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Monobromomalononitrile: An efficient regioselective mono brominating agent towards active methylene compounds and enamines under mild condition

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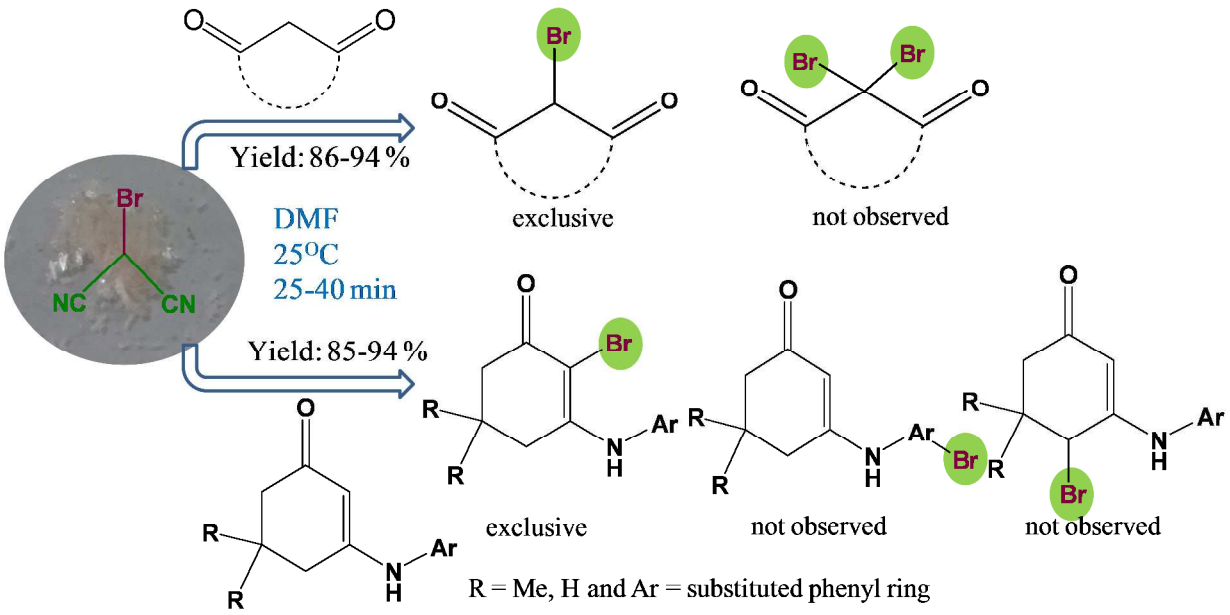


Abstract: The potential of monobromomalononitrile (MBM) as a convenient source of cationic bromine in organic bromination reaction has been explored. Studies reveal that MBM can be a good substitute of *N*-bromosuccinimide (NBS) in various respects. Enamines and active methylene compounds bearing aromatic rings are selectively mono brominated on the vinylic

and active methylene group respectively on reaction with MBM. This methodology has the advantages of easy preparation of MBM, shorter reaction time and high yields of the product formation. Moreover it provides a metal free green brominating agent which is more convenient in the pharmaceutical industry. Mono bromination reaction takes place only on active methylene group even after addition of excess amount of MBM. Enamines containing electron withdrawing, electron donating and ortho substituted amines react smoothly affording only the vinylic mono bromo products in good yields without producing any side products.

Bromination on organic molecules has been a workhorse in the field of organic synthesis because of commercial significance of intermediate bromoorganics for the construction of important natural products, as well as in the production of intermediates for agrochemicals, pharmaceuticals. As for example, a huge number of commercially important products such as herbicides, pesticides, fire retardants, and other new important materials have bromo functionality.[1] Formation of C-C bond using cross-coupling reactions can be employed with these bromides. Therefore, the halide compounds have huge impact on Heck,[2] Stille-Suzuki[3] and Sonogashira[4] and other hetero coupling reaction *via* aromatic functionalization process.[5] The use of elemental bromine is the traditional method of bromination. Careful control of the temperature and rate of bromine addition to avoid undesirable side reactions are the main disadvantages for the use of elemental bromination.[6] Moreover, corrosive and toxic nature of elemental bromine is a serious drawback for handling elemental bromine. Therefore, milder brominating agents are urgently needed for the bromination on organic molecules.[7–13] Various solid organic ammonium tribromides like 2,4-diamino-1,3-thiazole hydrotribromide,[8b] Bu_4NBr_3,[8d,e] $PyHBr_3$,[8e–g] 1,2-dipyridiniumditribromide-ethane (DPTBE),[8h] Me_4NBr_3,[8a] 1,8-diazabicyclo[5.4.0]undec-7-ene

hydrobromide perbromide ($DBUHBr_3$),[8c] and phenyltrimethylammonium tribromide[8e] are employed for bromination avoiding the direct use of molecular bromine. Another method involves oxidative bromination using hydrogen bromide and bromide salts as a bromine source where bromine is generated *in situ* in the reaction mixture upon oxidation of bromide ions.[9–13] The mostly employed bromides and oxidants combinations are H_2O_2–V_2O_5–Et_4NBr,[9d] oxone/HBr,[10b] oxone (the active component is potassium monopersulfate, $KHSO_5$)/NaBr,[10a] H_2O_2–HBr,[9a–c] t-BuOOH–HBr,[9b,c] Selectfluor®/KBr,[12] $NaBrO_3$–NaBr,[13] CAN/LiBr,[11b] and cerium(IV) ammonium nitrate (CAN)/KBr[11a]. In all these reactions the use of binary solvent systems (an organic solvent and water) is necessary for satisfactory result. The most significant drawback of all these methods is the undesirable oxidation of the sensitive functional groups present in the substrates by the oxidizing agents.

