doi:10.1246/cl.130317
Published on the web June 11, 2013

Bromodimethylsulfonium Bromide (BDMS)-catalyzed Synthesis of Substituted Pyrroles through a One-pot Four-component Reaction

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(Received April 10, 2013; CL-130317; E-mail: atk@iitg.ernet.in)

Trisubstituted *N*-benzylpyrrole derivatives were synthesized through a one-pot four-component reaction from β-keto esters, benzylamines, aromatic aldehydes, and nitromethane in the presence of 10 mol % bromodimethylsulfonium bromide (BDMS) as catalyst at room temperature. Some of the salient features of the present protocol are simple and mild reaction conditions, good yields, and applicability with a wide range of substrates.

Multicomponent reactions (MCRs) are a well-recognized synthetic strategy to synthesize complex bioactive molecules from readily available starting materials in a single step due to simplicity, superior atom-economy, low costs, high substrates variability, and bond-forming efficiency (BFE).[1–4] Pyrrole constitutes an important class of heterocyclic[5] compounds, which are widely distributed in nature,[6] valuable building blocks for synthesizing conducting polymers,[7–9] and synthetic pharmaceuticals.[10] Among them, substituted pyrroles possess antimycobacterial, antibiotic, antioxidant, and cytotoxic properties[11] as shown in Figure 1.

They are usually synthesized[12] by well-known reactions namely the Hantzsch[13,14] or Knorr[15,16] or Paal–Knorr[17,18] reaction. Recently substituted pyrroles were synthesized preferably from β-diketones, aromatic aldehydes, primary amine, and nitroalkane with various metal catalyst such as $FeCl_3$,[19] the palladium-mediated Suzuki coupling,[20] $NiCl_2 \cdot 6H_2O$,[21] iodine,[22] ionic liquid $[Hbim]BF_4$,[23] and solid-phase synthesis.[24] Some of these procedures have disadvantages such as harsh conditions,[19–24] prolonged reaction time, and use of expensive metal namely palladium. Though these methods are quite useful, there is further scope to develop a synthetic methodology which might work under mild reaction conditions. Interestingly, the synthesis of highly substituted pyrroles using β-keto esters is relatively less explored. As a part of our ongoing research program to develop new methodologies, we showed that bromodimethylsulfonium bromide (BDMS) is a useful catalyst in organic synthesis,[25,26] and its usefulness was also exploited by others in recent times.[27] We also demonstrated that it is an efficient catalyst for a diverse range of multicomponent reactions.[26c,26d] In this letter, we would like to disclose BDMS-catalyzed one-pot four-component synthesis of substituted pyrrole derivatives using β-keto esters, benzylamines or substituted benzylamines, aromatic aldehydes, and nitromethane as shown in Scheme 1.

To find suitable reaction conditions, a mixture of methyl acetoacetate (**1a**), benzylamine (**2a**), and 4-fluorobenzaldehyde (**3a**) in nitromethane (**4**) at room temperature was examined in the presence of 5, 10, and 15 mol % BDMS, respectively, and the results are summarized in Table 1. It was observed that 10 mol % BDMS is sufficient to provide the best result in terms of yield and reaction time.

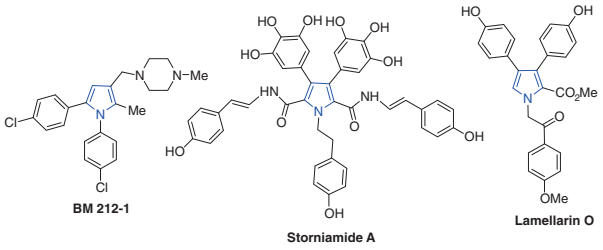
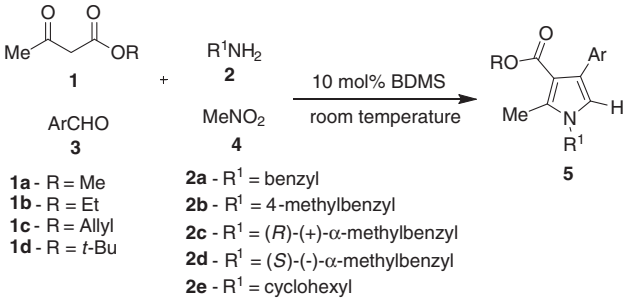
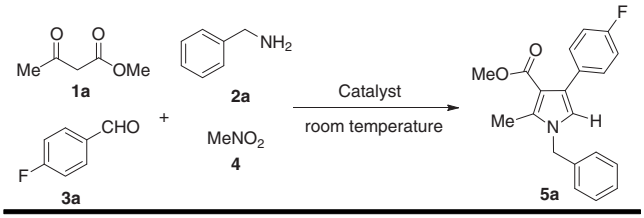


