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Practical Methylenation Reaction for Aldehydes and Ketones Using New Julia-Type Reagents

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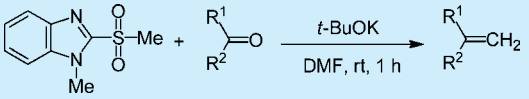
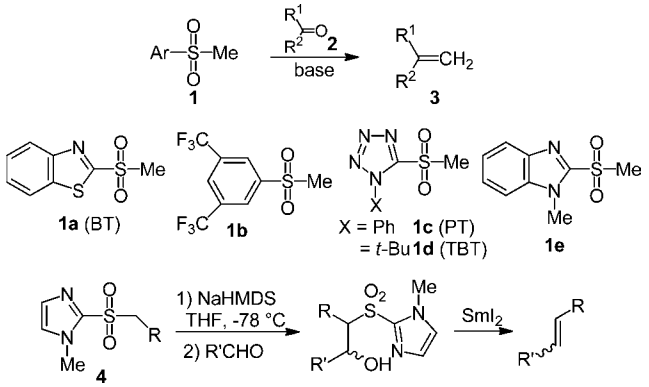
Supporting Information

ABSTRACT: A new Julia-type methylenation reagent, 1-methyl-2-(methylsulfonyl)benzimidazole (**1e**), reacts with a variety of aldehydes and ketones in the presence of either NaHMDS (−55 °C to rt) or *t*-BuOK (rt, 1 h) in DMF to give the corresponding terminal alkenes in high yields. The byproducts are easily removed, and the reaction conditions are mild and practical.



The synthesis of alkenes from carbonyl compounds is one of the most fundamental reactions in organic synthesis. Since terminal alkene structures are frequently observed in natural products and terminal alkenes are often used as the substrates for many synthetic reactions such as olefin metathesis and sigmatropic reactions, their preparation has been studied intensively. Many methylenation reagents were developed by Wittig,[1] Peterson,[2] and Johnson,[3] along with *gem*-dimetallic reagents such as Tebbe's reagent and Nysted reagent.[4] Recently, transition-metal-catalyzed methylenation reactions have also been reported.[5] The Julia–Kocienski reactions (one-pot Julia olefination) are a very efficient tool for direct alkene synthesis via metalated heteroarylsulfones with carbonyl compounds.[6] The four methylenation reagents of Julia–Kocienski-type reagents have been reported (Scheme 1). Julia and co-workers studied the

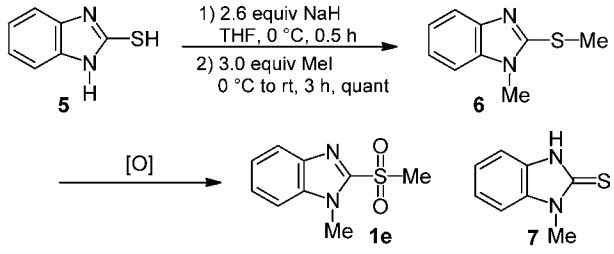
Scheme 1. Julia-Type Methylenation Reagents



methylenation reaction briefly with the benzothiazol-2-yl (BT) methyl sulfone **1a**.[7] Nájera and co-workers studied the reaction of 3,5-bis(trifluoromethyl)phenyl methyl sulfone **1b**.[8] 1-Phenyl-1*H*-tetrazol-5-yl (PT) methyl sulfone **1c**, the methyl version of the Kocienski reagent,[9] has been used in several total syntheses of natural products.[10] Aïssa reported the reaction of 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) methyl sulfone **1d** with a variety of aldehydes and ketones to give terminal alkenes in moderate to high yields using two efficient procedures (NaHMDS in THF at −78 °C to rt, and Cs_2CO_3 in THF/DMF(3:1) at 70 °C),[11] and **1d** was successfully used in the syntheses of some natural products.[12] Since Kocienski and co-workers demonstrated that the anions derived from TBT alkyl sulfones are more stable than the PT and BT counterparts,[9b] **1d** seems to be the best methylenation reagent. However, since the starting material for the preparation of **1d** is expensive, the metalation reaction requires rather expensive bases such as NaHMDS or Cs_2CO_3, and there is some room for improvement of the yields, we felt the need to develop a more practical route to the methylenation reaction. Kende and Mendoza reported that the imidazolyl sulfones **4** react with aldehydes to give *β*-hydroxy imidazolyl sulfones, which can be transformed to alkenes using SmI_2.[13] We had a working hypothesis that the benzo-fused imidazolyl sulfone **1e**[14] can react with carbonyl compounds to afford alkenes directly. New reagent **1e** can be prepared from cheap 2-mercaptobenzimidazole **5** by dimethylation and oxidation. Here, we report the methylenation reaction of various aldehydes and ketones using **1e**.