With respect to the above mentioned methodologies, *N*-bromosuccinimide (NBS) is one of the most potent brominating agents due to its stability and safe and easy handling.[14] NBS can brominate efficiently the activated aromatic compounds like phenols, amines *etc*.[14d,e] It can also brominate double bonds to 1,2-dibromo compounds; carbonyl compounds to α-brominated compounds;[14c] active methylene compounds to mon- and di-brominated compounds[14f] and enamines to vinylic and allylic brominated compounds.[14g] Though it is a mild brominating agent, it gives various side products on bromination of aromatic compounds[14d,e] and enamines or active methylene group.[14c,g] So it is a less selective brominating agent. For bromination of enamines containing electron rich aromatic ring, the selectivity of NBS is lost as it may brominate both the active aromatic ring and enamines, moreover the latter may also give rise to a mixture of vinylic and allylic brominated compounds. Herein we wish to report a general,

efficient and highly selective brominating agent for mono bromination of active methylene compounds and enamines under mild reaction condition.

Monobromomalononitrile (MBM)[15] is reported in the literature for the syntheses of various important compounds where it participates mainly in addition reaction with carbonyl group,[15a-c] α,β-unsaturated double bond[15a-c] and isolated double bond.[15d] It is also used for synthesis of biologically important heterocycles.[15e] In all the cases malononitrile part of MBM is added in the products. To the best of our knowledge, the appropriate reaction condition is not explored as yet for MBM where it may act solely as a brominating agent. Therefore initially an optimization study is carried out with a model reaction between acetylacetone and MBM in various non polar solvents to examine whether it gives only the brominated product or the products from the usual addition reaction with carbonyl group and O or C-alkylation reaction of enol substrate. When the reaction is carried out in non polar solvents like CCl_4, hexane, benzene and toluene employing 1.2 equivalent of MBM at room temperature, the reaction does not proceed at all (Table 1, entries 1-5). Literature results show that polar solvent is necessary to carry out the bromination reaction with NBS on double bond or active methyelene group. Since MBM is chemically analogous to NBS, various polar solvents are chosen for bromination (Table 1, entries 6-12). When polar protic solvent methanol is used as a reaction medium, TLC analysis suggests the formation of only one product along with substantial amount of unreacted starting material (Table 1, entry 6). The structure of the isolated product (yield ~ 30%) is confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis, which establishes the formation of only the mono brominated product 3-bromopentane-2,4-dione **2a** (Table 2, entry 1). This result incites us to perform the reaction in various polar solvents of varying polarities. However when the reaction is carried out in ethanol or water, the yield of the product **2a** is only 32 and 25 %

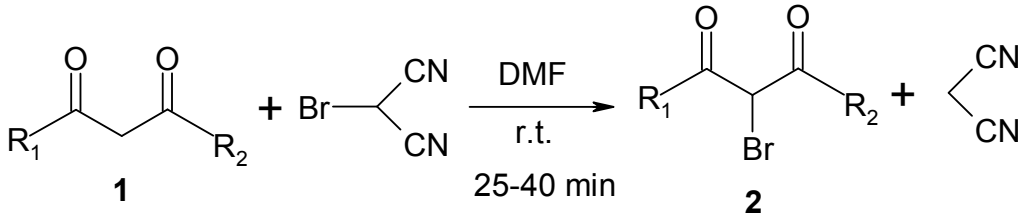
respectively indicating the unsuitability of protic polar solvent for the reaction (Table 1, entries 7, 8). Intriguingly, the yield of the product **2a** increases substantially in aprotic polar solvents in presence of 1.2 equivalent of MBM at room temperature (Table 1, entries 9-11). Moreover when the polarity of the employed aprotic solvents increases in the order THF, EtOAc and CH_3CN the yield of **2a** also increases from 45% to 70% (Table 1, entries 9-11). Gratifyingly, the maximum yield of the product **2a** is obtained in aprotic polar solvent DMF, nearly 91%, employing 1.2 equivalent of MBM at room temperature (Table 1, entry 12).

Table 1 Optimization of reaction conditions for bromination of acetylacetone with MBM

Entry	Solvent (10 ml)	Time (h)	Yield (%)
1	CCl_4	2	—
2	$CHCl_3$	2	—
3	Hexane	2	—
4	Benzene	2	—
5	Toluene	2	—
6	Methanol	2	30
7	Ethanol	2	32
8	H_2O	2	25
9	Tetrahydrofuran	2	45
10	Ethyl acetate	2	49

