Selective Formation of α-Methylene-*β*-amino acid Derivatives through the Aza Version of the Baylis−Hillman Reaction

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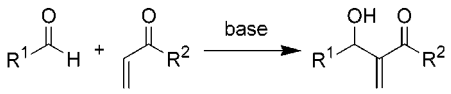
Introduction

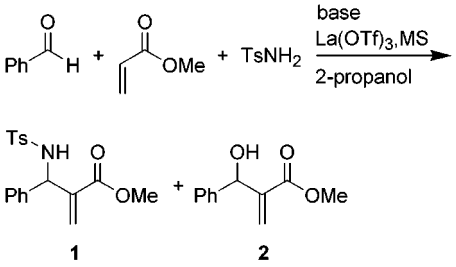
The selective formation of carbon−carbon bonds remains as an important challenge in organic synthesis. The Baylis−Hillman reaction allows the direct formation of α-methylene-*β*-hydroxycarbonyl compounds in a base-catalyzed tandem reaction (Michael and enolate addition followed by elimination) of α,*β*-unsaturated carbonyls with aldehydes (Scheme 1).[1,2] There are a number of different bases employed to catalyze this reaction, but the most frequently used catalysts are nucleophilic nonsterically hindered tertiary amines like 1,4-diazabicyclo[2.2.2]nonane (DABCO). Recently, it was found that employing a combination of Lewis acids and nucleophilic bases further improved the reaction.[3]

The aza version of the reaction, i.e., exchanging the aldehyde reactant for an aldimine and thus forming α-methylene-*β*-aminocarbonyl compounds, has previously been reported,[4] although no general protocol for the reaction has been established. α-Methylene-*β*-aminocarbonyl compounds can be obtained by a simple substitution reaction on the adducts formed in the regular Baylis−Hillman reaction, displacing the alcohol functionality by an amine.[5] This reaction, though, normally leads to a loss in selectivity since competing S_N2' reactions or Michael additions on the allylic substrates result in the formation of regioisomers.[5a,b,6] Herein, we like to report on a selective three-component one-pot procedure forming unsaturated *β*-amino acid derivatives from aldehydes, sulfonamides, and α,*β*-unsaturated carbonyls based on the aza version of the Baylis−Hillman reaction.

Scheme 1



Scheme 2



Results and Discussion

The standard Baylis−Hillman reaction is very sensitive toward the reaction conditions employed, and long reaction times are typically required to obtain synthetically useful yields of the desired adducts. Furthermore, the reaction is very substrate selective and a variety of reaction conditions are available for specific substrates.[1a] The latter is true also for the formation of α-methylene-*β*-aminocarbonyl compounds employing the Baylis−Hillman protocol.[4] Therefore, we decided to investigate the formation of α-methylene-*β*-aminocarbonyls using a three-component system and to optimize the reaction conditions required for a general protocol for the aza version of the Baylis−Hillman reaction. As a model system we chose to study the reaction between *p*-toluenesulfonamide (tosylamide), benzaldehyde, and methyl acrylate, in the presence of a base catalyst (Scheme 2).

Previous studies showed that triphenylphosphine[4b] and DABCO[4a,e] were, at elevated temperatures, efficient catalysts for the reaction, although in these cases the aldimine component was sometimes preformed. In an initial experiment, mixing all three components in stoichiometric amounts and using a catalytic amount of DABCO (15 mol %) as base, we obtained after 48 h a moderate yield of the tosylamido adduct **1** together with a small amount of the alcohol adduct **2** (Table 1, entry 1). Recent developments of the classic Baylis−Hillman reaction involve the introduction of Lewis acids in combination with nucleophilic bases to increase the rate of the adduct formation.[3] Several lanthanide triflates, e.g., $La(OTf)_3$, used in catalytic amounts were shown to accelerate the reaction.[3a] Adding 2 mol % of $La(OTf)_3$ combined with 15 mol % DABCO to the three-component reaction resulted in yields in the same range as obtained without having the Lewis acid present (entry 2).

