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Ammonium persulfate activated DMSO as the one-carbon synthon for the synthesis of methylenebisamides and other applications

Pankaj S. Mahajan, Subhash D. Tanpure, Namita A. More, Jayant M. Gajbhiye, and Santosh B. Mhaske*

CSIR-National Chemical Laboratory, Division of Organic Chemistry, Pune 411 008, India

*Corresponding Author: sb.mhaske@ncl.res.in

Abstract:

Activation of DMSO to work as an economical and environmentally benign one-carbon synthon has been achieved by using a bench-top reagent ammonium persulfate for a general and efficient access to symmetrical methylenebisamides from primary amides. This methodology was used to achieve a three-component Mannich reaction using acetophenone, saccharin and DMSO to furnish *β*-amino ketone. It also provided a metal-free synthesis of thiadiazole and bis(phenyl)methane. Effectively, this method uses DMSO as a safer surrogate to formaldehyde. A mechanism for methylenebisamide formation involving radical intermediates has been proposed based on mechanistic studies.

Introduction

The sulfonium salts generated in situ by the activation of DMSO using various electrophiles for the "Swern oxidation" class of reactions are one of the most important synthetic transformations.[1] Similarly activation of DMSO to serve as a one-carbon synthon or for other useful organic transformations has been a subject of contemporary interest (Figure 1).[2] Organic solvents such as $CHCl_3$, DMF or DMSO, are becoming increasingly utilized as a reagent in synthetic transformations.[3] We were mainly interested in the transformation of primary amides to

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methylenebisamides using DMSO as a one-carbon synthon, because bisamides are of considerable interest in the synthesis of peptidomimetic compounds,[4] natural products[5] and potential key intermediates for the synthesis of bioactive compounds.[6,7] In particular, they are key fragments for the introduction of *gem*-diaminoalkyl residues in retro-inverso pseudopeptide derivatives synthesized for structure-activity relationship studies.[8] Generally, methylenebisamides are prepared (Figure 2) by the reaction of amides or nitriles with formaldehyde using strong acid catalysts.[7,9] Hexamethylenetetramine[10] and activated DMSO have been also used instead of formaldehyde.[11] A review of literature shows that methylenebisamides can be obtained in low yields by activation of DMSO using various electrophiles.[11] Li et al reported the synthesis of methylenebisamides in good to fair yields from amides by using 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride) and 2,4-dichloro-6-methoxy[1,3,5]triazine to activate DMSO.[12]

However, the development of a general synthetic process to bisamides is still challenging.[13] During the C-H activation studies on primary amide substrates using Pd as catalyst, ammonium persulfate (APS) as an oxidant and small amount of DMSO (5% v/v), we noticed the formation of bisamides. In view of their importance in bioorganic, natural product and medicinal chemistry research and our interest in the development of facile synthetic processes, we planned to explore our observation to establish a general method for the synthesis of bisamides from primary amides using DMSO activated by APS as a new approach. It is an effort to replace formaldehyde, acids and other corrosive/toxic reagents to make a greener process.

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Results and discussion

Permutations and combinations of solvents, reagents and their mole ratios at varying temperatures (Table 1) provided the optimum reaction condition, wherein heating the 1,4-dioxane solution of benzamide (**1**, 1 equiv) in the presence of APS (2 equiv) and DMSO (6 equiv) smoothly furnished the methylenebisamide **2** in quantitative yield (Scheme 1). We planned for the substrate scope study on varyingly substituted aromatic/aliphatic amides. The benzamides substituted with -CF_3, -Br and -I at the *ortho*-position of the amide furnished the corresponding bisamides **3**-**5** respectively in good yields. The benzamides with electron withdrawing *m*-NO_2 functionality provided methylenebisamide **6** in 65% yield. The effect of electron donating and withdrawing substituents at the *para*-position was also studied. The alkyl substituted bisamides **7** and **8** were obtained in good to excellent yields and the methoxy substituted bisamide **9** formed equally well. However, the yield of bisamide **10** from the *p*-NO_2 substituted benzamide was similar to the yield of the *m*-NO_2 substituted bisamide **6**. These observations suggest that under the developed protocol the reactivity of aromatic amides with electron donating groups is high as compared to the electron withdrawing substituents. *p*-Chloro benzamide too gave the corresponding bisamide **11** in good yield. The polyaromatic bisamide **12** was obtained in good yield from 2-naphthamide, though in lower yield than bisamide **2**. However, 3-hydroxybenzamide and *p*-toluenesulfonamide remained unreactive and the corresponding bisamides **13** and **14** were not observed at all (figure 3). Amides **15** and **17** did not furnish the expected bisamides (Scheme 2). Under the standard protocol phthalamide (**15**) was converted to pthalimide (**16**) in quantitative yield. Benzothioamide (**17**) was converted to diphenylthiadiazole **18** in excellent yield. This example represents an efficient and simple alternative protocol for the formation of thiadiazoles from thioamides.[14] Probably, both the

