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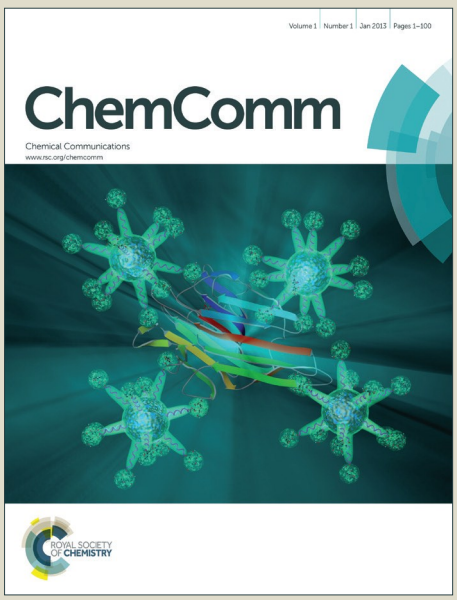

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Betaine mediated synthesis of annulated dihydrofurans from oxobis(methylthio)ketene acetals and N-butyl-N'-methyl ethane-1,2-diamine as precursors via NHC elimination

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Abstract : First in-situ generation of betaine intermediate has been developed using two new precursors oxobis(methylthio)ketene acetals and N-butyl-N'-methyl ethane-1,2-diamine for the synthesis of annulated dihydrofurans. This protocol adds a new dimension for the formation of annulated dihydrofurans through a series of selective consecutive formation of C-C & C-O bonds after reacting with enone rings. This in-situ generated betaine intermediate corresponds to deoxy-Breslow intermediate in the reaction via elimination of NHC.

The annulated dihydrofuran nucleus is an important privileged heterocyclic scaffold in numerous biologically active pharmacophores for example many neolignans, resveratrol oligomers and peptide - derived natural products and bioactive metabolites[1] (Fig. 1). Variety of methodologies and protocols have been reported by a number of organic chemists but they often suffer from low yields, limited scope or a need for specialized equipment[2]. Recently Yoon et al has reported synthesis of dihydro annulated furan via photocatalytic oxidative [3+2] cycloaddition of phenols[3] using expensive $Ru(bpz)_3(PF_6)_2$ catalyst.

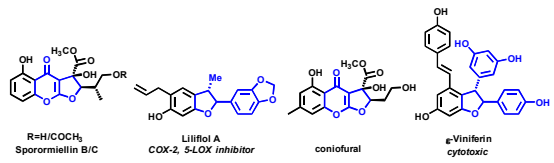


Fig. 1 Some Bioactive annulated dihydrofuran-containing natural products

A part of that, usually important organocatalytic intermediates are synthesized in the development of new domino transformation, specially the organocatalytic functionalization of aldehydes, ketones as well as their α,β-unsaturated carbonyl compounds, for example breslow intermediate was

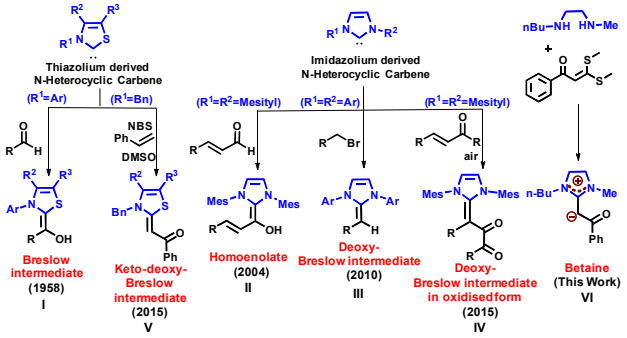
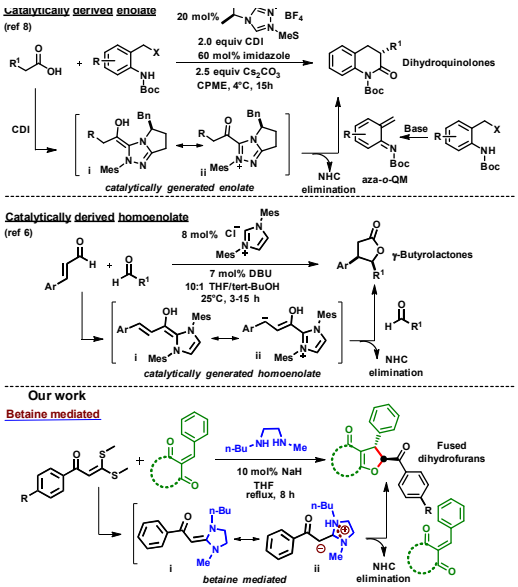


