

RSC Advances



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

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

methylenebisamides using DMSO as a one-carbon synthon, because bisamides are of considerable interest in the synthesis of peptidomimetic compounds,⁴ natural products⁵ 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} Hexamethylenetetramine¹⁰ 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.

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 varying substituted aromatic/aliphatic amides. The benzamides substituted with -CF₃, -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*-NO₂ 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*-NO₂ substituted benzamide was similar to the yield of the *m*-NO₂ 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 phthalimide (**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

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

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 ^1H 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).

For indirect evidence, the thio compound **33** was prepared as per the literature procedure¹⁹ 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.

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 ^1H , ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 50/100/125 MHz NMR spectrometers, respectively in $\text{CDCl}_3/\text{DMSO}-d_6$. 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 $[(\text{NH}_4)_2\text{S}_2\text{O}_8]$ (2 equiv) and DMSO (6 equiv) in 1,4-dioxane (2 mL) was heated at 100 °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.

Acknowledgments

P.S.M. thanks CSIR-New Delhi for the research fellowship. S.B.M. gratefully acknowledges generous financial support from DST, CSIR-ORIGIN, CSIR-OSDD New Delhi as well as CSIR-NCL (start-up grant).

Notes and references

- (1) (a) T. V. Nguyen, M. Hall, *Tetrahedron Lett.*, 2014, **55**, 6895. (b) J. R. McConnell, J. E. Hitt, E. D. Daus, T. A. Rey, *Org. Process Res. Dev.*, 2008, **12**, 940. (c) L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.*, 2001, **66**, 7907. (d) A. J. Mancuso, D. Swern, *Synthesis*, 1981, 29377.
- (2) (a) S. Mohammed, R. A. Vishwakarma, S. B. Bharate, *J. Org. Chem.*, 2015, **80**, 6915. (b) S. Song, X. Sun, X. Li, Y. Yuan, N. Jiao, *Org. Lett.*, 2015, **17**, 2886. (c) X. Gao, X. Pan, J. Gao, H. Jiang, G. Yuan, Y. Li, *Org. Lett.*, 2015, **17**, 1038. (d) Y.-F. Liang, K. Wu, S. Song, X. Li, X. Huang, N. Jiao, *Org. Lett.*, 2015, **17**, 876. (e) K. Sun, X. Wang, Y. Jiang, Y. Lv, L. Zhang, B. Xiao, D. Li, Z. Zhu, L. Liu, *Chem. Asian J.*, 2015, **10**, 536. (f) X. Jiang, C. Wang, Y. Wei, D. Xue, Z. Liu, J. Xiao, *Chem. Eur. J.*, 2014, **20**, 58. (g) F.-L. Liu, J.-R. Chen, Y.-Q. Zou, Q. Wei, W.-J. Xiao, *Org. Lett.*, 2014, **16**, 3768. (h) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu, Q. Zhang, *Chem. Commun.*, 2013, **49**, 6439.
- (3) (a) J. Mottweiler, T. Rinesch, C. Besson, J. Buendia, C. Bolm, *Green Chem.*, 2015, **17**, 5001. (b) W. Ghezali, K. D. O. Vigier, R. Kessas, F. Jérôme, *Green Chem.*, 2015, **17**, 4459. (c) S. K. R. Parumala, R. K. Peddinti, *Green Chem.*, 2015, **17**, 4068. (d) S. Song, X. Li, X. Sun, Y. Yuan, N. Jiao, *Green Chem.*, 2015, **17**, 3285. (e) S. Song, X. Huang, Y.-F. Liang, C. Tang, X. Li, N. Jiao, *Green Chem.*, 2015, **17**, 2727. (f) S. N. Gockel, K. L. Hull, *Org. Lett.*, 2015, **17**, 3236. (g) X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.*, 2015, **137**, 4924. (h) J. Mao, Faming Zhuanli Shenqing CN 104447391 A 20150325, 2015. (i) A. Borah, L. Goswami, K. Neog, P. Gogoi, *J. Org. Chem.*, 2015, **80**, 4722. (j) C. Laugel, B. Estrine, J. Le Bras, N. Hoffmann, S. Marinkovic, J. Muzart, *ChemCatChem*, 2014, **6**, 1195. (k) Y. Li, D. Xue, W. Lu, C. Wang, Z.-T. Liu, J. Xiao, *Org. Lett.*, 2014, **16**, 66.