Figure 1. Some biologically active substituted pyrroles.



Scheme 1. Synthesis of substituted pyrroles.

Table 1. Optimization of reaction conditions for the synthesis of substituted pyrrole[a]



S.No	Catalyst	Catalyst amount/mol %	Time/h	Yield[b]/%
1	No catalyst	—	24	NR
2	BDMS	5	9	65
3	**BDMS**	**10**	**7**	**78**
4	BDMS	15	8	75
5	48% aq. HBr	10	14	41
6	TBATB	10	12	55
7	$HClO_4$	5	16	30
8	CSA	10	18	21

[a]The reactions were carried out using 1 mmol of each methyl acetoacetate (**1a**), benzylamine (**2a**), and 4-fluorobenzaldehyde (**3a**) in 1 mL of nitromethane (**4**) at room temperature. [b]Isolated yield.

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The reactions were also scrutinized in different solvents such as CH_3CN, THF, DMF, and MeOH using 1 equivalent of nitromethane at room temperature using 10 mol % BDMS as catalyst, and it afforded lower yields as well as required longer reaction times. It is noteworthy to mention that nitromethane acts as reagent-cum-solvent in the present protocol. The isolated product **5a** was characterized from ^{1}H NMR in which the H-5 proton appears at δ 6.56 ppm as a singlet whereas the C-5 carbon signal comes at δ 110.9 ppm.

After optimization, the reactions were examined with methyl acetoacetate (**1a**), benzylamine (**2a**) and with various aromatic aldehydes such as 4-chlorobenzaldehyde, benzaldehyde, furan-2-carbaldehyde in nitromethane (**4**) in the presence of 10 mol % BDMS at room temperature and the desired products **5b**–**5d** were isolated in 68–72% yields (Table 2, Entries 2–4). Similarly, 4-methylbenzylamine (**2b**), methyl acetoacetate (**1a**), and 4-chlorobenzaldehyde afforded the desired product **5e** in 75% yield (Table 2, Entry 5) under identical reaction conditions.

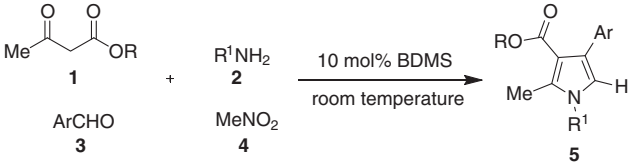
The scope of the present protocol was further examined by carrying out reactions with methyl acetoacetate (**1a**) and (*R*)-(+)-α-methylbenzylamine (**2c**) with various aromatic aldehydes having substituents Me, OMe, NO_2, Br, and F in the aromatic ring under similar reaction conditions and the products **5f**–**5k** were obtained in good yields (Table 2, Entries 6–11). Likewise, a reaction with 2-naphthaldehyde, methyl acetoacetate (**1a**), (*R*)-(+)-α-methylbenzylamine (**2c**), and nitromethane under identical reaction conditions provided the desired product **5l** in 62% yield (Table 2, Entry 12). In addition, a wide variety of β-keto esters such as ethyl acetoacetate (**1b**), allyl acetoacetate (**1c**), and *t*-butyl acetoacetate (**1d**) and different aromatic aldehydes such as 4-fluorobenzaldehyde, 3-hydroxybenzaldehyde, and 4-bromobenzaldehyde were treated with (*R*)-(+)-α-methylbenzylamine (**2c**) and nitromethane under similar reaction conditions, respectively, and the desired products **5m**–**5p** were obtained in good yields (Table 2, Entries 13–16). Similarly, methyl acetoacetate (**1a**) or ethyl acetoacetate (**1b**), (*S*)-(−)-α-methylbenzylamine (**2d**), nitromethane reacted with various aromatic aldehydes having substituents such as Cl, Me, OH, OMe, NO_2, and F on the aromatic ring under similar reaction conditions and the required products **5q**–**5w** were isolated in 58–78% yield (Table 2, Entries 17–23).