Fig. 2 Chronological development of NHC type intermediates in organic synthesis



Scheme 1 Synthesis of annulated ring heterocycles

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reported by Breslow in 1958 by the use of aldehydes and later in situ generated enolate from aldehyde[4] (Fig 2; I). In 2004, Glorius[5] and Bode[6] separately reported organocatalytic homoenolate intermediate reaction (Fig 2; II). In 2006, Fu and coworkers extended the scope of Breslow intermediate and reported the triazole-derived carbene-catalyzed β-alkylations of Michael acceptors[7a]. The isolation of deoxy-Breslow intermediates was reported by the group of Jacobi von Wangelin[7b,c] (2010) by the use of alkyl halides & NHC (Fig 2; III). Recently the synthesis of NHC derived deoxy-Breslow intermediate in their oxidized form has been developed by Biju [7d] using chalcones (Fig 2; IV). Moreover the isolation of keto-deoxy-Breslow intermediate was disclosed by Sudalai[7e] by the reaction of NHC with styrene employing DMSO & NBS as an oxidative system (Fig 2; V). These catalytic intermediates are generated by using NHC (N-heterocyclic carbene) as precursor and in the final step NHC is eliminated to afford the desired heterocycles (Fig 2 & Scheme 1). In our work analogous betaine intermediate is generated using two different precursors oxobis(methylthio)ketene acetals and N-butyl-N'-methylethane-1,2-diamine. The reaction proceeds via NHC elimination to afford useful annulated furans in contrast to the use of NHC as precursor (Fig 2; VI). Therefore we now document the catalytically generated betaine and its application to the stereoselective synthesis of diverse annulated dihydrofurans via C-H activation and C-C activation. The similarity of all organocatalytic intermediates and its recent application in the synthesis of annulated ring heterocycles along with our work has been shown[6,8] in Fig 2. and Scheme 1.

Our aim is to introduce a organocatalytic intermediate betaine[9] a novel nucleophilic intermediate which can be explored for their nucleophilicity and high reactivity towards electrophiles as cycloaddition partners. Betaines of pseudo-cross-conjugated mesomeric type (Figure 3) are isoconjugate with even non-alternant hydrocarbon dianions categorised as heterocyclic mesomeric betaines[10a]. Characteristic & systematic resonance hybrid can be depicted from various resonance structures (Figure 3; I)[10b]. Nodal positions of the HOMO of the anionic building block (Figure 3; II)[10c] & charge distributions according to valence bond theory[9] (Figure 3, III) within limits also can be represented. The anionic part of the betaine is joined by union bonds ("u") to the cationic part via unstarred positions[10d] (Figure 3; IV).

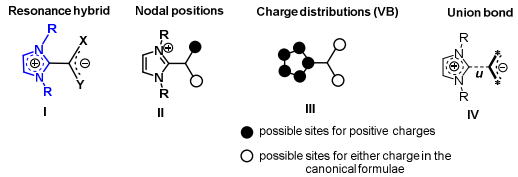
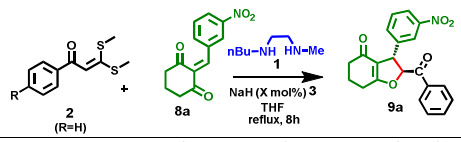