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reactions followed the APS-DMSO mediated deaminative and desulfurative cyclization pathway respectively, and their mechanism may be similar to our previous report on dehydrative cyclization of amic acids to imides.[15]

The suitability of symmetrical heteraromatic methylenebisamides was studied. Thiophene-2-carboxamide provided bisamide **19** in high yield; however, quinoline-3-carboxamide did not furnish bisamide **20**, plausibly due to oxidation of the highly basic quinoline nitrogen (Figure 4).

The synthesis of non-aromatic methylenebisamides was examined using the usual procedure (Figure 5). Cinnamamide, an *α,β*-unsaturated amide worked well to provide the bisamide **21** in good yield. Formation of various bisamides **22**-**24** from the corresponding arylacetamides was feasible in good to moderate yields.

Short and long chain aliphatic amides **25** and **26** were examined as substrates; however, complex mixture of products rather than methylenebisamides was obtained (Figure 6). We assumed that the instability of the generated radical intermediate might be the reason, hence the reaction was performed on trichloroacetamide, however the expected product **27** was not observed. The exact reason for the failure of aliphatic amides to provide bisamides under these conditions is obscure (Figure 6). Li et al also reported difficulties in preparing aliphatic bismethyleneamides from aliphatic amides.[12]

During the course of our studies Sun et al reported an interesting multicomponent Mannich reaction of a ketone, saccharine and DMSO using $RuCl_3$ and Selectfluor® (Figure 1).[2e] We performed our standard reaction on their substrates, compounds **28** and **29**, and found that the desired *β*-amino ketone **30** was obtained in moderate yield (Scheme 3). Further optimization of our standard protocol might improve the efficiency of this multicomponent reaction. Application

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of Mannich reaction under similar condition and formation of bisamide with *N*-methyl benzamide did not work.

Performing the reaction with amide **1** as substrate in the presence of free radical scavengers such as TEMPO or BHT resulted in only trace amounts of bismethyleneamide **2** (Scheme 4). This result suggests that the reaction proceeds via mechanism involving the formation of free radicals. The source of methylene unit was confirmed to be DMSO by performing isotopic labelling experiment using DMSO-d_6 (Scheme 5). The deuterium labelled methylenebisamide **2a** was identified by ^{1}H NMR and HRMS-ESI.

Two noteworthy publications appeared during the compilation of this manuscript, wherein the activation of DMSO was achieved using NH_4I to synthesize β-alkoxy methyl sulphides by a multicomponent reaction[2c] and substituted pyridines from ketones and ammonium acetate.[16] We repeated our reaction on benzamide (**1**) by using NH_4I instead of APS, however there was no reaction at all, thus suggesting a different mode of activation in our process.

Formation of a formaldehyde equivalent intermediate during the reaction was confirmed by performing the standard reaction on 1,3,5-trimethoxybenzene (**31**) to obtain methylene inserted product **32**. Diarylmethanes of this type are important because of their presence in supramolecular architectures, pharmaceuticals, and biologically active compounds (Scheme 6).[20]

We have previously proved that APS oxidizes DMSO to form dimethyl sulfone (DMS) in 1,4-dioxane.[15] Taking that into consideration we envisaged formation of the sulfonyl compound **34** as a probable intermediate formed by the reaction of amide with DMSO/DMS radical species. Reaction of benzamide (**1**) using DMS instead of DMSO under the standard protocol also furnished the desired bisamide **2** (Scheme 7).

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For indirect evidence, the thio compound **33** was prepared as per the literature procedure[19] and reacted with *p*-methoxybenzamide in the presence of APS. The expected unsymmetrical methylenebisamide **35** was obtained as a major product, which confirms our both hypothesis; oxidation of thio compound **33** to form sulfonyl intermediate **34** and its further elimination and reaction with another amide to furnish unsymmetrical bisamide **35**. Formation of symmetrical bisamide **9** and benzamide (**1**) as minor products were also observed, which probably suggests that the formation of compound **34** and its conversion to DMS radical and benzamide (**1**) is a reversible reaction (Scheme 8). Bisamide **2** was not observed under this condition probably because of low temperature of the reaction and less reactivity of benzamide (**1**) as compared to *p*-methoxybenzamide.