Furthermore, the reaction was also examined with cyclohexylamine (**2e**), methyl acetoacetate (**1a**), and 4-chlorobenzaldehyde in the presence of 10 mol % BDMS at room temperature, and it gave the product **5x** in 62% yield. All the products were characterized by IR, ^{1}H and ^{13}C NMR spectra as well as their elemental analyses. The structure of the product **5n**[29] was further confirmed by single-crystal XRD and the ORTEP diagram of **5n** and their intermolecular H-bonding interaction through O–H···O bonds (H···O = 0.821 Å, O···O = 2.823 Å, <O–H···O = 172.64°) is shown in Figure 2.

The formation of products **5** may be proposed as follows: β-Keto ester on reaction with bromodimethylsulfonium bromide gives the intermediate **A** and HBr in the reaction medium. Then the liberated HBr catalyzes the formation of enamino ester **C** from β-keto ester and benzylamine. At the same time, carbanion **B** is generated from nitromethane **4** in the presence of benzylamine **2**, which reacts instantly with an aromatic aldehyde **3** to form nitrostyrene **D**. Subsequently, the enamino ester **C** reacts with nitrostyrene **D** to form Michael adduct **E**, which undergoes tautomerization into **F**. Finally, it gives the intermediate **G** on cyclization, which is converted into the desired product **5** with the elimination of H_3NO_2 as shown in Scheme 2.

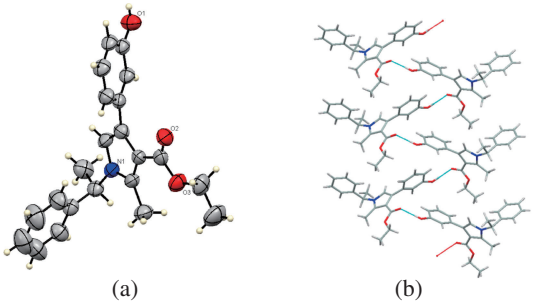
In conclusion, we have devised a simple and efficient synthetic protocol for the synthesis of substituted pyrrole derivatives using β-keto esters, benzylamines, aromatic alde-

Table 2. Synthesis of substituted pyrrole derivatives[28]



S.No	Aldehyde (**3**)	R (**1**)	R^1 (**2**)	Product[a] (**5**)	Time /h	Yield /%[b]
1	4-F-C_6H_4	**1a**	**2a**	**5a**	7	78
2	4-Cl-C_6H_4	**1a**	**2a**	**5b**	8	72
3	C_6H_5	**1a**	**2a**	**5c**	9	70
4	2-Furanyl	**1a**	**2a**	**5d**	8	68
5	4-Cl-C_6H_4	**1a**	**2b**	**5e**	7	75
6	C_6H_5	**1a**	**2c**	**5f**	5	76
7	4-Me-C_6H_4	**1a**	**2c**	**5g**	5	80
8	4-OMe-C_6H_4	**1a**	**2c**	**5h**	7	68
9	4-NO_2-C_6H_4	**1a**	**2c**	**5i**	8	70
10	4-Br-C_6H_4	**1a**	**2c**	**5j**	6	78
11	4-F-C_6H_4	**1a**	**2c**	**5k**	5	82
12	2-Naphthyl	**1a**	**2c**	**5l**	8	62
13	4-F-C_6H_4	**1b**	**2c**	**5m**	5	75
14	3-OH-C_6H_4	**1b**	**2c**	**5n**	8	60
15	4-Br-C_6H_4	**1c**	**2c**	**5o**	6	67
16	4-Br-C_6H_4	**1d**	**2c**	**5p**	7	65
17	4-Cl-C_6H_4	**1a**	**2d**	**5q**	5	78
18	4-Me-C_6H_4	**1b**	**2d**	**5r**	5	76
19	3-OH-C_6H_4	**1b**	**2d**	**5s**	8	60
20	2,4-Di-OMe-C_6H_3	**1b**	**2d**	**5t**	8	58
21	2-NO_2-C_6H_4	**1b**	**2d**	**5u**	8	67
22	2-F-C_6H_4	**1b**	**2d**	**5v**	5	68
23	3-F-C_6H_4	**1b**	**2d**	**5w**	6	62
24	4-Cl-C_6H_4	**1a**	**2e**	**5x**	9	62

