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N-Carbamate Protected α-Amidoalkyl-*p*-tolylsulfones: Convenient Substrates in the aza-Morita−Baylis−Hillman Reaction

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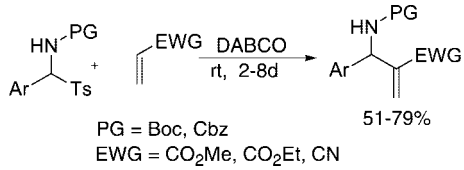
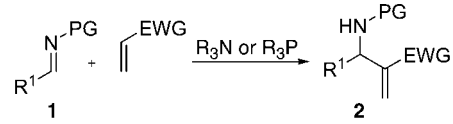


An efficient and practical one-pot approach to aza-Morita−Baylis−Hillman adducts has been developed. The reaction occurs between *N*-Boc or *N*-Cbz imines, generated in situ from stable and easy to handle *N*-Boc or *N*-Cbz protected α-amidoalkyl-*p*-tolylsulfones, and electron-deficient alkenes in the presence of DABCO. The presented procedure eliminates the use of the relatively unstable *N*-carbamate imines prior to the coupling reaction. The reaction is limited to α-amidosulfones derived from aromatic and heteroaromatic aldehydes.

The aza-Morita−Baylis−Hillman (aza-MBH) reaction[1] occurring between activated imines **1** and α,β-unsaturated carbonyl compounds, in the presence of tertiary amine or tertiary phosphine, provides straightforward and atom-economic method for the synthesis of highly functionalized N-protected α-methylene-β-aminocarbonyl compounds **2**, potential building blocks often used for the preparation of biologically important compounds[1a,b,d,g,2] (Scheme 1). Recently, the asymmetric version of the aza-MBH reaction is also the subject of intensive and very promising studies.[1h,e,f,3] N-Sulfonylated imines, derived from aryl and heteroaryl aldehydes or cinnamaldehyde, are the commonly used electrophiles in aza-MBH reactions.[3a−n,4−6] Aromatic N-carbamate activated imines, especially Boc protected ones, are seldom used in aza-MBH reactions,[3t,u,7] despite their high reactivity and easy removal of the protecting group (Scheme 1), because of their substantial hydrolytic lability, especially for those derived from aliphatic aldehydes. Therefore, certain precautions have to be taken in their preparation, handling, and storage.

SCHEME 1. Aza-MBH Reaction



PG = RSO_2, RS(O), $Ph_2P(O)$, $Ph_2P(S)$, $(EtO)_2P(O)$, $(EtO)_2P(S)$, Ar, Boc, CO_2Et, CO_2Me

R^1= Ar, CO_2Et

EWG = CO_2R, C(O)R, CHO, CN

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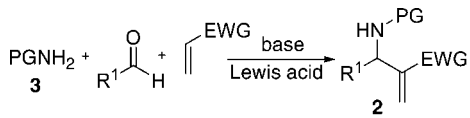
SCHEME 2. Three-Component aza-MBH Reaction



PG = $ArSO_2$, Ms, $Ph_2P(O)$, SES, Boc, Cbz
R^1 = Ar, *i*-Bu, *t*-Bu, *c*-Hex
EWG = CO_2Me, CO_2Et, CN, C(O)Me, SO_2Ph

The instability of imines could be partly circumvented in a one-pot three-component aza-MBH reaction[3w,8] in which aldehydes and amides **3** reacted with electron-deficient alkenes in the presence of tertiary amines such as DABCO, 3-hydroxyquinuclidine, or triphenylphosphine (Ph_3P) (Scheme 2).