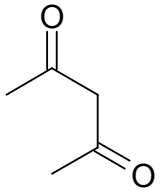
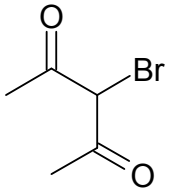
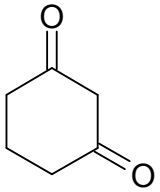
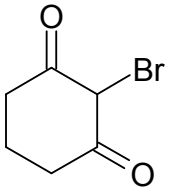
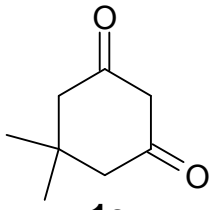
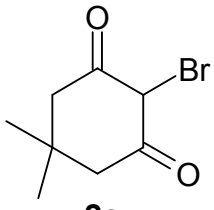
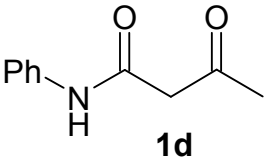
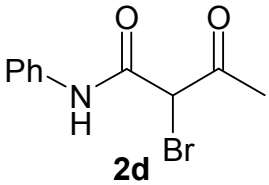
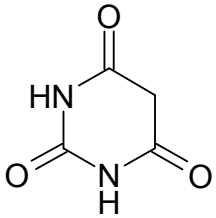
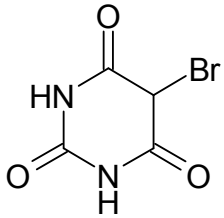
11	Acetonitrile	2	70
12	DMF	0.5	91

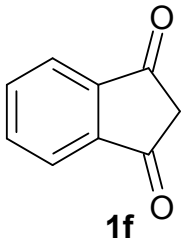
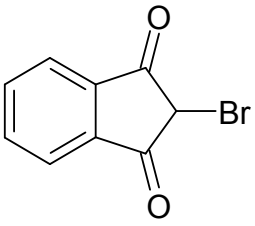
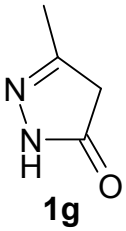
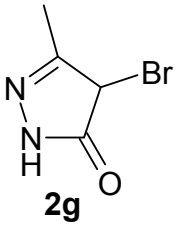
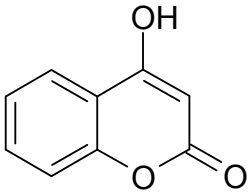
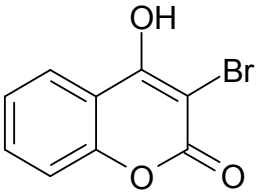
After having prepared **2a** successfully, we decide to explore the scope and generality of this reaction with various 1,3-dicarbonyl compounds including 1,3-cyclohexanedione (**1b**), 5,5-dimethylcyclohexane-1,3-dione (**1c**), acetoacetanilide (**1d**), barbituric acid (**1e**) and 1,3-indandione (**1f**) to furnish expected mono bromo-compound **2** in the optimized reaction conditions (Scheme 1, Table 2). The results show that the reactions can produce the mono brominated products **2a-f** in high yields within 25-40 min at room temperature (Table 2). This reaction is applicable to both cyclic as well as acyclic active methylene compounds. It is interesting to note that in presence of aromatic ring, bromination takes place only on active methylene group (**1d**) even after addition of excess amount of MBM (2.2 equivt.), confirmed by single crystal X-ray diffraction study (Fig. 1). Even the presence of excess amount of MBM (2.2 equivt.), cannot produce α,α-dibromo derivatives. The reaction stops selectively at mono bromo stage. This result establishes that the reaction of MBM is very specific for the formation of mono bromo derivatives of 1,3-dicarbonyl compounds. Activated compounds like 5-methyl-2*H*-pyrazole-3-ol (**1g**) and 4-hydroxycoumarin (**1h**) are also brominated with MBM to produce 4-bromo-5-methyl-2*H*-pyrazole-3-ol (**2g**) and 3-bromo-4-hydroxycoumarin (**2h**) respectively in high yields within 30 min at room temperature (Table 2, entries 7,8).



Scheme 1 Bromination on active methylene group using MBM.

Table 2 Scope of bromination on active methylene compounds **1** with MBM

Entry	Substrates (**1**)	Products (**2**)	Time (min)	Yield (%)	Melting point/[16]
1	 **1a**	 **2a**	30	91	137-139 /138-140
2	 **1b**	 **2b**	25	94	168-170 /168–170
3	 **1c**	 **2c**	25	93	172-176 /174–176
4	 **1d**	 **2d**	35	89	130-132 /129
5	 **1e**	 **2e**	40	86	195-197 /196

6	 **1f**	 **2f**	30	90	115-117 /115–118
7	 **1g**	 **2g**	25	86	180-182 /182
8	 **1h**	 **2h**	35	93	190-192 /192-194