The dimethylation of **5** gave a quantitative yield of **6** by using NaH and MeI in THF (Scheme 2). The oxidation of **6** was first performed using *m*-CPBA to give **1e** in 62% yield. The oxidation

Scheme 2. Preparation of the Benzoimidazolyl Sulfone 1e



m-CPBA (3 equiv), CH_2Cl_2, rt, 19 h	62% yield
$(NH_4)_6Mo_7O_{24}$-$4H_2O$ (0.1 equiv), 35% H_2O_2 (9 equiv), EtOH, rt, 17 h	14% yield
Oxone (3 equiv), MeOH-H_2O (1:1), rt, 21 h	73% yield
Oxone (3 equiv), MeOH-H_2O (1:1), rt, 5 h	92% yield

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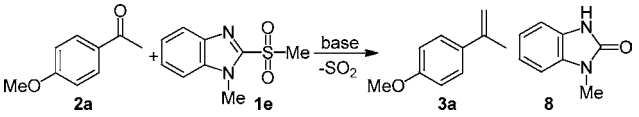
with hydrogen peroxide catalyzed by ammonium molybdate gave only 14% yield of **1e**, and the main product was **7** (yield 85%),[15] which seemed to be produced by the Pummerer-type rearrangement of the corresponding sulfoxide. When Oxone was used, 92% yield of **1e** (BI sulfone) was obtained after 5 h. Longer reaction time was harmful and caused some hydrolysis of **1e**.

Since the Julia–Kocienski reactions are generally more efficient when the Barbier-type procedure was used, a solution of **1e** was treated with base in the presence of either aldehyde or ketone. The methylenation reaction using **1e** was first carried out with *p*-methoxyacetophenone **2a**. The results are summarized in Table 1. When 1.3 equiv of NaHMDS was added to a THF

Table 1. Methylenation of *p*-Methoxyacetophenone with 1e[a]



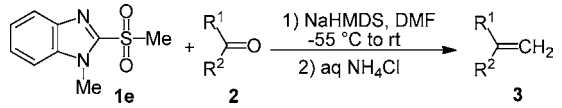
entry	base (equiv)	solvent	conditions	yield (%)
1	NaHMDS (1.3)	THF	−78 °C to rt	42
2	LiHMDS (1.3)	THF	−78 °C to rt	21
3	NaHMDS (1.3)	DME	−55 °C to rt	54
4	KHMDS (1.3)	DME	−55 °C to rt	25
5	NaHMDS (1.3)	DMF	−55 °C to rt	79
6	NaHMDS (1.7)	DMF	−55 °C to rt	88
7	Cs_2CO_3 (3)	THF/DMF[b]	90 °C, 3 d	38
8	*t*-BuOK (1.7)	DMF	rt, 5 h	58
9	*t*-BuOK (2.5)	DMF	rt, 1.5 h	79
10[c]	*t*-BuOK (3.0)	DMF	rt, 1 h	87
11[d]	*t*-BuOK (3.0)	DMF	rt, 1 h	92
12[d,e]	*t*-BuOK (3.0)	DMF	rt, 1 h	93

[a]0.3 mmol of **2a** and 0.3 mmol of **1e** were used. [b]3:1 mixture. [c]1.1 equiv of **1e** was used. [d]1.2 equiv of **1e** was used. [e]5 mmol scale.

solution of **1e** and **2a** at −78 °C and the mixture was gradually warmed to room temperature, 42% yield of the alkene **3a** was obtained along with 34% of **1e**, 50% of **2a**, and **8**[16] (entry 1). LiHMDS was less effective, and NaHMDS in DME (−55 °C to rt) gave **3a** in slightly higher 54% yield (entries 2 and 3). The use of DMF as solvent increased the yield to 79%, and 88% yield was obtained by increasing the quantity of NaHMDS (1.7 equiv) (entry 6) (method A). More practical conditions for the methylenation reaction of **2a** using **1e** were further studied. Following Aïssa's procedure,[11] the suspension of Cs_2CO_3 (3 equiv), **2a**, and **1e** in THF–DMF (3:1) was heated at 70 °C for 16 h. However, the reaction hardly proceeded. Therefore, further heating was continued at 90 °C for 3 days to give **3a** in 38% yield (entry 7). When the DMF solution of **1e** and **2a** was treated with *t*-BuOK (1.7 equiv) at room temperature, **3a** was obtained in 58% yield (entry 8). Increasing the quantity of *t*-BuOK to 2.5 equiv gave a higher 79% yield, and both increasing the quantity of **1e** (1.2 equiv) and *t*-BuOK (3 equiv) gave **3a** in 92% yield in 1 h (entry 11) (method B). This procedure is more convenient and economical and the reaction proceeded in 1 h at room temperature. To establish scalability, the reaction was also run at the 5 mmol scale to give **3a** in 93% yield (entry 12).