The small, but still significant, amount of alcohol adduct formed in the reaction indicated that the rate of the aldimine formation was on the same level as or possibly even slower than the Michael addition forming the enolate. To increase the rate of aldimine formation, and thus push the equilibrium toward the aldimine, molecular sieves (4 Å) were added to trap the water formed in the reaction. This resulted in a significant overall rate and selectivity enhancement in the three-component reaction. After 24 h we obtained 72% yield of

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(1) (a) Basaviah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(2) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, **1972** (*Chem. Abstr.* **1972**, *77*, 34174q).

(3) (a) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183. (b) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S. *Tetrahedron* **1998**, *54*, 11813. (c) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, *2*, 2397.

(4) (a) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951. (b) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731. (c) Cyrener, J.; Burger, K. *Monatsh. Chem.* **1994**, *125*, 1279. (d) Campi, E. M.; Holmes, A.; Perlmutter, P.; Teo, C. C. *Aust. J. Chem.* **1995**, *48*, 1535. (e) Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729.

(5) (a) Drewes, S. E.; Horn, M. M.; Ramesar, N. *Synth. Commun.* **2000**, *30*, 1045. (b) Takagi, M.; Yamamoto, K. *Chem. Lett.* **1989**, 2123. (c) Brown, J. M.; James, A. P.; Prior, L. M. *Tetrahedron Lett.* **1987**, *28*, 2179.

(6) (a) Kulkarni, B. A.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 373. (b) Kundu, M. K.; Bhat, S. V. *Synth. Commun.* **1999**, *29*, 93. (c) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981. (d) Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr.* **1989**, 403.

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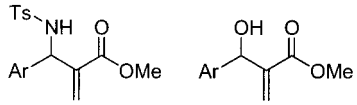
Table 1. Conditions for the Aza Version of the Baylis−Hillman Reaction[a,b]

entry	base (mol %)	$La(OTf)_3$ (mol %)	MS 4 Å	time (h)	**1** (%)	**2** (%)
1	DABCO (15)		−	48	62	10
2	DABCO (15)	2	−	48	63	9
3[c]	DABCO (15)	2	+	24	72	
4[d]	DABCO (15)	2	+	24	76	
5[e]	DABCO (15)	2	+	24	22	6
6	DABCO (5)	2	+	19	13	
7	3-HQD (15)	2	+	23	87	4
8	cinchonidine (15)	2	+	25	7	
9	DBU (15)	2	+	24	15	
10	PPh_3 (15)	2	+	24	50	10

[a] Reaction conditions: benzaldehyde, *p*-toluensulfonamide, and methyl acrylate (1 equiv of each), base, $La(OTf)_3$, and molecular sieves (4 Å, 200 mg) as above in 2-propanol at ambient temperature. [b] Yields determined by ^{1}H NMR with internal standard. [c] 86% yield of **1** after 48 h. [d] Temperature 40 °C. [e] Temperature 0 °C.

the tosylamido adduct and, most importantly, no alcohol adduct was formed (entry 3). Prolonging the reaction time to 48 h resulted in an 86% yield of **1**, and the alcohol adduct was not observed. Increasing the temperature to 40 °C resulted in a slightly higher yield of **1** (entry 4). Further increase of temperature to refluxing 2-propanol resulted, however, in a lower yield (50%, 20 h). Reducing the temperature to 0 °C, which recently was reported to increase the rate of the classic Baylis−Hillman reaction,[7] resulted in low yield and poor selectivity (entry 5). The ratio between the base and the Lewis acid turned out to be crucial; decreasing the amount of DABCO to 5 mol % without changing the amount of $La(OTf)_3$ resulted in a substantially lower yield (entry 6). This can be explained by coordination of the base to the Lewis acidic metal center, thereby decreasing the concentration of the active nucleophilic catalyst. In fact, running the reaction under the same conditions (5 mol % DABCO) without any Lewis acid present resulted in higher yield (**1**, 58%; **2**, 4%; 19 h at 40 °C). In a recent attempt to classify Lewis acids on the basis of activity and selectivity in enolate additions to aldehydes and aldimines, respectively, Kobayashi et al. demonstrated that lanthanide chlorides are very imine selective.[8] Other Lewis acids showing high selectivity for imine activation included copper(I/II) chlorides, and exchanging the chloride for other weakly basic noncoordinating counteranions, e.g., the triflate anion, further increased the aldimine selectivity. Thus, replacing $La(OTf)_3$ with $Cu(OTf)_2$ (2 mol %) in the three-component reaction resulted in a highly selective, albeit slightly lower yielding, formation of **1** (60%, 24 h). Previously, 3-hydroxyquinuclidine (3-HQD) has successfully been used as base in the Baylis−Hillman reaction.[9] The rate enhancement of the reaction observed using 3-HQD was attributed to a stabilization of the zwitterionic enolate via hydrogen bonding from the alcohol. Replacing DABCO for 3-HQD resulted in a higher yield of **1** although with slightly reduced selectivity (entry 7). When the sterically more demanding cinchonidine was employed as base, low conversion to the adduct was observed (entry 8).[10] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), recently reported as the optimum catalyst for the Baylis−Hillman reaction,[11] performed poorly in the aza version of the reaction, resulting only in low yield of the tosylamido adduct (entry 9). Using triphenylphosphine as base under these conditions resulted in moderate yield and selectivity (entry 10). To conclude, the best conditions found were employing DABCO or 3-HQD (15 mol %) together with $La(OTf)_3$ (2 mol %) and molecular sieves.