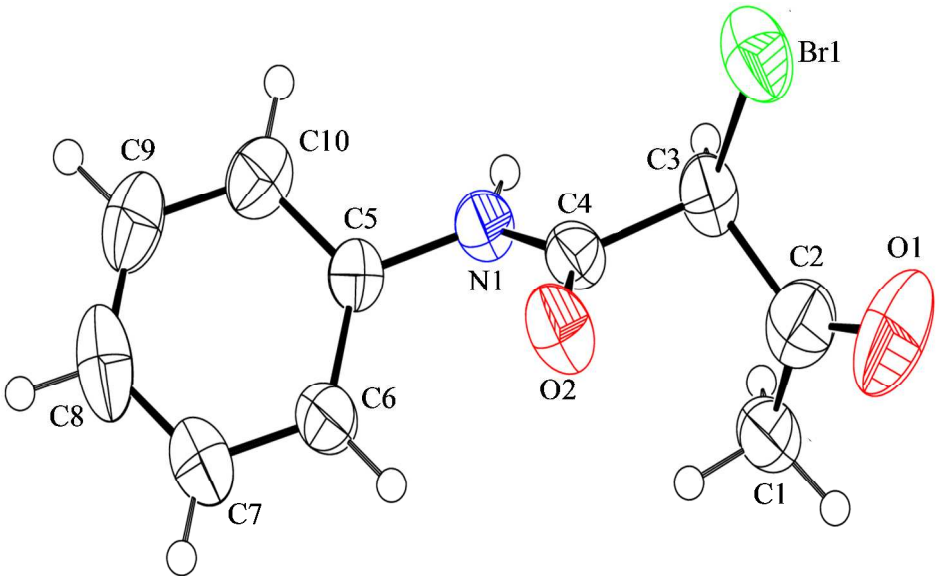


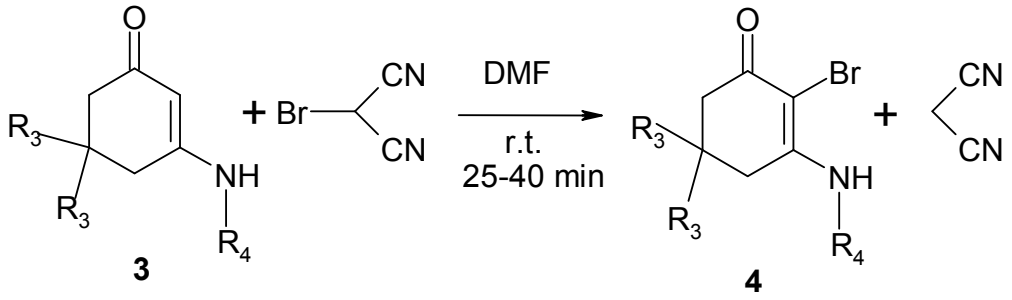
Fig. 1 The crystal structure of **2d**, the mono brominated product of acetoacetanilide (**1d**).

Subsequently we explore the brominating ability of MBM with various substituted phenols (phenol, *m*-cresol, *o*-cresol, *p*-cresol, *p*-methoxyphenol, *o*-chlorophenol and *m*-aminophenol),

anilines (aniline, *m*-anicidine, *m*-anicidine, *o*-chloraniline and *p*-fluorophenol), methylketone carbonyl compounds (acetophenone, *p*-chloroacetophenone, *p*-nitroacetophenone and *p*-methoxyacetophenone), alkenes (styrene) and alkynes (phenylacetylene). But MBM does not react with all these substrates even when the reactions are carried out at high temperature using excess amount of MBM (2.2 equivalent) and allowing a prolonged reaction time. It is interesting to note that even activated aromatic ring like *m*-aminophenol does not produce any brominated product. Since phenoxide ion is more reactive than phenol, the above reaction has also been carried out in basic medium employing aqueous sodium hydroxide and organic base triethyl amine separately. But in both the cases the brominated compounds are not formed. In fact MBM is destroyed in aqueous sodium hydroxide solution. The results demonstrate that MBM does not react with aromatic compounds even under drastic condition.

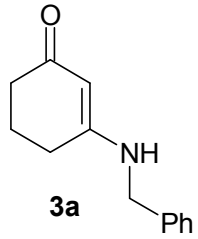
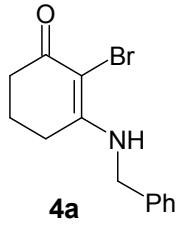
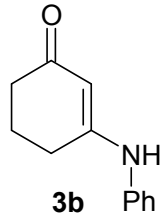
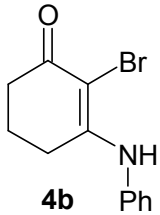
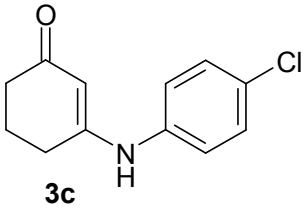
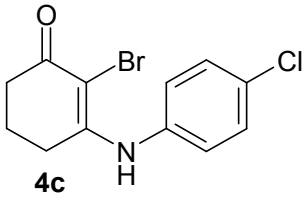
There are several reports of bromination of enamino compounds by using Br_2/CCl_4, NBS/MeOH, BrCN and NBS/montmorillonite (K-10).[17] All these procedures give low to moderate yield of the vinylic brominated enamines after prolonged reaction time.[17a,c] Moreover some of these methods have serious drawbacks of formation of side products like allylic brominated enamines.[17a,b] But when the enamine of 1,3-cyclohexandione and benzylamine is treated with MBM in DMF at room temperature, only the vinylic brominated enamine is formed in good yield (Scheme 2, Table 3). Then this simple procedure has been applied to different enamines of 1,3-cyclohexandione and dimedone. As evident from Table 3, several enamines **3** containing electron withdrawing and electron donating amines react smoothly with MBM affording the vinylic mono bromo products **4** in good yields without producing any side products. The enamines **3f**, **3g**, **3o** and **3p** although contain electronically rich aromatic ring; bromination takes place only at the vinylic position. Even in presence of ortho substituted amine as in the case of enamines **3e** and

