Synthesis of 2,4-bifunctionalised cyclopentenones from 2-furaldehyde

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Herein we report a new approach to the synthesis of 2,4-bifunctionalised cyclopentenones *via* one-pot conversion of 2-furaldehyde with morpholine followed by concomitant 1,4 addition and elimination. This protocol has also been extended to afford 2-hydroxy, 2-amino and 2-phenyl cyclopentenones.

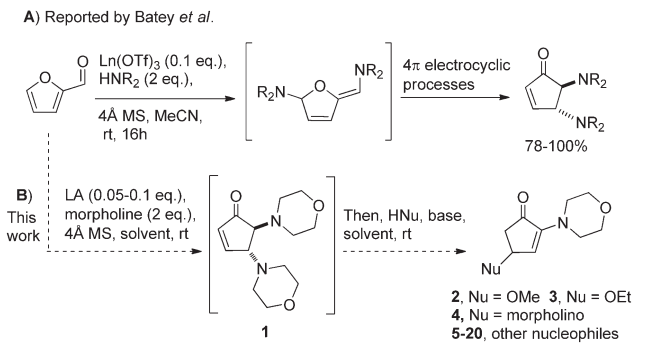
Bifunctionalised cyclopentenones are versatile building blocks for the synthesis of natural products. In particular, C-2 amino cyclopentenones could be utilised as intermediates towards antitumor natural products such as agelastatin A,[1] (−)-cephalotaxine ester derivatives,[2] (+)-nakadomarin,[3] roseophilin[4] and palau'amine.[5] C-2 hydroxy cyclopentenones have also been proposed as intermediates for (−)-cephalotaxine as well,[6] terpestacin,[7] nakadomarin A,[8] connatusin A,[9] dactylospongenone A[10] and aphagranins A and B.[11]

Whilst there are some methods for synthesis of C-2 hydroxyl cyclopentenones[7,8,12] and C-2 amino cyclopentenones,[13] it is still the case that there is a need for new practical and general procedures. Of particular interest to us were previous methods affording 4,5-diamino cyclopentenones,[14,15] which were recently improved upon by Li and Batey[16] by means of a one-step conversion of 2-furaldehyde to *trans*-4,5-diamino cyclopentenones *via* electrocyclic rearrangement of an intermediate enamine as shown (Scheme 1A).

We were drawn to this reaction in light of our previous work on optically pure *trans*-4,5-dioxygenated cyclopentenones in which we had proposed a similar intermediate to that by Batey *et al.*[17] We believe we can expand on previous reports on formation of selected 2,4-diamino cyclopentenones,[14a,16,18] including a similar transformation from 4-(mesyloxy)-cyclopentenones,[19] by studying the scope for conjugate addition of nucleophiles to *trans*-4,5-dimorpholino cyclopentenone **1** and thence elimination of morpholine. Herein we present efficient methods for synthesis of 2,4-bifunctionalised cyclopentenones from 2-furaldehyde (Scheme 1, B) that, given the dearth of existing methods[14,19,20] we hope will have broad utility in organic synthesis.

We began by optimising formation of diamine **1** from 2-furaldehyde with morpholine and found that most hard oxophilic Lewis acids were effective (see Supporting Information† Tables S1 and S2). We then examined the reactivity of the diamine intermediate **1** with alkoxides as nucleophiles using a sequential procedure involving addition of alkoxide after complete formation of amine **1** from 2-furaldehdye to avoid undesirable side reactions. During the process of optimisation we also observed improved reaction rates and yields using protic solvents such as MeOH. An optimum 3 equivalents of NaOMe afforded 67% **2** and 18% **4**, as lower amounts gave incomplete conversion and higher amounts led to formation of undesired **4** (see Supporting Information† Table S3). Formation of **4** is most likely due to competing conjugate addition of morpholine and was predominant with other alkoxides such as NaOEt.

Next we examined thiols as nucleophiles and using the sequential protocol we obtained promising results. We also found



Scheme 1 A) Reported transformation of 2-furaldehyde with amines by Li and Batey.[16] B) Explored transformations in this work.

