 ml) and $InCl_3$ (0.147 g, 0.67 mmol) was introduced. The reaction mixture was stirred at room temperature for 24 or 48 h. The product was isolated by filtration of the precipitate and washing with a small amount of acetonitrile or, if no precipitation occurred, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (Et_2O–petrol). Compound **4i** ν_{max} (cm^{-1}) (KBr) 3446, 2918, 2850, 1662, 1588, 1503, 1254, 1078; δ_H (500 MHz, $CDCl_3$) 10.26 (1H, s, N*H*), 7.33–7.25 (7H, m, Ar), 7.21 (1H, m, Ar), 7.17 (2H, d, *J* 7.5, Ar), 7.10–7.05 (5H, m, Ar), 6.61 (1H, t, *J* 7.0, Ar), 6.53 (2H, d, *J* 8.5, Ar), 6.46 (1H, s, 2-H), 6.30–6.28 (2H, m, Ar), 5.15 (1H, m, 6-H), 3.86 (3H, s, Me), 2.88 (1H, dd, *J* 15.3 and 5.8, 5-H_a), 2.77 (1H, dd, *J* 15.3 and 2.3, 5-H_b); δ_H (125 MHz, $CDCl_3$) 168.6 (C, *C*$OOCH_3$), 156.3 (C), 146.9 (C), 143.9 (C), 142.7 (C), 137.8 (C), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.1 (CH), 126.6 (CH), 126.4 (CH), 126.3 (CH), 125.9 (CH), 125.8 (CH), 116.1 (CH), 112.9 (CH), 97.9 (C, C-3), 58.2 (CH, C-6), 55.1 (CH, C-2), 51.0 (CH_3, $COOCH_3$), 33.6 (CH_2, C-5); MS (ES) 461 ($M+H^+$, 12), 386 (8), 280 (34), 182 (100), 150 (10), 121 (23), 106 (36), 94 (31); HRMS (ES) 461.2224 ($M+H^+$) $C_{31}H_{29}N_2O_2$ requires 461.2224.