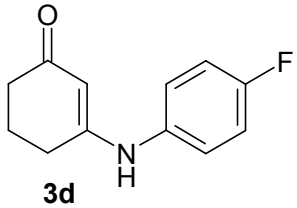
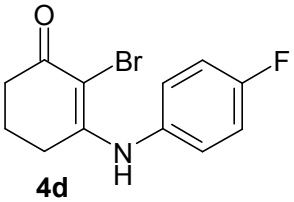
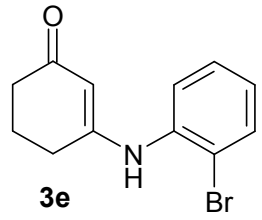
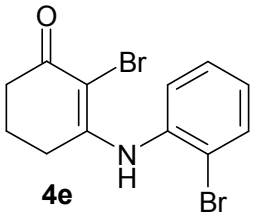
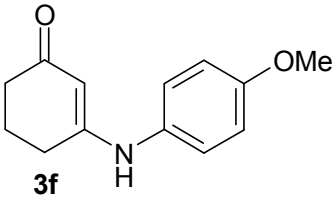
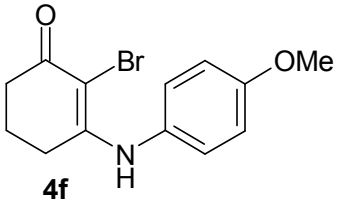
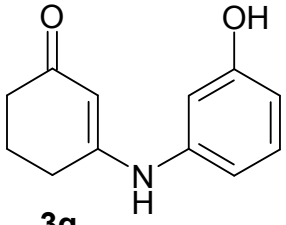
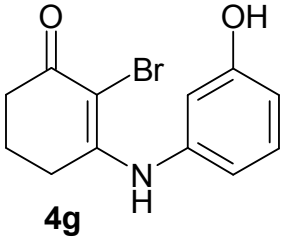
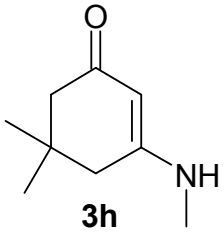
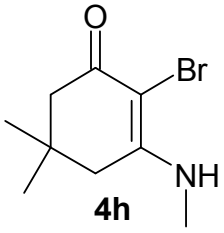
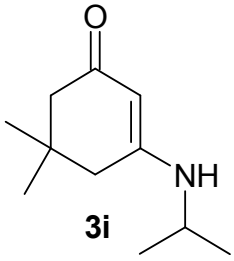
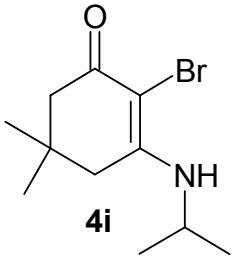
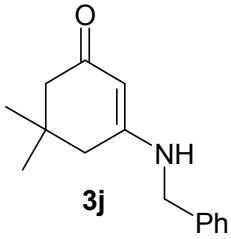
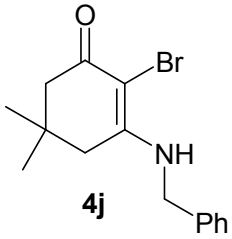
3n, the formation of vinylic brominated product is not hindered due to the steric reason. The structures of all the mono brominated products were determined by matching the reported melting points and also the spectroscopic data. Furthermore, the formation of product **4a** is confirmed by X-ray crystallographic analysis (Fig. 2).

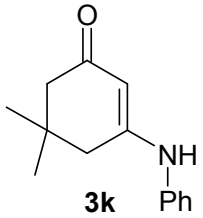
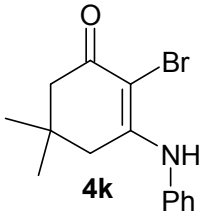
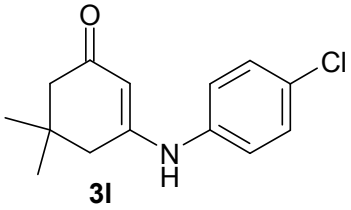
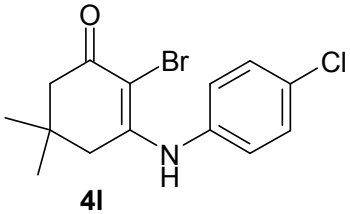
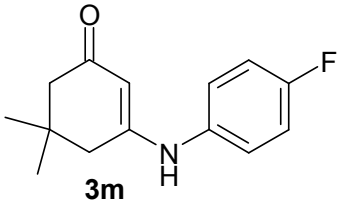
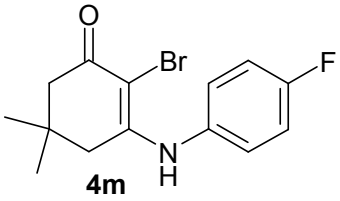
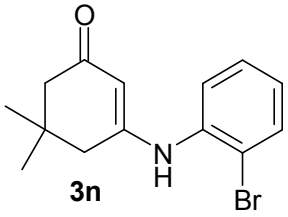
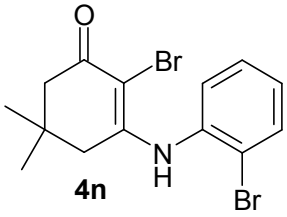
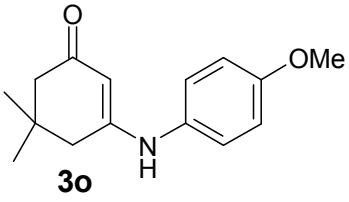
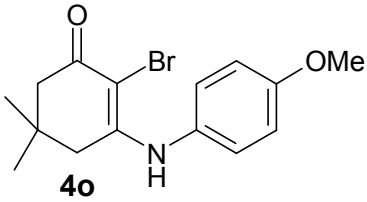
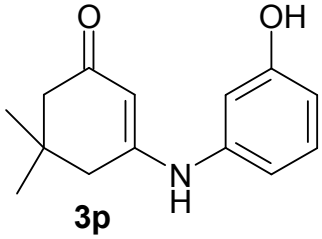
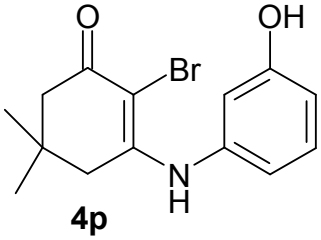


Scheme 2 Bromination on enamines of 1,3-cyclohexanedione and dimedone.