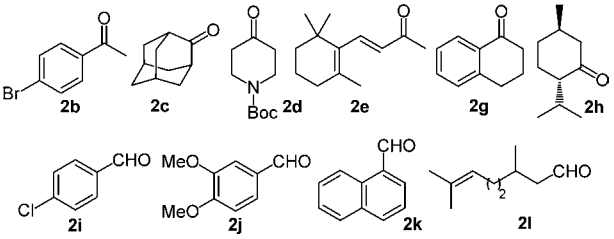
The methylenation reactions of **1e** with a variety of ketones and aldehydes were performed using method A (NaHMDS in DMF, Table 2). The reactions of *p*-bromoacetophenone **2b** and aliphatic ketones **2c** and **2d** gave the corresponding alkenes in 86–95% yield. When aldehyde **2j** was reacted with **1e** using 1.7 equiv of NaHMDS, **3j** was obtained in 72%, while 97% yield was

Table 2. Methylenation of Ketones and Aldehydes with 1e by NaHMDS[a]



entry	2	NaHMDS (equiv)	1e (equiv)	yield (%)
1	**2a**	1.7	1.0	88
2	**2b**	1.7	1.0	86
3	**2c**	1.7	1.0	95
4	**2d**	1.7	1.0	95
5	**2j**	1.7	1.0	72
6	**2j**	1.3	1.0	97
7	**2k**	1.3	1.0	90

[a]0.3 mmol of **2** and 0.3 mmol of **1e** were used.



obtained by using 1.3 equiv of NaHMDS. Therefore, methylenation reactions of aldehydes should be performed by using 1.3 equiv of NaHMDS as a standard procedure. The reaction of aldehyde **2k** gave **3k** in 90% yield using this procedure.

The methylenation reactions of **1e** with a variety of ketones and aldehydes were performed using method B (*t*-BuOK in DMF, Table 3). The methylenation reaction of **2b** using the standard conditions gave **3b** in 82% yield, while 95% yield was obtained by using 4 equiv of *t*-BuOK (entries 2 and 3). The reactions of aliphatic ketones were also efficient, and not only **2c** and **2d** but also α,β-unsaturated ketone **2e** were transformed to the corresponding alkenes in high yields (91–99%, entries 5, 6, and 8). Although the Wittig reagent $CH_3P(C_6H_5)_3Br$ is the most often used methylenation reagent, problems occur in the separation of triphenylphosphine oxide (FW 278) from the products in a large scale. In our reaction, the anion derived from **1e** and base reacts with **2** to give the alkoxide **A**, from which nucleophilic addition to the benzimidazole part occurs to give **B** (Scheme 3).[6] Terminal alkene **3** would be formed by Smiles rearrangement along with **C** and SO_2. Since we could not detect any gas bubble even in a 5 mmol scale reaction, SO_2 probably reacts with *t*-BuOK to form *t*-$BuOSO_2K$. After aqueous workup with aq NH_4Cl, **3** and **8** were obtained. The byproduct **8** (FW 148) is a small molecule and was easily removed from the reaction mixture by either filtration or column chromatography. When the reaction mixture of **1e** and **2c** was diluted with hexane and washed with 1 M NaOH, the usual workup gave almost pure **3c**. The alkene **3c** was obtained in 96% yield after column chromatography (entry 5). This method greatly simplifies purifications of the product alkenes, and the crude mixture is almost pure. The reaction of aliphatic ketone **2d** and aldehydes **2i** and **2l** was performed in the same way to give the corresponding alkenes in 93–99% yields (entries 6, 15, and 19). For the methylenation of aldehydes, 2.6 equiv of *t*-BuOK is enough except for some improvement of yields were observed for **2i** and **2k** by using 3.0 equiv of *t*-BuOK (entries15 and 18). Although it was reported that treatment of α-tetralone **2g** with methylene-