In several protocols high yields were additionally ensured by using catalytic amounts of Lewis acids such as $La(OTf)_3$, $Ti(OPr^i)_4$, or $TiCl_4$ and molecular sieves as additives.[8c−g,j−l] Generally, the transformations mentioned above were limited to aromatic and heteroaromatic aldehydes. In some cases the concomitant formation of the corresponding hydroxy-MBH adducts was additionally observed.[8c,g] Arylsulfonamides, 2-trimethylsilylethylsulfonamide (SES-NH_2), and diphenylphosphinamide were very often used as a source of amine-protecting group. For the synthesis of *N*-sulfonylated aza-MBH adducts derived from aliphatic aldehydes, microwave-assisted three-component aza-MBH reaction was especially useful.[8i]

The isolated examples of the *N*-Boc and *N*-Cbz protected aza-MBH adducts,[9] formed in Ph_3P-catalyzed reaction of *tert*-butyl or benzyl carbamate, benzaldehyde, and MVK or methyl acrylate as Michael acceptors, were also reported.[8a] Nevertheless, Balan and Adolfsson[8c] found that *tert*-butyl and benzyl carbamate, previously reported to yield aza-MBH adducts[8a] gave no desired products in the three-component aza-MBH reactions either by using Lewis acid/base catalyzed three-component protocol or when Ph_3P was applied as catalyst.[10]

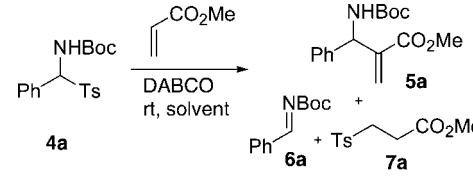
It is well documented that *N*-Boc and *N*-Cbz protected α-amidoalkyl-*p*-tolylsulfones[11,12] **4** can be considered as stable, crystalline, and easy to handle equivalents of *N*-Boc and *N*-Cbz imines. Therefore nucleophilic additions to *N*-carbamate imines generated in situ from the α-amidosulfones mentioned above by base-induced elimination have been recently the subject of extensive studies.[9i,13]

For this reason, we thought it would be of interest to develop a new protocol, which for the first time would give the opportunity to use the *N*-carbamate protected α-amidoalkyl-*p*-tolylsulfones in the aza-MBH reactions. Herein we report our efforts to achieve this goal.

At first, we examined the model reaction of *N*-Boc α-amidoalkyl-*p*-tolylsulfone **4a** with methyl acrylate using DABCO simultaneously as a base and catalyst. The results are summarized in Table 1.

Initially, the reaction was performed under the standard MBH conditions using 20 mol % DABCO and methyl acrylate as a solvent. However, the reasonable yield of the desired aza-adduct **5a** was achieved only after 9 d at room temperature (Table 1, entry 1). In turn, increasing DABCO amount to 1.2 equiv with respect to **4a** resulted in the formation of **5a** in 68% yield within 2 d at room temperature (Table 1, entry 2). Further increase of DABCO amount to 2.0 equiv had no influence on either the reaction rate or its yield (Table 1, entry 3). Finally, reducing the amount of methyl acrylate to 2 equiv and using THF as solvent caused a dramatic decrease of the reaction rate. After 8 d at room temperature the conversion was still very low, as confirmed by ^1H NMR analysis of the reaction mixture (Table 1, entry 4).

TABLE 1. Optimization of the aza-MBH Reaction[a]



entry	DABCO (equiv)	methyl acrylate (equiv)	solvent	time (d)	Yield
1	0.2	25	acrylate	9	65
2	1.2	25	acrylate	2	68
3	2.0	25	acrylate	2	69
4	1.2	2	THF	8	*b*

[a] Reactions were run with **4a** (5.0 mmol) and DABCO (0.2−2 equiv) in methyl acrylate (2−25 equiv) at room temperature. The progress of the reaction was monitored by TLC (hexanes/AcOEt 2:1 v/v) and ^1H NMR. Disappearance of the starting **4a** and the intermediate *N*-Boc imine **6a** was traced. [b] A large amount of **6a** was still present in the reaction mixture after 8 d at room temperature.

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(10) In our hands, attempted repetition of a three-component procedure elaborated by Bartenshaw and Kahn[8a] using *tert*-butyl or benzylcarbamate, benzaldehyde, methyl acrylate, and Ph_3P (20 mol %) as catalyst, resulted in the formation of the desired *N*-Boc or *N*-Cbz aza-adducts in less than 7% yield after 2 d at 40 °C in 2-propanol, as confirmed by ^1H NMR analysis of the crude reaction mixture.