Table 3 Possibility of bromination on enemines **3** with MBM

Entry	Substrate	Product	Time (min)	Yield (%)	Observed/ Lit. Melting point (ºC) [17c]
1	 **3a**	 **4a**	30	94	128-130
2	 **3b**	 **4b**	35	92	96-98
3	 **3c**	 **4c**	37	91	131-133

4	 **3d**	 **4d**	40	89	122-124
5	 **3e**	 **4e**	40	86	158-160
6	 **3f**	 **4f**	28	92	140-142
7	 **3g**	 **4g**	25	91	176-178
8	 **3h**	 **4h**	25	95	179-181 /177-179
9	 **3i**	 **4i**	25	94	89-91 /90-92
10	 **3j**	 **4j**	30	94	183-185 /186-188

11	 **3k**	 **4k**	36	90	156-158 /158-159
12	 **3l**	 **4l**	39	88	178-180
13	 **3m**	 **4m**	42	86	156-158
14	 **3n**	 **4n**	45	85	146-148
15	 **3o**	 **4o**	30	90	128-130
16	 **3p**	 **4p**	35	92	188-190

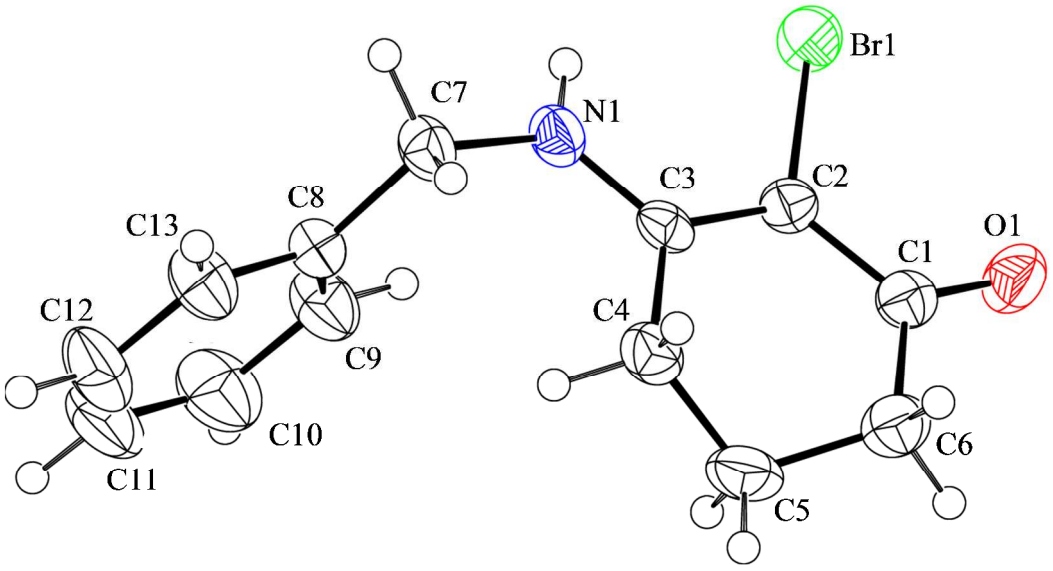
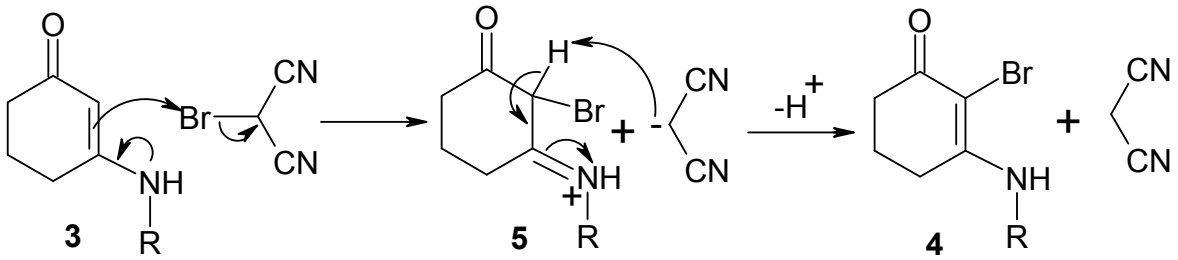


Fig. 2 The crystal structure of **4a**, the mono brominated product of **3a**.

The formation of brominated compounds **4** from enamines **3** can be explained on the basis of the proposed mechanism depicted in Scheme 3.[18] At first, the activated double bond of enamine attacks the electropositive bromine of MBM to generate bromo intermediate **5** and malononitrate anion. Finally malononitrate anion abstracts proton from cationic intermediate **5** to form mono bromo emino derivatives **4**. Since the reaction passes through an ionic path way, a polar medium is necessary for the reaction. The poor product formation in protic polar solvents *e.g.* methanol, ethanol and water may be due to the protonation of malononitrate anion from solvents (Table 1, entries 6-8).