[a]All the reactions were performed using β-keto ester (1 mmol), benzylamine or substituted benzylamine (1 mmol), and aldehyde (1 mmol) in nitromethane (1 mL) with BDMS (10 mol %) at room temperature. [b]Isolated yield.



(a) (b)

Figure 2. (a) ORTEP diagram of **5n**. (b) Intermolecular H-bonding interactions (CCDC no. is 848584).

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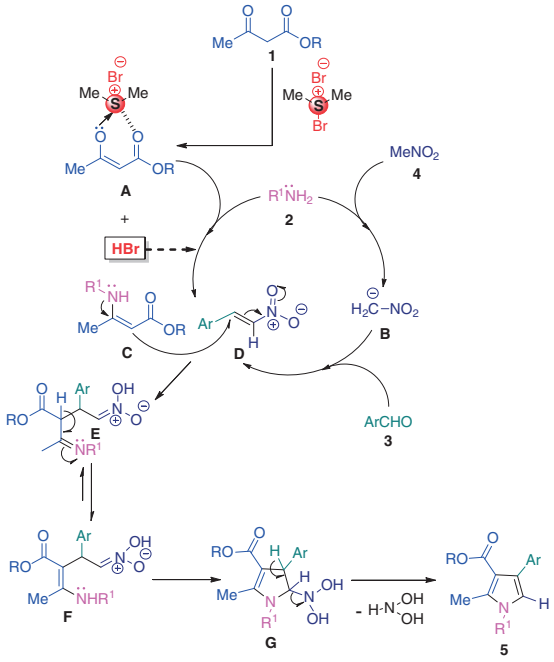

Scheme 2. Plausible mechanism for the formation of substituted pyrroles.

hydes, and nitromethane in the presence of 10 mol % BDMS at room temperature. The advantages of the present protocol are an ecofriendly metal-free catalyst, mild reaction conditions, good yields, and compatibility with a wide range of substrates.

PRB acknowledges UGC, New Delhi for his research fellowship. RSB and ML are also thankful to CSIR, New Delhi for their research fellowships. The authors are grateful to the Department of Science and Technology (DST) for providing access to the single XRD facility under the FIST program to the Department of Chemistry as well as to the Director, IIT Guwahati for providing general facilities. We are thankful to the referees for their valuable comments and suggestions.

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28 General procedure for the synthesis of substituted pyrrole derivatives **5**: Bromodimethylsulfonium bromide (BDMS, 0.1 mmol) was added to a mixture of β-keto ester (1 mmol) and benzylamine (1 mmol) in 1 mL of nitromethane and the reaction mixture was stirred at room temperature for 10 min, until a yellow color appeared. The aromatic aldehyde (1 mmol) was then added and stirring was continued until completion of the reaction. The mixture was concentrated to dryness under reduced pressure and the crude was purified on silica gel column (hexane/ethyl acetate, 10:1) affording the pure products **5**.
29 Complete crystallographic of **5n** (CCDC 848584) has been deposited with the Cambridge Crystallographic Data Centre, Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: http://www.ccdc.cam.ac.uk). Spectral data of all compounds and copies of ^{1}H, ^{13}C NMR spectra of products associated with this paper can be found in Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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