A plausible mechanism has been depicted in figure 7 based on all the above observations and literature precedence.[20b,21] Formation of methane sulfonic acid is also known.[21a]

In summary, we have developed an efficient protocol for the conversion of primary amides to the corresponding symmetrical methylenebisamides by using environmentally benign DMSO as the source of the methylene unit. The activation of DMSO was achieved by using APS, a commonly used oxidant. The scope of the developed protocol is wide and it avoids the use of formaldehyde, strong acids and transition-metal catalysts. Application of the protocol to a three component Mannich reaction was demonstrated. It is also applicable in the synthesis of thiadiazoles and bis(phenyl)methane. A plausible mechanism of the protocol has been proposed and supported by mechanistic studies. Currently, we are exploring the other synthetic applications of this interesting reagent combination.

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Experimental section

All reagents and solvents were used as received from commercial sources unless otherwise noted. All amides were procured from commercial sources and used as it is. All experiments were carried out under air atmosphere. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin layer chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (240–400 mesh) using petroleum ether and ethyl acetate as eluents. The ^{1}H, ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 50/100/125 MHz NMR spectrometers, respectively in $CDCl_3$/DMSO-d_6. Chemical shifts were reported as δ values from standard peaks. Melting points are uncorrected. Mass spectra were taken on LC-MS (ESI) mass or GC-MS mass spectrometer. HRMS were scanned on Quadrupole-Orbitrap Mass Spectrometer available at our institutional facility.

General procedure for the synthesis of methylenebisamides

A solution of amide (50 mg, 1 equiv), ammonium persulfate [$(NH_4)_2S_2O_8$] (2 equiv) and DMSO (6 equiv) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C in a round bottom flask, equipped with a stirring bar and water condenser, until the reaction was complete as indicated by thin layer chromatography. After completion, the reaction mixture was filtered through a cotton plug and 1,4-dioxane was removed under vacuum. The residue was then dissolved in ethyl acetate (10 mL) and washed with warm water (4 mL) and brine (3 mL x 2). The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by flash column chromatography to furnish corresponding methylenebisamides in good to excellent yields.

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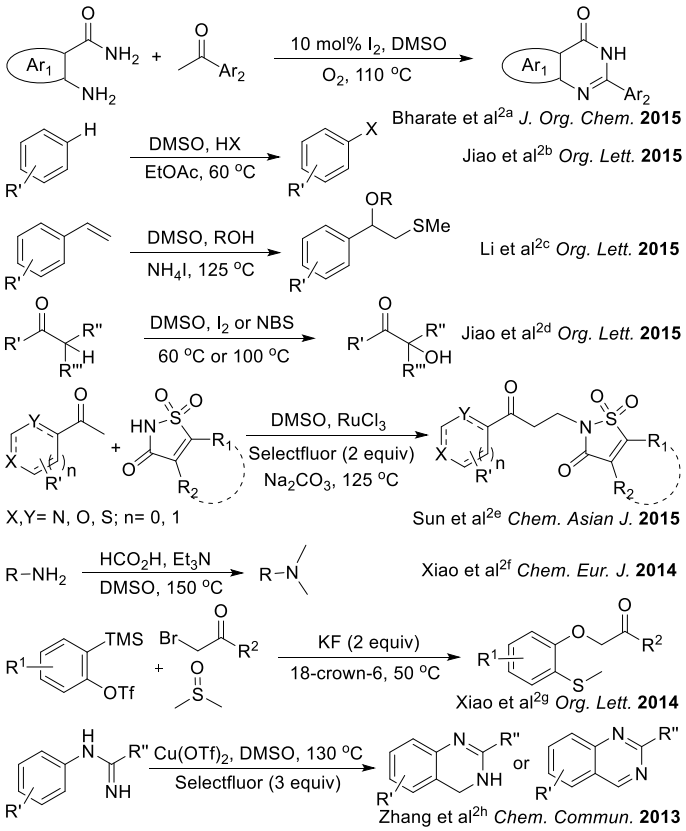

