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Diastereoselective Baylis–Hillman reaction using *N*-glyoxyloyl camphorpyrazolidinone as an electrophile: synthesis of optically pure 2-hydroxy-3-methylene succinic acid derivative

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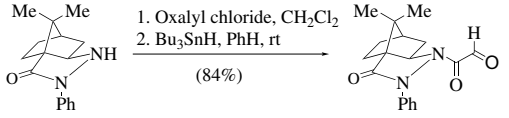
Abstract—The camphorpyrazolidinone derived *N*-glyoxylate was efficiently prepared and used as an electrophile in the Baylis–Hillman reaction under classical DABCO catalyzed conditions. The corresponding 2-hydroxy-3-methylene succinic acid derivative was generally obtained with excellent diastereoselectivity and moderate chemical yields (51–75%).

Increasing attention has been focused on the coupling of an aldehdyde with α,β-unsaturated carbonyls/nitriles in the presence of a tertiary amine (Baylis–Hillman reaction).[1] The corresponding (α-methylene-β-hydroxy)carbonyl derivatives represent versatile intermediates in organic chemistry.[2] The asymmetric Baylis–Hillman reaction has been studied extensively by several research groups to achieve a wide range of stereoselectivities.[3] The aza version of the Baylis–Hillman reaction using aldimine derivatives instead of an aldehyde to generate (α-methylene-β-amino)carbonyls has previously been reported.[4] Bauer and Tarasiuk reported on the use of (−)-8-phenylmenthyl glyoxylate as an electrophile in the Baylis–Hillman reaction using dimethyl sulfide in the presence of titanium tetrachloride, which gave the corresponding adducts in high diastereoselectivity.[5] However this reaction is limited to the use of α,β-unsaturated cycloketones. The Baylis–Hillman reaction is notorious for its extremely poor reaction rate, which requires long reaction times to achieve synthetically useful yields of the desired products. Numerous attempts have been made to increase the rate of the reaction.[6] In this context, we wish to report a rapid and general protocol for the formation of 2-hydroxy-3-methylene succinic acid derivatives using *N*-glyoxyloyl camphorpyrazolidinone (**2**) as a chiral electrophile in the Baylis–Hillman reaction under classical DABCO catalyzed conditions. In addition, excellent stereoselectivity was obtained when the Baylis–Hillman adduct (**4c**) was treated with *N*-aminophthalimide in the presence of lead tetraacetate.

The starting camphorpyrazolidinone (**1**) was designed and synthesized in this laboratory and has proved to be an efficient chiral auxiliary in asymmetric synthesis.[3g,7] The synthesis of *N*-glyoxyloyl camphorpyrazolidinone (**2**) is problematic at beginning, many synthetic routes have been examined (e.g., ozonolysis of the camphorpyrazolidinone derived acrylate, the direct coupling of camphorpyrazolidinone with glyoxylic acid and its derivatives, the reduction of the camphorpyrazolidinone derived α-carbonyl ester and etc.) and none have been found to give the desired glyoxylate in a reasonable material yield. Optimum conditions for this reaction are finally defined.[8] Treatment of camphorpyrazolidinone with oxalyl chloride (10 equiv) in CH_2Cl_2 gave the monoacylated product, which was reduced with Bu_3SnH (1.0 equiv) in benzene at room temperature for 10 min, affording **2** in 84% overall yield (Scheme 1).

With the*N*-glyoxyloyl camphorpyrazolidinone in hand we then turned our attention to the Baylis–Hillman



1 **2**

Scheme 1. The synthesis of *N*-glyoxyloyl camphorpyrazolidinone (**2**).

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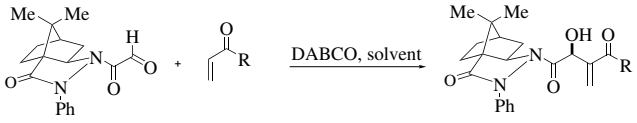
reaction. The reaction of α-naphthyl acrylate with *N*-glyoxyloyl camphorpyrazolidinone in CH_3CN in the presence of DABCO (0.3 equiv) for 2 h gave the desired Baylis–Hillman product in 30% yield (entry 1). A survey of various solvents was undertaken in an attempt to increase the efficiency of the reaction. To this end, the use of CH_2Cl_2 and benzene resulted in low material yields while the use of MeOH further decreased the reactivity (entries 2–4). The reaction rate could, however, be improved when a polar aprotic solvent was employed (entry 6). Thus, treatment of **2** with α-naphthyl acrylate in DMSO affords the desired product in a 51% material yield in a 10 min reaction. The chemical yield was further improved to 65% yield when DMSO/H_2O 10:1 was used (entry 7). In this homogeneous DMSO/H_2O medium, although the reactivity is lower, side reactions that complicate product purification are minimized. The diastereoselectivity was determined to be in excess of 90% de based on ^1H NMR analysis of the relevant peaks. The absolute stereochemistry of the newly generated stereogenic center was determined to have an *S* configuration by single crystal X-ray analysis of one of the analogous adducts (**4e**) (Table 1).