- (4) C. Alemh, J. Puiggali, *J. Org. Chem.*, 1995, **60**, 910.
- (5) (a) K. H. Kim, S. U. Choi, K. R. Lee, *Tetrahedron Lett.*, 2012, **53**, 1490. (b) T. N. Duong, R. A. Edrada, R. Ebel, V. Wray, W. Frank, A. T. Duong, W. H. Lin, P. Proksch, *J. Nat. Prod.*, 2007, **70**, 1640.
- (6) M. Szostak, J. Aube, *Org. Biomol. Chem.*, 2011, **9**, 27.
- (7) (a) N. Mamede, M. R. Marri, S. Peraka, A. K. Macharla, S. Kodumuri, D. Chevella, G. Naresh, N. Nama, *Catal. Commun.*, 2015, **61**, 41. (b) B. F. Mirjalili, M. A. Mirhoseini, *J. Chem. Sci.*, 2013, **125**, 1481. (c) M. R. M. Shafiee, *J. Saudi Chem. Soc.*, 2014, **18**, 115. (d) A. H. Fernandez, R. M. Alvarez, T. M. Abajo, *Synthesis*, 1996, 1299.
- (8) (a) T. Yamazaki, K.-I. Nunami, M. Goodman, *Biopolymer*, 1991, **31**, 1513. (b) M. Rodriguez, P. Dubreuil, J.-P. Bali, J. Martinez, *J. Med. Chem.*, 1987, **30**, 758. (c) P. V. Pallai, R. S. Struthers, M. Goodman, *Biochemistry*, 1985, **24**, 1933.
- (9) (a) L. Pan, L. Huang, C. Xie, *Lett. Org. Chem.*, 2013, **10**, 770. (b) M. Tajbakhsh, R. Hosseinzadeh, H. Alinezhad, P. Rezaee, *Synth. Commun.*, 2013, **43**, 2370. (c) G. Hrichandran, S. D. Amalraj, P. Shanmugam, *Ind. J. Chem.*, 2011, **50B**, 77. (d) E. E. Gilbert, *Synthesis*, 1972, 30. (e) E. E. Magat, B. F. Faris, J. E. Reith, L. F. Salisbury, *J. Am. Chem. Soc.*, 1951, **73**, 1028. (f) R. C. Brian, A. H. Lamberton, *J. Chem. Soc.*, 1949, 1633.
- (10) C. W. Sauer, R. J. Bruni, *J. Am. Chem. Soc.*, 1955, **77**, 2559.
- (11) (a) N. N. Bochkareva, E. P. Trub, *J. Gen. Chem.*, 1984, *USSR* **54**, 619. (b) T. E. Varkey, G. F. Whitfield, D. Swern, *J. Org. Chem.*, 1974, **39**, 3365.
- (12) Q. Wang, L. Sun, Y. Jiang, C. Li, *Beil. J. Org. Chem.*, 2008, **4**, 51.
- (13) A. R. Katritzky, W.-Q. Fan, M. Black, J. Pernak, *J. Org. Chem.*, 1992, **57**, 541.
- (14) (a) K. Yajima, K. Yamaguchi, N. Mizuno, *Chem. Commun.*, 2014, **50**, 6748. (b) A. Yoshimura, A. D. Todora, B. J. Kastern, S. R. Koski, V. V. Zhdankin, *Eur. J. Org. Chem.*, 2014, 5149. (c) L. Forlani, C. Boga, *J. Chem. Soc., Perkin Trans. 2*, 2002, 768. (d) L. Forlani, A. Lugli, C. Boga, A. B. Corradi, P. Sgarabotto, *J. Heterocycl. Chem.*, 2000, **37**, 63. (e) C. Boga, L. Forlani, C. Silvestroni, A. B. Corradi, P. Sgarabotto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1363. (f) T. Isobe, *J. Org. Chem.* 1999, **64**, 6989.
- (15) D. N. Garad, S. D. Tanpure, S. B. Mhaske, *Beil. J. Org. Chem.*, 2015, **11**, 1008.
- (16) X. Pan, Q. Liu, L. Chang, G. Yuan, *RSC Adv.*, 2015, **5**, 51183.