Table 2. Formation of α-Methylene-β-tosylamido Carbonyl Compounds[a]



A **B**

		DABCO[b]			3-HQD[b]		
entry	Ar	*t* (h)	**A**[c] (%)	**B** (%)	*t* (h)	**A**[c] (%)	**B** (%)
1	3-chlorophenyl	24	83 (58)	5	23	80	11
2	3-nitrophenyl	24	81 (59)	9	23	69	23
3	4-nitrophenyl	72	43 (14)	14	72	73(56)	23
4	4-methoxyphenyl	72	27 (12)		72	50	
5	2-naphthyl	72	42 (36)		72	90(77)	
6	2-furanyl	24	75 (57)	10	23	80	12
7	2-pyridyl	24	54 (51)	13	24	88(83)	7

[a] Reaction conditions: arylaldehyde, *p*-toluensulfonamide, and methyl acrylate (1 equiv of each), base (0.15 equiv), $La(OTf)_3$ (0.02 equiv), and molecular sieves (4 Å, 200 mg) in 2-propanol at ambient temperature. [b] Yields determined by ^{1}H NMR with internal standard. [c] Isolated yields within parentheses.

With the optimized conditions in hand we then focused on the scope of the reaction. In Table 2 we have summarized the results from using a number of different arylaldehydes. Arylaldehydes with electron-withdrawing substituents performed well under the conditions employed, although their greater electrophilicity resulted in the formation of alcohol adducts to various degrees. The use of DABCO as base gave somewhat better selectivities than using 3-HQD. When 4-methoxybenzaldehyde and 2-naphthaldehyde were used as electrophiles, higher yields and excellent selectivities were obtained using 3-HQD as base, whereas DABCO catalyzed the formation of the adducts in a substantially lower yield. Hetereocyclic aldehydes showed high reactivity, although the selectivities for the aza adduct were moderate. Using the standard conditions, the intermediate *N*-sulfonyl aldimines were formed in yields ranging from 50% to 80%.[12] Thus, this procedure has the potential of being used in *N*-sulfonyl aldimine formation, a substance class widely used in organic synthesis.[13]

Aliphatic aldehydes, however, did not yield any aza adducts under these conditions, due to very slow formation of the intermediate imines.

(7) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521.

(8) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491.

(9) (a) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1565. (b) Bailey, M.; Markó, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron Lett.* **1990**, *31*, 4509. (c) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32*, 5611.

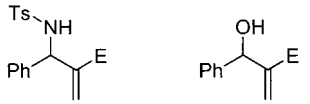
(10) Employing cinchonidine as nucleophile resulted in the formation of **1** in 40% enantiomeric excess. The low conversion, however, disfavors the use of this base. The asymmetric Baylis−Hillman reaction, using modified cinchona alkaloids, was recently reported; see: Iwabuchi, Y.; Nakatani, M.; Yokohama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

(11) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311.