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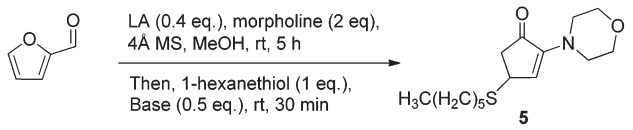
† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data for all new compounds and HPLC methods for reaction conditions screenings are included. See DOI: 10.1039/c3ra42663g

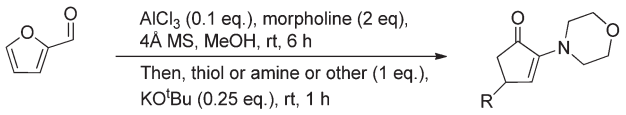
Table 1 Lewis acid and base screening for the synthesis of **5**[a]

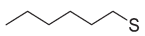
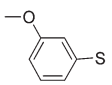
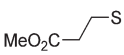
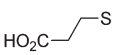
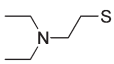
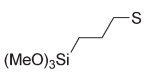
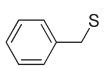
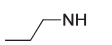
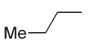


Entry	Lewis acid (used KO^{t}Bu as base)	**5** (%)	Entry	Base (used $AlCl_3$ as Lewis acid)	**5** (%)
1	$Dy(OTf)_3$	87	7	n/a	30
2	$BF_3{\cdot}Et_2O$	77	8	Im	26
3	$TiCl_4$	36	9	Et_3N	51
4	$SnCl_2$	97	10	DBU	79
5	$SnCl_4$	55	—	—	—
6	$AlCl_3$	93	—	—	—

[a] Conditions: 2-furaldehyde in MeOH (0.083 M), Lewis acid (LA) (0.4 eq.), morpholine (2 eq.), 4 Å MS, rt; after 5 h added 1-hexanethiol (1 eq.) and base (0.5 eq.), rt. Samples taken 30 min after addition; yields determined by HPLC.

Table 2 Scope for the formation of 2-morpholino-4-functionalised cyclopentenones[a]



	**5** 79%		**13** 79%
	**6** 73%		**14** 74%
	**7** 77%		**15** 55%[b]
	**8** 72%		**16** 77%
	**9** 76%		**17** 76%
	**10** 71%		**18** 52%
	**11** 80%		**19** 29%[c]
	**12** 63%		**20** 79%[d]

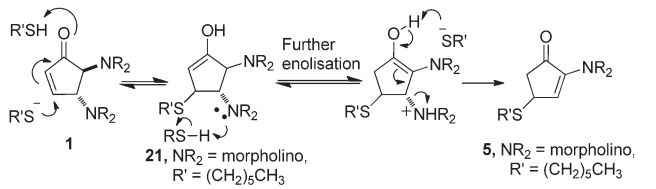
[a] Conditions: 2-furaldehyde in MeOH (0.25 M), $AlCl_3$ (0.1 eq.) morpholine (2 eq.), 4 Å MS, rt, 6 h; afterwards added to mixture with **1** in MeOH thiol (1 eq.) and KO^{t}Bu (0.25 eq.), rt 1 h. [b] Used KO^{t}Bu (1.25 eq.) and added HCl 2 M (1 eq.) to aqueous work up. [c] Also isolated enones **2** and **4** in 21% and 20% yields respectively. [d] Diamine intermediate **1** was isolated and added over $LiCu(n\text{Bu})_2$ (1 eq.) prepared in Et_2O at −78 °C from CuI and *n*BuLi, no KO^{t}Bu was used. Yields for isolated products by flash chromatography on silica gel.

that methanol was the preferred solvent. Further optimisation of Lewis acid and base was explored by HPLC screening (Table 1).

From these results we selected $AlCl_3$ (0.1 eq.) as the optimal Lewis acid and KO^{t}Bu as base for a further study on the application of this method for a range of thiols with good yields (Table 2). Amines fared worse due to competition with morpholine but incorporation of an alkyl substituent *via* addition of lithium di-*n*-butylcuprate was shown to work well.

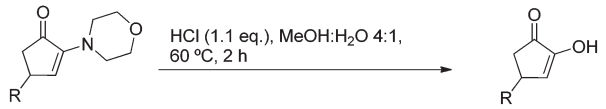
During optimisation of the conversion of furaldehyde into enone **10** (see Supporting Information† Table S4) we found the reaction to be highly sensitive to the quantity of base with increasing amounts leading to the formation of **2**, most likely from attack of KOMe formed *in situ*. In the absence of base, products such as 4-hexylthio-2,3-dimorpholino cyclopentanone **21** were formed, which on treatment with base in MeOD-d4 led to **5** (see Supporting Information† Fig. S1). Base catalysed deuterium incorporation at the C-5 positions suggests enolization as the rate limiting step prior to morpholine elimination. We propose a mechanism as previously suggested[14a,19] involving conjugate addition of thiolate to give intermediate diamine **21**, followed by E1cB elimination with prior protonation of morpholino at C-4 (Scheme 2).