- (17) M. A. Ali, S. M. A. H. Siddiki, K. Kon, J. Hasegawa, K. Shimizu, *Chem. Eur. J.*, 2014, **20**, 14256.
- (18) J. Tummatorn, C. Thongsornkleeb, S. Ruchirawat, *Tetrahedron*, 2012, **68**, 4732.
- (19) L. Bernardi, R. DeCastiglione, U. Scarponi, *J. C. S. Chem. Commun.*, 1975, 320.
- (20) (a) Q. Chen, K. Gao, C. Peng, H. Xie, Z. K. Zhao, M. Bao, *Green Chem.*, 2015, **17**, 4546.
(b) Y. Xu, T. Cong, P. Liu, P. Sun, *Org. Biomol. Chem.*, 2015, **13**, 9742. (c) D. Chen, C. Xu, J. Deng, C. Jiang, X. Wen, L. Kong, J. Zhang, H. Sun, *Tetrahedron*, 2014, **70**, 1975. (d) X. Li, Y. Feng, L. Lin, G. Zou, *J. Org. Chem.*, 2012, **77**, 10991.
- (21) (a) R. Herscu-Kluska, A. Masarwa, M. Saphier, H. Cohen, D. Meyerstein, *Chem. Eur. J.*, 2008, **14**, 5880. (b) X. Qiao, S. Chen, L. Tan, H. Zheng, Y. Ding, Z. Ping, *Magn. Reson. Chem.*, 2001, **39**, 207. (c) M. K. Eberhardt, R. Colina, *J. Org. Chem.*, 1988, **53**, 1071.