Fig. 3 Characteristic representation of Betaines

Our preliminary work was based on organocatalysis as well as multicomponent reactions (MCRs) using efficient and economic approach for the synthesis of various biological important heterocyclic compounds[11]. Our studies exploring the betaine mediated cycloaddition using precursors 3-oxobis(methylthio)ketene acetal[12] (or 3,3-bis(methylthio)-1-phenylprop-2-en-1-one) and N-butyl-N'-methylethane-1,2-diamine, were initiated by treating with adduct of 1,3-cyclohexanedione & 4-nitro benzaldehyde (i.e. 2-(3-nitrobenzylidene)cyclohexane-1,3-dione) during preliminary screening. We initiated our studies by exploring representative bases and solvents (Table 1).

The bases DABCO, Na_2CO_3, Cs_2CO_3, KOH, NaOH, DBU, DMAP, & NaH were subjected under investigation. All the bases were taken in 20 mol% by using the solvent THF, but it has been observed among various bases, NaH gave rise to the most satisfactory result (Table 1, entry 8-11), while THF proved to be the solvent of choice for the required transformation (Table 1, entry 8-10). Considering this point of observation, we decreased the amount of NaH 20 to 10 mol% & increased 10 to 15 mol% at reflux condition and demonstrated that the yield of the product increased 68 to 87 % (Table 1, entry 8, 10) & decreased to 87 to 78 % (Table 1, entry 9, 10). The required betaine intermediate (7) was formed in situ by the reaction of 3,3-bis(methylthio)-1-phenylprop-2-en-1-one and N-butyl-N'-methylethane-1,2-diamine in the presence of basic conditions using the solvent as THF in refluxing condition (Scheme 2)[13]. We have also done the reaction in the absence of N-butyl-N'-methylethane-1,2-diamine and NaH, but the satisfactory result was not obtained in this case that indicates diamine (1) is a key component for the formation of required betaine.

Table 1 Optimization of reaction conditions.[a]

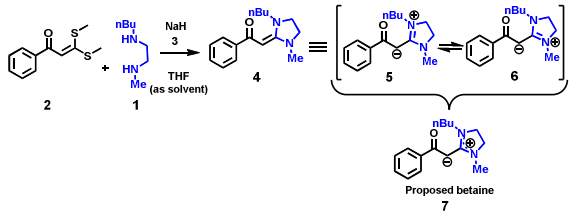


Entry	Base	X mol% of base	Solvent	Time(h)	Yield of 9a(%)[b]
1	DABCO	20	THF	24	9
2	Na_2CO_3	20	THF	24	13
3	Cs_2CO_3	20	THF	24	25
4	KOH	20	THF	24	11
5	NaOH	20	THF	24	8
6	DBU	20	THF	24	20
7	DMAP	20	THF	24	-
8	NaH	20	THF	24	68
9	NaH	15	THF	12	78
10	NaH	10	THF	8	87
11	NaH	20	ACN	24	38
12	NaH	10	ACN	12	28

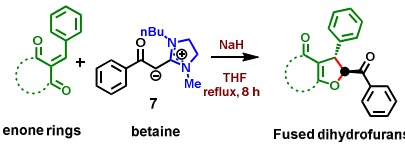
[a] Reaction conditions: Bis(methylthio)-1-phenylprop-2-en-1-one (1 mmol), N-butyl-N'-methylethane-1,2-diamine (1 mmol) & 2-(3-nitrobenzylidene)cyclohexane-1,3-dione (1 mmol) & base (X mol%) in given solvent at reflux for given hrs in the presence of N_2 atmosphere. [b] isolated yield.