(12) *N*-Sulfonyl aldimines were formed in moderate to high yields using the following conditions: Sulfonamide (1 equiv) and aldehyde (1 equiv) were dissolved in 2-PrOH (0.5 mL) followed by the addition of $La(OTf)_3$ (0.02 equiv), MS (4 Å, 200 mg/mmol), and DABCO (0.15 equiv). Stirring for 24−72 h at ambient temperature. For other methods for the preparation of *N*-sulfonyl aldimines, see: Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75 and references cited therein.

(13) (a) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 125. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

Table 3. Formation of α-Methylene-*β*-tosylamido Carbonyl Compounds[a]

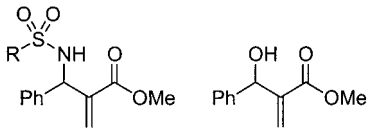


C **D**

		DABCO[b]			3-HQD[b]		
entry	Michael acceptor	*t* (h)	**C**[c] (%)	**D** (%)	*t* (h)	**C**[c] (%)	**D** (%)
1	methyl acrylate	48	86 (80)		23	87	4
2	*tert*-butyl acrylate	72	45 (27)		72	78(68)	
3	acrylonitrile	20	63 (53)	9	23	65	20
4	phenyl vinyl sulfone	72	32 (16)		72	21	13

[a] Reaction conditions: benzaldehyde, *p*-toluensulfonamide, and Michael acceptor (1 equiv of each), base (0.15 equiv), $La(OTf)_3$ (0.02 equiv), and molecular sieves (4 Å, 200 mg) in 2-propanol at ambient temperature. [b] Yields determined by ^1H NMR with internal standard. [c] Isolated yields within parentheses.

Table 4. Formation of α-Methylene-*β*-sulfonylamido Carbonyl Compounds[a]



E **2**

		DABCO[b]			3-HQD[b]		
entry	*R*	*t* (h)	**E** (%)	**2** (%)	*t* (h)	**E** (%)	**2** (%)
1	phenyl	23	74	4	23	82	4
2	4-methoxyphenyl	23	74		22	90	4
3	2-nitrophenyl	24	45	8	22	33	26
4	methyl	24	87		22	80	5

[a] Reaction conditions: benzaldehyde, sulfonamide, and methyl acrylate (1 equiv of each), base (0.15 equiv), $La(OTf)_3$ (0.02 equiv), and molecular sieves (4 Å, 200 mg) in 2-propanol at ambient temperature. [b] Yields determined by ^1H NMR with internal standard.

We then investigated the range of possible Michael acceptors working in the three-component reaction (Table 3). When comparing acrylic esters, the steric bulkiness of the ester turned out to be of high importance for the reactivity. Methyl acrylate reacted readily as described above, whereas *tert*-butyl acrylate reacted slower and gave much lower yield in the case of using DABCO as base and slightly lower yield using 3-HQD. Acrylonitrile reacted rather fast under these conditions although the chemoselectivity was poor. Phenyl vinyl sulfone reacted poorly, and a surprisingly big difference in selectivity was observed depending on the choice of base. The low yield can be explained by an interesting side reaction, resulting from a competing double Michael addition of tosylamide on the vinyl sulfone. Other Michael acceptors known to give Baylis−Hillman adducts, e.g., vinyl phosphonates, gave using these conditions no detectable amounts of adducts. Michael acceptors substituted in the *β*-position, e.g., ethyl crotonate and cyclohex-2-enone, gave no adducts under these conditions.