Scheme 3 Plausible mechanism for bromination of enamines **3** by MBM.

In order to assess the relative efficiency and selectivity of NBS and MBM in mono bromination of active methylene compounds and enamines some representative studies have been carried out under similar reaction conditions (Table 4). In case of NBS the formation of mixture of products is observed by TLC and NMR analysis and the results are included in Table 4. The results clearly demonstrate that NBS is less selective in bromination producing mixture of brominated products. On the other hand MBM produces only mono brominated product without formation of any side products. Therefore MBM is a superior mono brominating agent towards active methylene compounds and enamines.[19]

Table 4 Comparative studies with different brominating agents towards active methylene compounds and enamines

Substrate	MBM[a]		NBS[a]	
	Product	Yield (%)	Product	Yield (%)
1a	**2a**	91	**2a**	91
1b	**2b**	94	**2b**[b]	65
1c	**2c**	93	**2c**[b]	74
1d	**2d**	89	**2d**[b]	53
1e	**2e**	86	**2e**[b]	66
1f	**2f**	90	**2f**[b]	69
1g	**2g**	86	**2g**[b]	75
1h	**2h**	93	**2h**	89
3b	**4b**	92	**4b**	89
3c	**4c**	91	**4c**	90
3e	**4e**	86	**4e**	80
3f	**4f**	92	**4f**[b]	80
3g	**4g**	91	**4g**[b]	73

3k	**4k**	90	**4k**	89
3l	**4l**	88	**4l**	85
3n	**4n**	85	**4n**	75
3o	**4o**	90	**4o**[b]	60
3p	**4p**	92	**4p**[b]	60

[a] Reactions are carried out in DMF medium at room temperature with 1.2 equivalent brominating agent with respect to substrate. [b] Mixture of products obtained.

In conclusion, we have successfully developed a mild reaction condition for MBM where it can act as a selective and efficient mono brominating agent. The efficacy of the methodology lies in the bromination of 1,3-dicarbonyl compounds and enamines containing activated aromatic rings. This methodology has the advantages of easy preparation of MBM, shorter reaction time and high yields of the product formation. The less reactive MBM can be a very good substitute of relatively more reactive NBS in regioselective mono bromination of 1,3-dicarbonyl compounds and enamines. Moreover the application of this metal free organo brominating agent is environmental friendly and can be considered as a green reagent within the domain of *Green Chemistry* principles.

Experimental Section

General information:

Starting materials and solvents are purchased from commercial suppliers and used without further purification. Melting points are determined in open capillary tubes and are uncorrected. IR spectra are recorded on a Perkin-Elmer 782 spectrophotometer. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra are recorded on Bruker 300 MHz instrument in $[D_6]$DMSO or in $CDCl_3$. Elemental analyses (C, H and N) are performed using Perkin-Elmer 240C elemental analyzer.

The X-ray diffraction data for crystallized compounds are collected with MoKα radiation at 296K using the Bruker APEX-II CCD System. The crystals are positioned at 50 mm from the CCD. Frames are measured with a counting time of 5s. Data analyses are carried out with the Bruker APEX2 and Bruker SAINT program. The structures are solved using direct methods with the Shelxs 97 program (Sheldrick, 2008).

General procedure for the preparation of monobromomalononitrile (MBM): A solution of malononitrile (3.3 g, 0.05 mol) in water (10 ml) and 2-propanol (10 ml) was cooled in an ice cold water-bath at 20°C. Then bromine (8.0 g, 0.05 mol) was added slowly into the solution with constant stirring, during which the temperature of the reaction mixture will rise and the colour of bromine will disappear immediately. After the addition of bromine, the reaction mixture was stirred at room temperature for 15 min and left at 0°C for 10 h. The solid monobromomalononitrile was precipitated out from the reaction mixture and filtered off through suction.

General procedure for the preparation of 2a-h and **4a-p:** The compounds **1a-h** or **3a-p** (1.0 mmol) were dissolved in dimethylformamide (5 ml) at room temperature. Then monobromomalononitrile (00.174 g, 1.2 mmol) was added and the resulting mixture was stirred at room temperature for 25-45 min (as mentioned in Table 2). Then the reaction mixture was poured into cold water and extracted with ethylacetate. Ethylacetate was removed under reduced pressure to get a gummy mass which was purified by column chromatography on silica gel using ethylacetate/hexane to obtain pure **2a-h** and **4a-p**.

2-Bromo-3-oxo-*N*-phenylbutyramide (**2d**): IR (KBr) 3238, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.44 (br s, 1H), 7.52 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 8.4 Hz, 2H), 7.17 (t, J = 6.3 Hz,

1H), 4.88 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 198.1, 161.7, 136.7, 129.1, 125.4, 120.1, 49.5, 27.3.

3-Benzylamino-2-bromocyclohex-2-enone (**4a**): IR (KBr) 3180, 1570 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.42-7.24 (m, 5H), 6.08 (br s, 1H), 4.52 (d, J = 6 Hz, 2H), 2.59-2.48 (m, 4H), 2.00-1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 187.8, 161.1, 137.0, 129.1, 128.0, 126.7, 96.5, 47.3, 36.7, 26.7, 20.8.