With these initial conditions, we examined the impact of temperature, amount of base as well as solvent and best result

was obtained with NaH (10 mol%) in THF at reflux condition (Table 1, entry 9) and explored the dimension by varying the



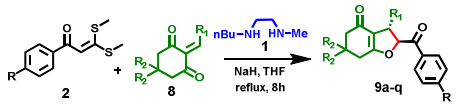
Scheme 2 Proposed formation of Betaine intermediate

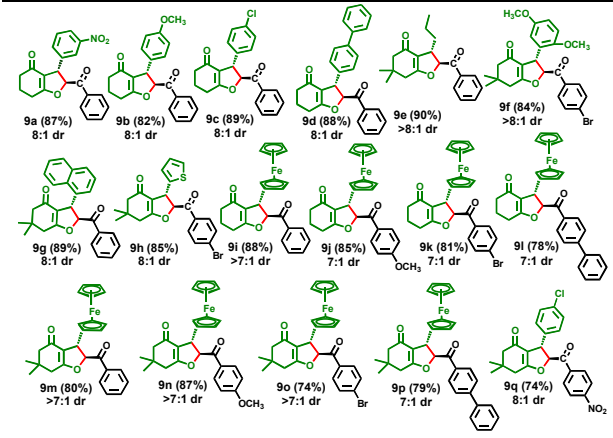


Scheme 3. Betaine based cycloaddition & formation of annulated dihydrofurans

enone rings with 2-benzylidene cyclohexane-1,3-dione /2-benzylidene-5,5 dimethylcyclohexane-1,3-dione /3-benzylidenechroman-2,4-dione / 3-benzylidene-6-methyl-2H-pyran-2,4(3H)-dione (Scheme 3) for the synthesis of heterocyclic annulated dihydrofurans such as tetrahydrobenzofuran-4(2H)-one/furo[3,2-c]chromen-4(3H)-ones and furo[3,2-c]pyran-4(3H)-ones and achieved in excellent yield. (Table 3, 4 & 5).

Table 3 Synthesis of Tetrahydrobenzofuran-4(2H)-ones[a,b,c]

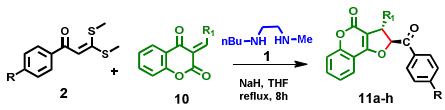


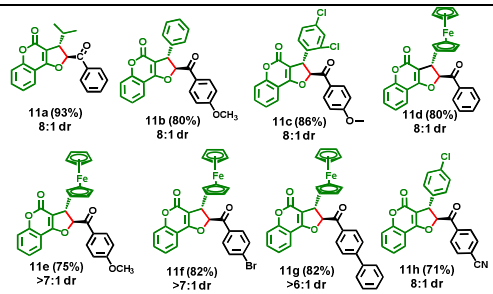


[a]Reaction condition: bis(methylthio)-1-phenylprop-2-en-1-ones (1 mmol), N-butyl-N'-methylethane-1,2-diamine (1 mmol) and 2-benzylidenecyclohexane-1,3-dione/ 2-benzylidene-5,5 dimethylcyclohexane-1,3-dione (1 mmol), NaH (10 mol%) were taken in THF at reflux for 8h in the presence of N_2 atmosphere, [b]Isolated yield, [c]The diastereomeric ratio determined by 1H NMR of the crude reaction mixture.

Experiments that probed the generality of this diastereoselective cycloaddition were performed. As summarized in Table 3-5, the reaction displays a broad scope, phenacyl moiety in 3,3-bis(methylthio)-1-phenylprop-2-en-1-one having electron-rich, electronically-neutral, and electron-deficient substitutents on the aryl rings all perform well, furnishing products with good yield. Notably, the feasibility of this reaction could also be realized effectively for α-ylidene-β-diketones containing aromatic, aliphatic, heteroaromatic as well as organometallic aldehyde.