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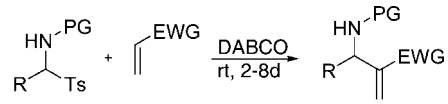
TABLE 2. Formation of *N*-Boc and *N*-Cbz Protected aza-MBH Adducts 5 and 9[a]



4 PG = Boc
8 PG = Cbz

5 PG = Boc
9 PG = Cbz

compd	R	PG	EWG	time (d)	yield[b]
5a	Ph	Boc	CO_2Me	2	68
5b	4-$MeOC_6H_4$			5	76
5c	4-BrC_6H_4			2	58
5d	2-$MeOC_6H_4$			5	72
5e	2-ClC_6H_4			2	65
5f	2-furyl			6	71
5g	3-py			5	51
5h	1-naphthyl			8	76
5i	Ph	Boc	CO_2Et	4	79
5j	4-$MeOC_6H_4$			6	66
5k	4-BrC_6H_4			2	67
5l	2-furyl			6	64
5m	Ph	Boc	CN	2	75
5n	4-$MeOC_6H_4$			2	66
5o	4-BrC_6H_4			2	63
9a	Ph	Cbz	CO_2Et	7[c]	70
9b	Ph	Cbz	CN	5[c]	57

[a] Reactions were run with **4** or **8** (5.0 mmol) and DABCO (1.2 equiv) in methyl or ethyl acrylate or acrylonitrile (25 equiv) at room temperature. [b] Yields of pure isolated compounds **5a**−**o** and **9a,b**, after flash chromatography. [c] Prolonged reaction time resulted from the partly heterogenic nature of the reaction mixture.

In all of the reactions mentioned above, the aza-adduct **5a** was accompanied by the formation of methyl 3-(toluene-4-sulfonyl)-propionate[14] (**7a**). Nevertheless, **5a** could be easily separated from the byproduct **7a** by flash chromatography. The presence of **7a** in the reaction mixture could be rationalized by the Michael-type addition of *p*-toluenesulfinate, released from the α-amidosulfone **4a** during the formation of the imine **6a**, to methyl acrylate.

Finally, we investigated the reactions of a series of *N*-Boc protected aromatic α-amidosulfones with selected Michael-type acceptors under the optimized protocol using 1.2 equiv of DABCO as a base. Methyl and ethyl acrylate and acrylonitrile were employed as Michael acceptors and as solvents concurrently.

The reaction was general, and a number of diverse aryl and heteroaryl substituted aza-MBH adducts **5a**−**o** were obtained in good yields. The results are summarized in the Table 2. The structures of products were unequivocally confirmed by NMR, elemental analyses, and mass spectra.

The results in Table 2 show that methyl and ethyl acrylates afford the corresponding aza-adducts **5a**−**l** in comparable yields (51−79%) after flash chromatography. While the presence of an electron-withdrawing bromine atom in the *para* position of the benzene ring of **4c** and **4k** reduced the reaction time to 2 d, the *N*-Boc protected α-amidosulfones **4b,j,f,l,g,h,** derived from 4-methoxybenzaldehyde, 2-furaldehyde, pyridine-3-carbaldehyde, or 1-naphthaldehyde required longer reactions time for completion. Moreover, the reaction tolerates also sterically hindered *ortho*-substituted α-amidosulfones **4d** and **4e**, giving the appropriate *o*-methoxy and *o*-chloro substituted adducts **5d** and **5e** in 72% and 65% yield, respectively. Unlike acrylates, acrylonitrile reacted faster under the optimized conditions affording the desired products **5m**−**o** in 63−75% yield within 2 d at room temperature.