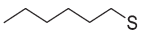
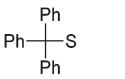
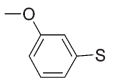
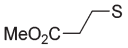
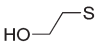
We then studied the prospects for conversion of the morpholino group into a hydroxy *via* hydrolysis with HCl (1.1 eq.) and found that wet MeOH with mild heating (60 °C) was effective. We applied this protocol to a selection of our previous 2-morpholino-4-thio cyclopentenones and this afforded the



Scheme 2 Possible mechanism for the formation of 2-morpholino-4-thio cyclopentenones.

Table 3 Scope for the formation of 2-hydroxy-4-functionalised cyclopentenones[a]



	**22** 82%		**28** 82%
	**23** 79%		**29** 69%
	**24** 82%		**30** 78%
	**25** 92%		**31** 80%
	**26** 94%		**32** 91%[b]
	**27** 49%	—	—

[a] Conditions: enone in MeOH : H_2O 4 : 1 (0.25 M), HCl 37% (1.1 eq.), 60 °C, 2 h. Yields for isolated products by flash chromatography on silica gel. [b] Used HCl (2 eq.) in THF : H_2O (4 : 1).

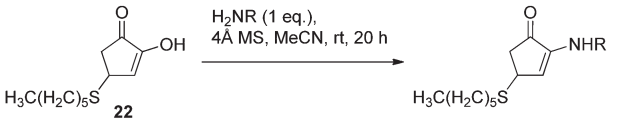
corresponding 2-hydroxy-4-thio cyclopentenones in high yields (Table 3). These enones exist as C-2 hydroxyl cyclopentenones as shown by NMR and IR. However, the incipient cyclic *meso*-1,2-diketone character is highlighted by the equal propensity towards enolization for both carbonyls as evidenced by the similar rate of deuteration for C-3 and C-5 (see Supporting Information† Fig. S2).

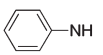
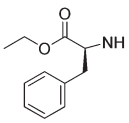
We then examined the possibility of further conversion of these 2-hydroxyl enones into 2-amino species and were pleased to observe that with primary amines such a transformation was possible, albeit in modest yields (Table 4).

Finally we have also extended this methodology in a similar fashion to a previous report by West *et al.*,[19] to secondary furfuryl alcohols that undergo an aza-Piancatelli rearrangement as reported by de Alaniz *et al.*[21] We did not pursue thorough optimisation studies but nevertheless established a two-step one-pot sequential method for the synthesis of 2-phenyl-4-thio-substituted 2-cyclopentenone. Thus treatment of 2-furylphenylcarbinol **41** with $BF_3{\cdot}Et_2O$ and aniline in MeCN at 60 °C led to **42** which was treated with thiol and catalytic KO^{t}Bu to afford compounds **43** to **48** (Table 5). Further studies will be required to delineate the scope of this useful process.

In conclusion, we have found and optimised a two step one-pot method for the synthesis of 2-morpholino-4-thiofunctionalised cyclopentenones from 2-furaldehyde by sequential condensation with morpholine followed by treatment with thiol and catalytic base. Acid hydrolysis of these enones was achieved in high yield

Table 4 Conversion of 2-hydroxy-cyclopentenones into 2-amino-4-thio cyclopentenones by displacement with primary amines[a]

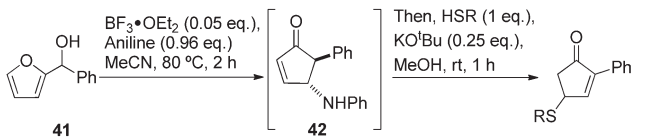


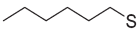
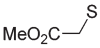
	**33** 51%		**37** 31%
	**34** 64%		**38** 51%
	**35** 35%		**39** 30%
	**36** 66%		**40** 38%

[a] Conditions: enone **22** in MeCN (0.25 M), 4 Å MS, rt, 20 h. Yields for isolated products by flash chromatography on silica gel.

affording *meso*-2-hydroxy-4-thio cyclopentenones, opening up possibilities for desymmetrization strategies. We have reacted these compounds with primary amines yielding 2-amino-4-thiofunctionalised cyclopentenones in moderate yields, which could be improved upon with further optimization. We have also extended this method to an aza-Piancatelli rearrangement from 2-furaldehyde and aniline to afford 2-phenyl-4-thiofunctionalised cyclopentenones.

Table 5 Scope for the formation of 2-phenyl-4-thio cyclopentenones[a]



	**43** 39%		**46** 61%
	**44** 21%		**47** 42%
	**45** 39%		**48** 49%

[a] Conditions: 2-furylcarbinol **41** in MeCN (0.25 M), $BF_3{\cdot}Et_2O$ (0.05 eq.) 80 °C, 2 h; afterwards added to mixture with **42** in MeCN thiol (1 eq.), KO^{t}Bu (0.25 eq.), MeOH, rt, 1 h. Yields for isolated products by flash chromatography on silica gel.

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