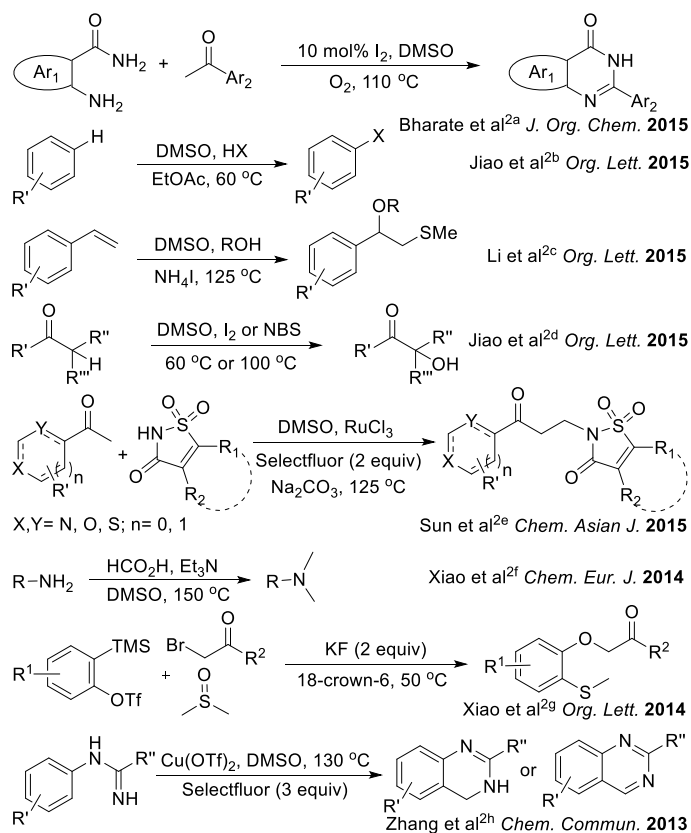


Figure 1. Recent advances demonstrating application of activated DMSO

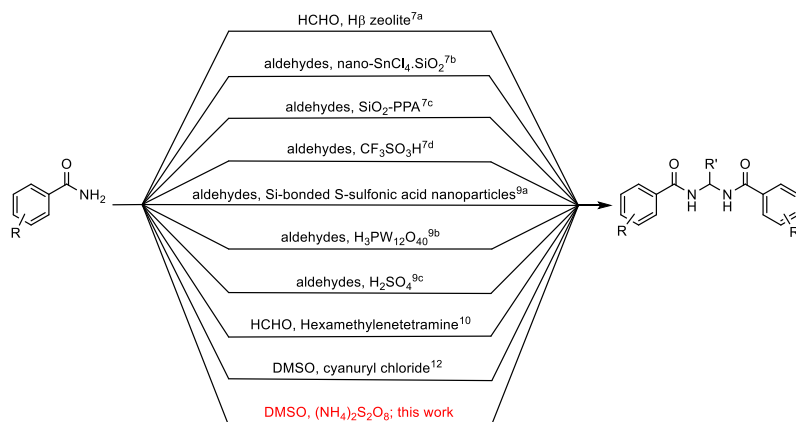
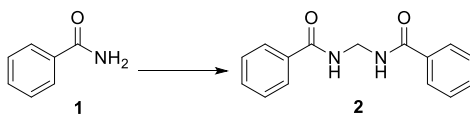
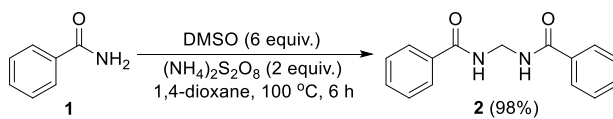


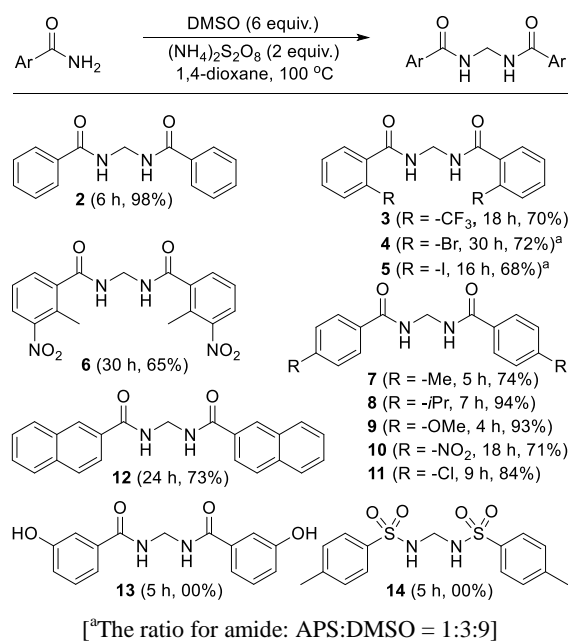
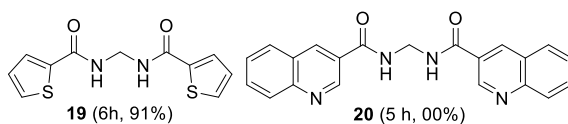
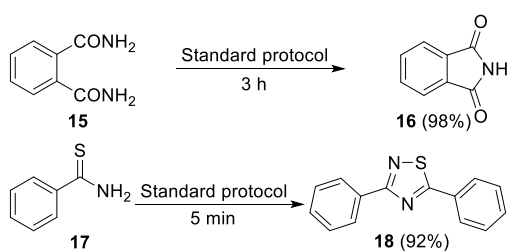
Figure 2. Traditional routes to methylenebisamides and this work

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 ₂ S ₂ O ₈ (2)/ 6	dioxane	100/06	35
13	<i>t</i> BuO-O- <i>t</i> 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 TM	dioxane	100/06	17
17	APS (2)/ 6	toluene	111/06	58
18	APS (2)/ 6	water	100/06	07