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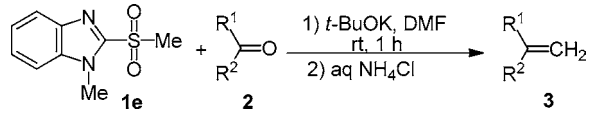
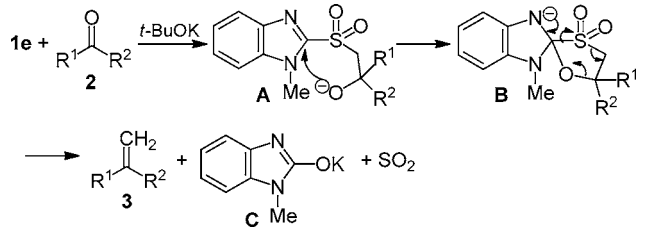
Table 3. Methylenation of Ketones and Aldehydes with 1e by *t*-BuOK[a]



entry	2	*t*-BuOK (equiv)	1e (equiv)	yield (%)
1	**2a**	3.0	1.2	92
2	**2b**	3.0	1.2	82
3	**2b**	4.0	1.3	95
4	**2c**	3.0	1.2	89
5[b]	**2c**	3.0	1.2	96
6[b]	**2d**	3.0	1.2	99
7	**2e**	3.0	1.2	84
8	**2e**	3.5	1.2	91
9[c]	2-octanone **2f**	3.0	1.2	91
10[b]	**2g**	3.0	1.2	71
11	**2g**	3.0	1.5	77
12	**2h**	3.0	1.2	59
13	**2h**	3.0	2.0	60
14	**2i**	2.6	1.1	88
15[b]	**2i**	3.0	1.1	93
16	**2j**	2.6	1.2	92
17	**2k**	2.6	1.1	86
18	**2k**	3.0	1.1	91
19[b]	**2l**	2.6	1.1	97
20[c]	*n*-octanal **2m**	2.6	1.1	63
21[c,d]	**2m**	2.6	1.5	74

[a]0.3 mmol of **2** was used, and the yield shows isolated yields except for entries 9, 20, and 21. [b]By basic aqueous workup. [c]NMR yield was determined by using methyl benzoate as an internal standard. [d]30 min instead of 1 h.

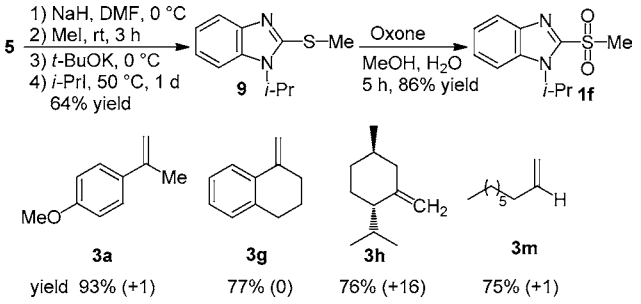
Scheme 3. Plausible Reaction Mechanism



triphenylphosphorane gave its enolate instead of leading to any alkene product,[4e] the reaction of **1e** with **2g** gave **3g** in 71% yield (entry 10). The yield was slightly improved to 77% by using 1.5 equiv of **1e** along with the recovered **2g** (23%) (entry 11). The reactions of 2-octanone **2f** and *n*-octanal **2m** were performed in a similar way to give the alkenes in 91 and 74% yields, respectively (entries 9 and 21). Furthermore, we tested the reaction of **1e** with the sterically hindered (−)-menthone **2h** (entries 12 and 13). The alkene **3h** was obtained in 59% yield along with the recovered **2h** (39%) and trace amount of **1e**. The yield was only slightly improved to 60% by using 2 equiv of **1e**. These results show that **1e** decomposes slowly in the presence of *t*-BuOK in DMF, and the yield of alkene **3h** was just moderate because of the low reactivity of sterically hindered **2h**. Generally, the combined yields of the product **3** and the recovered **2** were nearly equal to 100% except for the reaction with *n*-octanal **2m**, where **2m** was not detected at all in the reaction mixture (entry 21).