To widen the scope of this new protocol, we examined also the *N*-Cbz protected α-amidoalkyl-*p*-tolylsulfone **8a** (Ar = Ph) as starting material. It was found that the substitution of *N*-Boc α-amidosulfones **4** by *N*-Cbz protected α-amidosulfone **8a** afforded the analogues **9a** and **9b** in 70% and 57% yields, respectively. The longer reaction time required for the conversion of *N*-Cbz α-amidosulfone **8a** stemmed from its poor solubility in acrylonitrile and ethyl acrylate.

Unfortunately, the attempted use of our procedure for *N*-Boc or *N*-Cbz protected α-amidoalkyl-*p*-tolylsulfones (**4** or **8**) derived from aliphatic aldehydes did not provide any aza-MBH adducts. The lack of the desired products in these cases stems probably from the fast spontaneous tautomerization of the intermediate alkyl *N*-carbamate imines,[15] formed from parent α-amidosulfones, into enecarbamates that are not reactive under these conditions.[16]

In conclusion, we have demonstrated that the procedure described here provides a new and operationally simple one-pot access to structurally diverse aza-Morita−Baylis−Hillman adducts from easily available and stable *N*-Boc and *N*-Cbz protected α-amidoalkyl-*p*-tolylsulfones. Our protocol eliminates the preformation and sometimes tedious isolation of the unstable *N*-carbamate imines prior to the coupling reaction with Michael acceptors. The aza-MBH adducts with easily removable amine protecting group (Boc and Cbz) have been obtained in good yields. The method has been evaluated for a range of *N*-carbamate protected α-amidosulfones derived from heteroaromatic and aromatic aldehydes, including electron-poor and -rich as well as *ortho*-substituted derivatives.

Experimental Section

General Procedure. A mixture of α-amidosulfones **4** or **8** (5.0 mmol), Michael acceptor (methyl acrylate, ethyl acrylate or acrylonitrile) (25 equiv), and DABCO (6.0 mmol, 0.67 g, 1.2 equiv) was stirred for 2−8 d at room temperature until the substrates disappeared, as checked by TLC and ^{1}H NMR. Then the excess of the Michael acceptor was removed under reduced pressure, and diethyl ether (40 mL) was added to the residue. The crystalline methyl or ethyl 3-(toluene-4-sulfonyl)-propionate[14] or 3-(toluene-4-sulfonyl)-propionitrile[14,17] was filtered off and washed with ether (15 mL). Organic layers were combined and washed successively with water (10 mL), 5% aqueous $KHSO_4$ (10 mL), water (10 mL), 5% aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Crude products **5** and **9** were purified by silica gel flash chromatography using increasing amounts (from 0 to 15% v/v) of AcOEt in Hexanes.

Methyl 2-(*tert*-Butoxycarbonylamino-phenyl-methyl)acrylate (5a). This product was obtained after 2 d at room temperature as a colorless solid (0.99 g) in 68% yield after flash chromatography. Mp 77−78 °C; R_f = 0.53 (hexanes/AcOEt 2:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.38 (s, 1H), 5.92 (s, 1H), 5.68 (brd, 1H, J = 10.0 Hz), 5.50−5.45 (m, 1H), 3.67 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 154.8, 140.0, 139.8, 128.4, 127.3, 126.5, 126.3, 79.6, 55.9, 51.7,

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(16) A mixture of the corresponding (*Z*/*E*)-1-[(*tert*-butoxycarbonyl)amino]propenes (75:25 *Z*/*E*) was isolated in 72% yield from the reaction of *N*-Boc α-amidoalkyl-*p*-tolylsulfones **4**, derived from propionaldehyde (R = Et), and methyl acrylate in the presence of DABCO (1.2 equiv) after 2 weeks at room temperature.

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28.2; IR (film) 3448, 2976, 1724, 1632, 1492, 1464, 1440, 1392, 1368, 1328, 1272, 1164, 1048, 1024, 956 cm^{-1}; MS *m/z* (CI, isobutane) 292 (100%, MH^+). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81, Found: C, 65.75; H, 6.99; N, 5.00.

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Supporting Information Available: Experimental procedures and full characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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