^aAll reactions were performed on 50 mg scale of amide **1** in a round bottom flask equipped with a water condenser; ^bIsolated yields. ^cDBPO- dibenzoyl peroxide

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

**Figure 3.** Scope of aromatic amides**Scheme 2.** Different products than expected bisamides**Figure 4.** Heteroaromatic bisamides

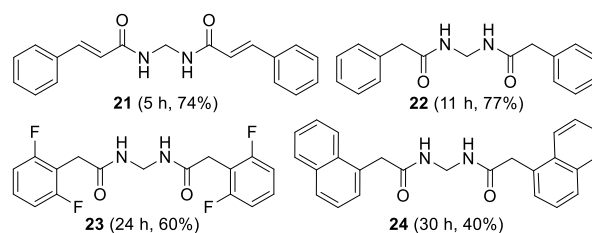


Figure 5. Cinnamide and aryacetamides.

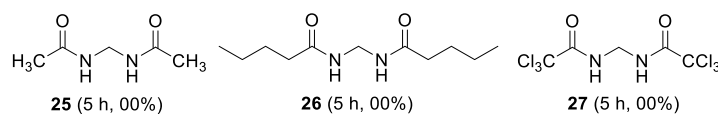
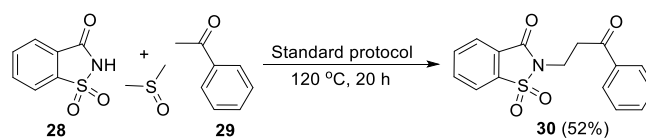
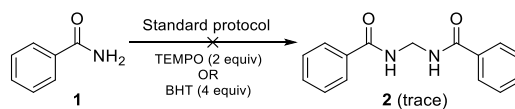


Figure 6. Aliphatic amides did not work

Scheme 3. Application to a multicomponent Mannich reaction



Scheme 4. Radical trapping experiment.



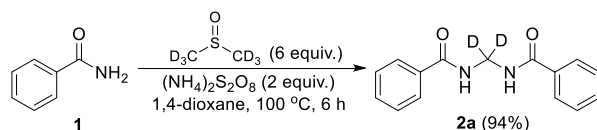
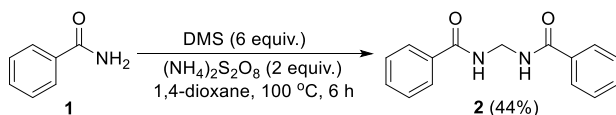
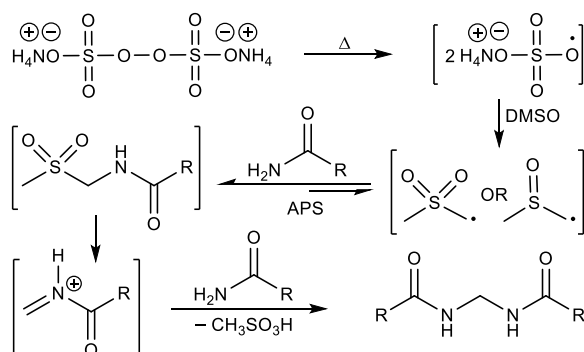
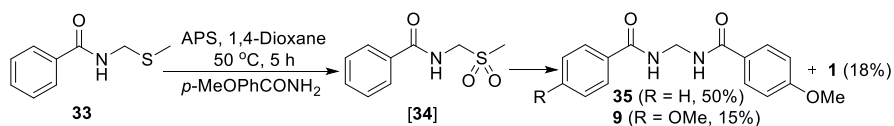
Scheme 5. Isotopic labelling experiment**Scheme 6.** Demonstration of DMSO as a formaldehyde equivalent**Scheme 7.** Reaction using dimethyl sulfone instead of DMSO**Scheme 8.** Intermediate **34** is a plausible intermediate in the key reaction**Figure 7.** Plausible mechanism

Table of Contents entry