Figure 1. Recent advances demonstrating application of activated DMSO

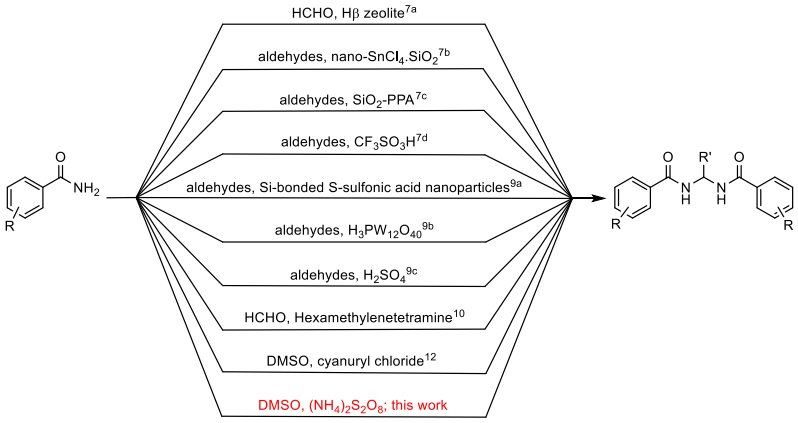

Figure 2. Traditional routes to methylenebisamides and this work

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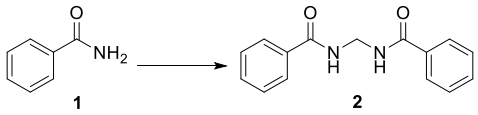
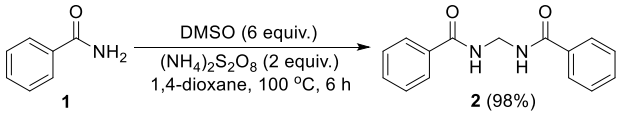
Table 1. Optimization studies[a]



Entry	Oxidant/DMSO (equiv)	Solvent (2 mL)	Temp/Time (°C/h)	Yield (%)[b]
1	APS (1)/ 4	dioxane	100/18	38
2	APS (1)/ -	dioxane	100/18	00
3	- / 4	dioxane	100/04	00
4	APS (1)/ excess	-	100/18	trace
5	APS (2)/ excess	-	100/10	05
6	APS (2)/ 4	dioxane	100/18	88
7	APS (3)/ 4	dioxane	100/18	71
8	APS (2)/ 5	dioxane	100/09	94
9	APS (2)/ 6	dioxane	100/06	98
10	APS (1)/ 6	dioxane	100/12	40
11	APS (2)/ 10	dioxane	100/06	97
12	$K_2S_2O_8$ (2)/ 6	dioxane	100/06	35
13	*t*BuO-O*t*Bu	dioxane	100/06	00
14	[c]DBPO (2)/ 6	dioxane	100/06	trace
15	$PhI(OAc)_2$ (2)/ 6	dioxane	100/06	trace
16	Oxone™	dioxane	100/06	17
17	APS (2)/ 6	toluene	111/06	58
18	APS (2)/ 6	water	100/06	07

[a]All reactions were performed on 50 mg scale of amide **1** in a round bottom flask equipped with a water condenser; [b]Isolated yields. [c]DBPO-dibenzoyl peroxide

Scheme 1. Protocol optimized on benzamide (**1**)



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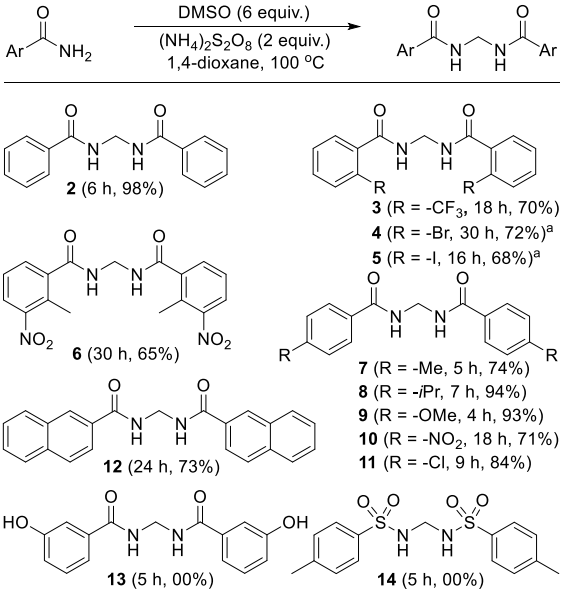
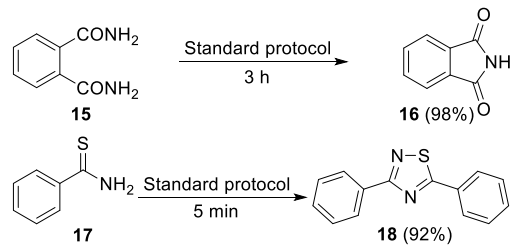