In order to improve the stability of the reagent, we prepared the *N*-isopropyl reagent **1f** by successive methylation and isopropylation following by oxidation with Oxone (Scheme 4). The compound **9** was obtained in 64% yield (not optimized)

Scheme 4. Preparation of 1f and the Reaction of 1f with 2a, 2g, 2h, and 2m

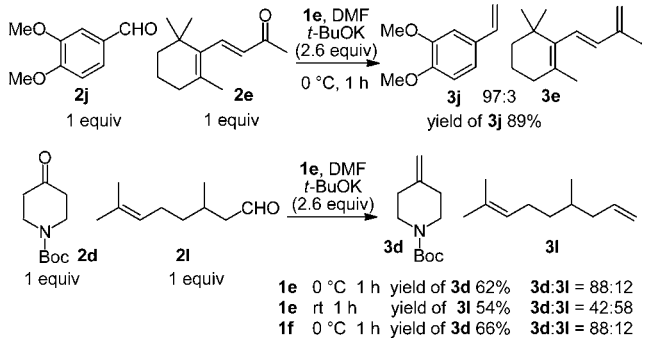


along with the *S*-methyl compound (22%) and the dimethyl **6** (4%). When the reaction of **1f** with **2h** was performed using *t*-BuOK in DMF, **3h** was obtained in 76% yield (16% higher yield). When the reactions of **1f** with **2a**, **2g**, and **2m** were performed, the yields were almost same as with the reaction of **1e**.

Since the PT sulfone **1c** have been used for many total syntheses,[10] the comparison of the reactivity of **1c** and **1e** was studied next. When the reaction of **1c** with **2d** was performed by using method B, 72% yield of **3d** was obtained along with the recovered **2d** (14%). The sulfone **1c** was not recovered at all. The same reaction of **1e** with **2d** gave 99% yield of **3d** (entry 6 in Table 3). In order to test the relative stability of the metalated sulfones, the DMF solutions of **1c**, **1e**, and **1f** were treated with *t*-BuOK (2.5 equiv) at 0 °C for 30 min and quenched with aq NH_4Cl solution, respectively. None of the starting sulfone **1c** was detected by ^{1}H NMR, while **1e** and **1f** were recovered in 49%[17] and 79% yield, respectively. Thus, both **1e** and **1f** are much more stable than **1c** in the presence of base, and this seems to be the reason that **1e** gave much higher yield of **3d**.

Next, we tested the chemoselectivity between aldehydes and ketones in the methylenation with **1e** (Scheme 5). When a

Scheme 5. Competitive Methylenation of Aldehyde and Ketone



mixture of aldehyde **2j** and ketone **2e** (both 1 equiv) were treated with **1e** (1 equiv) and *t*-BuOK (2.6 equiv) in DMF at 0 °C, the exclusive formation of alkene **3j** in 89% yield was observed (Scheme 3). The ^{1}H NMR of the crude mixture showed the selectivity between **3j** and **3e** was 97:3. Thus, selective methylenation of aldehyde **2j** occurred in the presence of ketone **2e**. When a mixture of ketone **2d** and aldehyde **2l** (both 1 equiv) was treated with **1e** (1 equiv) and *t*-BuOK (2.6 equiv) in DMF at 0 °C, **3d** was obtained in 62% yield as a main product. The ^{1}H

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NMR of the crude mixture showed the selectivity between **3d** and **3l** was 88:12. That is, ketone **2d** reacted preferentially in the presence of aldehyde **2l**. When the same reaction was performed at room temperature, the selectivity between **3d** and **3l** changed to 42:58. Although the selectivity depends on the reaction conditions and the steric and electronic character of carbonyl compounds, chemoselective reactions could occur in some cases. When the reaction of **1f** with **2d** and **2l** was performed at 0 °C, the yield of **3d** was improved to 66% with the same 88:12 selectivity.

In summary, we found that new methylenation reagents **1e** and **1f** react with a variety of aldehydes and ketones in the presence of *t*-BuOK in DMF at room temperature in 1 h to give terminal alkenes in high yields. The reagents can be prepared easily without any expensive reagents and the reaction conditions are mild and practical. We believe our new methylenation reagents are useful complements to the Wittig reagent $CH_3P(C_6H_5)_3Br$ and other methylenation procedures. In order to expand the scope and utility, further study on this olefination reaction is presently under active investigation in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Typical experimental procedures, compound characterization data, and the NMR spectra of compounds **1e**, **1f**, **6**−**9**, and **3a**−**m**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01049.

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Notes

The authors declare no competing financial interest.

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(17) A dimeric product was isolated in 19% from the reaction mixture along with **1e** (49%) and **8** (5%). Furthermore, *tert*-butoxybenzimidazole was detected in the crude mixture. See the Supporting Information for the proposed structures.

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