Finally we investigated the scope of using different amines (sulfonamides) in the reaction (Table 4). As observed above for tosylamide, benzenesulfonamide and its 4-methoxy analogue performed well under the optimized conditions and gave aza adducts in high yields and good selectivities. The electron-deficient 2-nitrosulfonamide, a useful protecting group for amines due to its mild cleavage protocol,[14] reacted however poorly and in the case of using 3-HQD as base with no chemoselectivity.[15] Perfoming the reaction with methanesulfonamide as amine source resulted in the formation of the aza adduct in high yield and good selectivity within reasonable time. As stated above, this protocol efficiently produces *N*-sulfonyl aldimines in high yields. However, primary aliphatic and aromatic amines did not form imines under these reaction conditions and thus no formation of aza adducts were observed. In fact, performing the reaction with preformed *N*-benzylideneaniline did not result in the formation of the aza adduct, an observation which strongly suggests that activated aldimines are required for the reaction to occur. Benzyl and *tert*-butyl carbamate, previously reported to yield aza adducts,[4b] did not result in the formation of the desired products, either using our optimized protocol or when we employed PPh_3 as catalyst.

Conclusions

We have demonstrated that employing a three-component reaction mixture of arylaldehydes, sulfonamides, and a Michael acceptor results in moderate to high yields of α-methylene-*β*-sulfonylamido carbonyl derivatives. The reactions were catalyzed by base (DABCO or 3-HQD) and Lewis acid ($La(OTf)_3$), in the presence of molecular sieves (4 Å), and the products were easily isolated by simple extraction. Regarding the choice of base, we generally would recommend DABCO, since better chemoselectivities were obtained with this catalyst. For less electrophilic aldehydes, however, the use of 3-HQD resulted in higher yields of the aza adducts.

Experimental Section

General Experimental Procedure[16] for the Aza Version of the Baylis−Hillman Reaction, Exemplified for the Formation of Methyl α-Methylene-*β*-[(*p*-toluenesulfonyl)-amino]-3-phenylpropionate (1).[4d] In a dried flask, tosylamide (855 mg, 5 mmol), DABCO (84 mg, 0.75 mmol), and $La(OTf)_3 \cdot H_2O$ (58.5 mg, 0.1 mmol) were measured together with molecular sieves (4 Å, 900 mg). 2-PrOH (2.5 mL),[17] benzaldehyde (505 μL, 5 mmol), and methyl acrylate (450 μL, 5 mmol) were added, and the reaction mixture was stirred for 48 h at ambient temperature. The mixture was filtered through a thin layer of Celite, which was rinsed three times with 2-PrOH (10 mL). The solvent was evaporated, and to the crude mixture were added methanol (25 mL) and aqueous sulfuric acid (10 mL, 1M).[18] The solution was stirred for 1 h, and then methanol was evaporated. The remaining acidic soulution was diluted with water and extracted with dichloromethane (3 × 30 mL). The organic phase was then successively washed with $NaHCO_3$ (saturated), NaOH (1 M), water, and NaCl (saturated) solutions and dried over Na_2SO_4.[19] Evaporation of the solvent gave 1.38 g (80%) of the pure product

(14) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(15) Prolonging the reaction time to 72 h did not improve the yield of the aza adduct.

(16) This procedure was applied for all reactions, except in the case of 2-pyridinecarboxaldehyde, where the Michael acceptor was added 24 h later to suppress the formation of the alcohol adduct.

(17) For solid aldehydes the amount of solvent was increased to 4 mL.

(18) The acidic workup facilitates cleavage of remaining sulfonylimine and efficiently removes the aldehyde. For reactions with low conversion, an additional stirring with sulfuric acid (1 M) was repeated after the basic workup.

(19) Alternative workup procedure: The crude reaction mixture was separated on silica gel (eluent: chloroform:methanol 20:1) followed by recrystallization in diethyl ether (in some cases an ethyl acetate diethyl ether mixture was employed). Using this procedure typically resulted in lower isolated yields.

as a white crystalline material: mp 76−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.61 (s, 3H), 5.31 (d, J = 8.9 Hz, 1H), 5.61 (d, J = 8.9 Hz, 1H), 5.83 (s, 1H), 6.22 (d, J = 0.7 Hz, 1H), 7.13−7.25 (m, 7H), 7.68 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.72, 52.20, 59.31, 126.64, 127.45, 127.98, 128.10, 128.80, 129.70, 137.84, 138.74, 138.81, 143.61, 165.98; MS (MALDI-TOF) (m/z) 384.071 (MK^+), 368.094 (MNa^+), 346.103 (MH^+).

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Supporting Information Available: Characterization data for all compounds in Tables 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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