[[a]The ratio for amide: APS:DMSO = 1:3:9]

Figure 3. Scope of aromatic amides

Scheme 2. Different products than expected bisamides



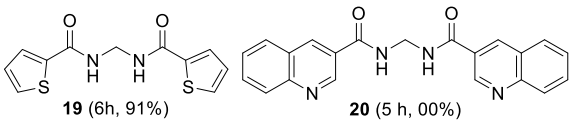


Figure 4. Heteroaromatic bisamides

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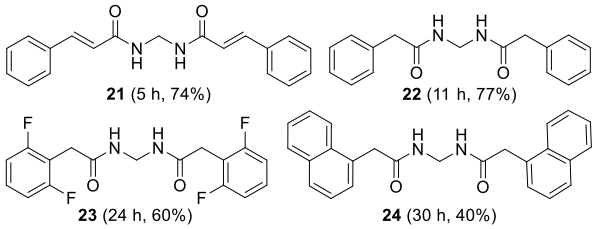


Figure 5. Cinnamide and aryacetamides.

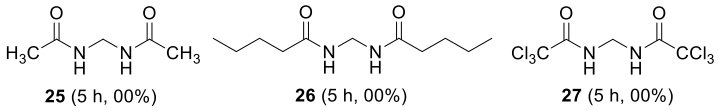
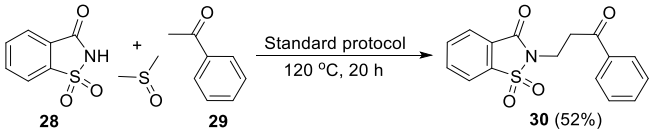
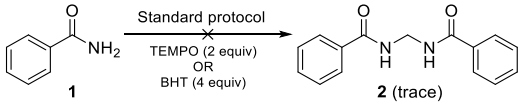


Figure 6. Aliphatic amides did not work

Scheme 3. Application to a multicomponent Mannich reaction



Scheme 4. Radical trapping experiment.



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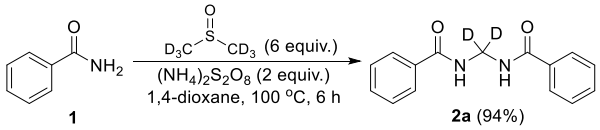
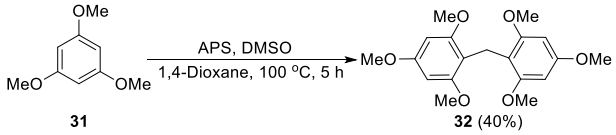
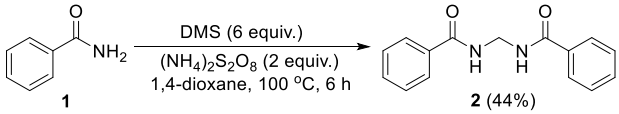
Scheme 5. Isotopic labelling experiment



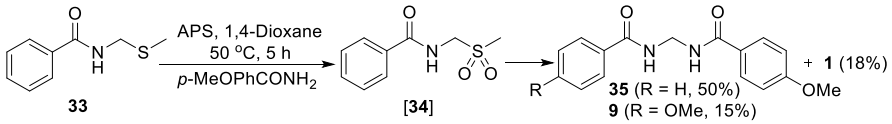
Scheme 6. Demonstration of DMSO as a formaldehyde equivalent



Scheme 7. Reaction using dimethyl sulfone instead of DMSO



Scheme 8. Intermediate **34** is a plausible intermediate in the key reaction



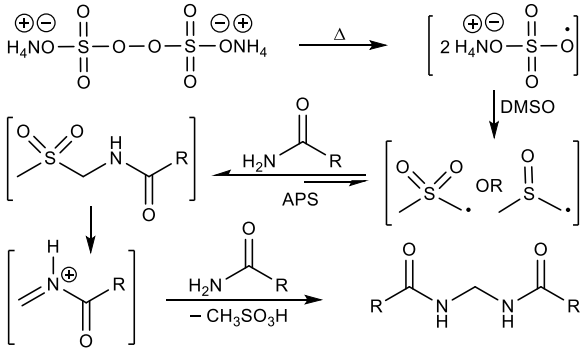


Figure 7. Plausible mechanism

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