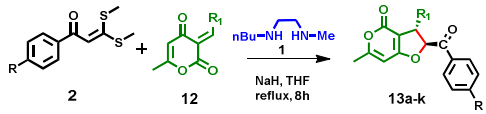
Table 4 Synthesis of Furo[3,2-c]chromen-4(3H)-ones[a,b,c]

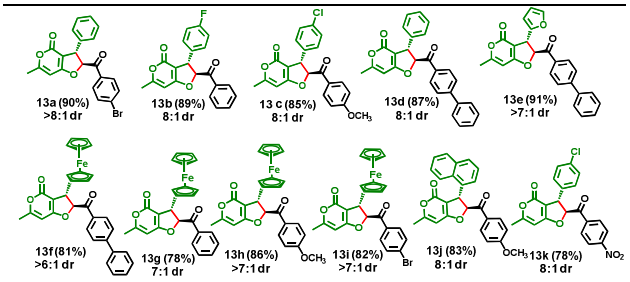




[a]Reaction condition: bis(methylthio)-1-phenylprop-2-en-1-ones (1 mmol), N-butyl-N'-methylethane-1,2-diamine (1 mmol) and benzylidenechroman-2,4-diones (1 mmol), NaH (10 mol%) were taken in THF at reflux for 8h in the presence of N_2 atmosphere, [b]Isolated yield, [c]The diastereomeric ratio determined by 1H NMR of the crude reaction mixture.

Table 5 Synthesis of Furo[3,2-c]pyran-4(3H)-ones[a,b]

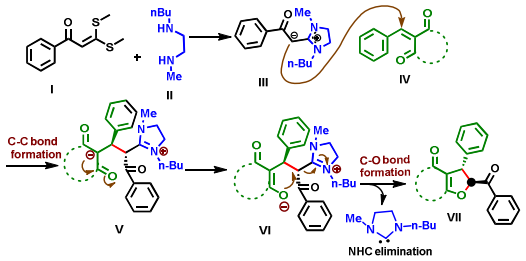




[a]Reaction condition: bis(methylthio)-1-phenylprop-2-en-1-ones (1 mmol), N-butyl-N'-methylethane-1,2-diamine (1 mmol) and 3-benzylidene-6-methyl-2H-pyran-2,4(3H)-dione (1 mmol), NaH (10 mol%) were taken in THF at reflux for 8h in the presence of N_2 atmosphere, [b]Isolated yield, [c]The diastereomeric ratio determined by 1H NMR of the crude reaction mixture.

The proposed mechanism are outlined in Scheme 4. The reaction of 3,3-bis(methylthio)-1-phenylprop-2-en-1-one with N-butyl-N'-methylethane-1,2-diamine generates the betaine (betaine intermediate III), in which the electron density of the

heterocyclic ring can then be translated to the α-carbon via the diene portion of the molecule.



Scheme 4 Proposed mechanistic pathways

This nucleophilic species then undergoes addition to the enone (IV). Once the C–C bond is formed, the intramolecular O-alkylation of the enolate with concomitant ring closure via the C–O bond formation occurs (V to VI) via NHC elimination. This leads the formation of required annulated dihydrofuran product (VII). The trapping of carbene has been achieved using BH_3.THF solution by the formation of borane complex.[14] The 1H NMR, spectrum of these compound has two doublets (J < 4.9 Hz), 1H-1H COSY, HSQC and HMBC confirmed the relative stereochemistry of C2 and C3 to be trans for all products. Finally single crystal analysis of 9g was unambiguous established by X-ray analysis of its crystal (Fig. 4).

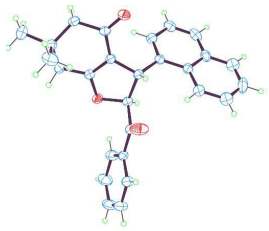


Fig 4 ORTEP diagram of 9g

In conclusion, a reactive intermediate betaine has been demonstrated using two new precursors oxobis(methylthio)ketene acetals and N-butyl-N'-methyl ethane-1,2-diamine in organocatalysis area in the synthesis of annulated heterocycles, which is previously limited to enolate, homoenolate and deoxy-homoenolate equivalents reactions. These betaine mediated annulations are efficient and afforded diversely annulated dihydrofurans by a series of selective consecutive formations of C–C and C-O bonds via elimination of NHC and also highlights a new and unexplored area with significant potential. We believe present catalytically derived betaine approach has immense potential in organic synthesis.

Acknowledgements

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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