2-Bromo-3-phenylaminocyclohex-2-enone (**4b**): IR (KBr) 3195, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.43-7.27 (m, 3H), 7.16 (d, J = 7.5 Hz, 2H), 2.59-2.57 (m, 4H), 196-1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.5, 159.4, 137.3, 129.5, 126.9, 125.8, 97.9, 37.2, 28.2, 21.4.

2-Bromo-3-(4-chlorophenylamino)-cyclohex-2-enone (**4c)**: IR (KBr) 3202, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39-7.28 (m, 2H), 7.12-7.10 (m, 2H), 2.59-2.47 (m, 4H), 1.99-1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.56, 158.81, 135.8, 132.5, 129.5, 126.9, 98.4, 37.0, 28.0, 21.3.

2-Bromo-3-(4-fluorophenylamino)-cyclohex-2-enone (**4d)**: IR (KBr) 3233, 1633 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.30 (d, J = 1.8 Hz, 1H), 7.21-7.08 (m, 4H), 2.57-2.48 (m, 4H), 1.99-1.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.6, 163.0, 159.7, 133.3, 128.2, 128.1, 116.5, 116.2, 97.8, 37.1, 28.1, 21.3.

2-Bromo-3-(4-bromophenylamino)-cyclohex-2-enone (**4e**): IR (KBr) 3185, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.67 (d, J = 7.8 Hz, 1H), 7.48-7.16 (m, 3H), 2.60-2.49 (m, 4H), 2.02-1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.8, 158.8, 136.2, 133.5, 128.3, 128.3, 127.5, 121.2, 99.1, 37.1, 28.0, 21.4.

2-Bromo-3-(4-methoxyphenylamino)-cyclohex-2-enone (**4f**): IR (KBr) 3196, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.28 (br s, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 9 Hz, 2H), 3.85 (s, 3H), 2.5 (t, *J* = 6.3 Hz, 2H), 2.47 (t, *J* = 6 Hz, 2H), 1.96-1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.5, 160.3, 158.7, 129.9, 127.8, 114.6, 97.0, 55.5, 37.1, 28.1, 21.3.

2-Bromo-3-(4-hydroxyphenylamino)-cyclohex-2-enone **4g** : IR (KBr) 3350, 3215, 1575 cm^{-1}; ^1H NMR (300 MHz, D_6-DMSO) δ_H 9.62 (s, 1H), 8.56 (s, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.68-6.61 (m, 3H), 2.50-2.34 (m, 4H), 1.80-1.78 (m, 2H); ^{13}C NMR (75 MHz, D_6-DMSO) δ_C 187.6, 160.8, 158.2, 139.6, 130.0, 117.4, 113.8, 113.8, 96.2, 37.4, 29.0, 21.7.

2-Bromo-3-(4-chlorophenylamino)-5,5-dimethylcyclohex-2-enone (**4l**): IR (KBr) 3185, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.39 (d, *J* = 8.4 Hz, 2H), 7.28 (br s, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 2.43 (s, 2H), 2.38 (s, 2H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.2, 156.8, 135.9, 132.5, 129.6, 127.0, 97.3, 50.6, 41.4, 32.8, 27.9.

2-Bromo-3-(4-fluorophenylamino)-5,5-dimethylcyclohex-2-enone (**4m**): IR (KBr) 3205, 1622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.27-7.14 (m, 4H), 2.42 (s, 2H), 2.23 (s, 2H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.1, 163.0, 157.4, 133.3, 128.1, 128.0, 116.6, 116.3, 96.7, 50.7, 41.4, 32.7, 27.9.

2-Bromo-3-(2-bromophenylamino)-5,5-dimethylcyclohex-2-enone (**4n**): IR (KBr) 3201, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.69 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.26-7.21 (m, 2H), 2.44 (s, 2H), 2.31 (s, 2H), 1.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.3, 156.8, 136.3, 133.5, 128.4, 128.3, 127.9, 121.6, 97.3, 50.7, 41.3, 32.7, 28.0.

2-Bromo-3-(4-methoxyphenylamino)-5,5-dimethylcyclohex-2-enone (**4o**): IR (KBr) 3212, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.27 (br s, 1H), 7.08 (d, *J* = 7.2 Hz, 2H), 6.90 (d, *J* = 7.2

Hz, 2H), 3.87 (s, 3H), 2.42 (s, 2H), 2.32 (s, 2H), 0.96 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 188.0, 158.7, 158.2, 130.0, 127.9, 114.7, 95.9, 55.5, 50.7, 41.4, 32.5, 28.0.

2-Bromo-3-(3-hydroxyphenylamino)-5,5-dimethylcyclohex-2-enone (**4p**): IR (KBr) 3330, 3217, 1601 cm^{-1}; ^{1}H NMR (300 MHz, D_6-DMSO) δ_H 9.65 (br s, 1H), 8.60 (br s, 1H), 7.18 (t, J = 6.6 Hz, 1H), 6.92-6.60 (m, 3H), 2.43 (s, 2H), 2.29 (s, 2H), 0.93 (s, 6H); ^{13}C NMR (75 MHz, D_6-DMSO) δ_C 187.2, 158.6, 158.3, 139.6, 130.1, 117.4, 113.8, 113.1, 95.1, 50.8, 42.0, 32.8, 27.7.

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Graphical Abstract