To further determine the feasibility of the system, a range of Michael acceptors were tested under the optimum reaction conditions. The use of β-naphthyl acrylate affords the adduct with high diastereoselectivity in 30 min (entry 8). The use of phenyl acrylate and benzyl acrylate to provide comparable results (entries 9 and 10). The reactivity decreased when methyl acrylate was used (entry 11). The use of α,β-unsaturated ketones as the Michael acceptors effect efficiency, while a relative slow reaction rate was observed when acrylonitrile was used (entries 12–14). The observed enhanced reaction rate of the present system can be attributed to the greater electrophilicity of the *N*-glyoxylate toward the addition of ammonium enolate.

The stereochemical bias of the present study can be rationalized by the conformational preference of the glyoxylate moiety in the transition state. Similar to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam, the CO/CHO *s-cis* planar conformation (A) in **2** is electronically favored over its *s-trans* conformer (A′) with the carbonyl group oriented toward the phenyl moiety.[9] A series of conformational analyses of the camphorpyrazolidinone derived α,β-unsaturated amides indicate that for α-unsubstituted *N*-enones the planar, *s-cis* arrangement dominate while the nonplanar *s-trans*-like conformation is energetically favored for α-substituent and α,β-disubstituents in the solid state conformation. These are confirmed by single crystal X-ray analyses of various *N*-enoylcamphorpyrazolidinones. The *N*-glyoxyloyl camphorpyrazolidinone (**2**) is believed to be in analogy to its counter α-unsubstituted *N*-enones.[10] The initially formed aza enolate then attacks the formyl group from the less hindered bottom *si* face with the subsequent elimination of DABCO to afford the desired adduct (Fig. 1).

The structural array of the corresponding 2-hydroxy-3-methylene succinic acid derivative **4** can be further transformed to synthetic useful intermediates. An initial investigation involved the reaction of **4c** with *N*-amino-

Table 1. Reaction of *N*-glyoxyloyl camphorpyrazolidinone (**2**) with various α,β-unsaturated carbonyls (**3a**–**g**) and acrylonitrile[a]



2 **3a-g** **4a-h**

Entry	R	Solvent	*t* (min)	Product	Yield (%)[b]	Dr[c]	Absolute configuration[d]
1	–*O*-α-Naphthyl	CH_3CN	2 h	**4a**	30	Nd[e]	
2	–*O*-α-Naphthyl	CH_2Cl_2	24 h	**4a**	<10	Nd[e]	
3	–*O*-α-Naphthyl	C_6H_6	24 h	**4a**	<10	Nd[e]	
4	–*O*-α-Naphthyl	MeOH	2 d	**4a**	<10	Nd[e]	
5	–*O*-α-Naphthyl	THF	24 h	**4a**	35	>95:5	*S*
6	–*O*-α-Naphthyl	DMSO	10	**4a**	51	>95:5	*S*
7	–*O*-α-Naphthyl	DMSO/H_2O[f]	30	**4a**	65	>95:5	*S*
8	–*O*-β-Naphthyl	DMSO/H_2O[f]	30	**4b**	67	>95:5	*S*
9	–*O*Ph	DMSO/H_2O[f]	60	**4c**	70	>95:5	*S*
10	–*O*Bn	DMSO/H_2O[f]	30	**4d**	66	>95:5	*S*
11	–*O*Me	DMSO/H_2O[f]	6 h	**4e**	61	>95:5	*S*
12	$-CH_3$	DMSO/H_2O[f]	20	**4f**	71	>95:5	*S*
13	$-CH_2CH_3$	DMSO/H_2O[f]	20	**4g**	75	>95:5	*S*
14	Acrylonitrile	DMSO[g]	60	**4h**	54	>95:5	*S*

[a] All reactions were carried out using **2** (0.32 mmol), activated alkene (1.3 equiv), DABCO (0.3 equiv) in the solvent indicated.
[b] Isolated yield. An unidentified material (<10%) was generally isolated with the substrates investigated.
[c] Determined by ^1H NMR analysis of the relevant peaks from the crude products.
[d] The absolute stereochemistry of the newly generated stereogenic center was determined to have an *S* configuration by single crystal X-ray analysis of **4e**. The absolute stereochemistry of **4c** was further confirmed from compound **5** while the rest of the adducts are assigned by analogy.
[e] Not determined.
[f] 10:1.
[g] Slow reaction rate was observed when DMSO/H_2O 10:1 was used.

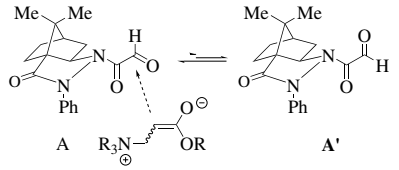
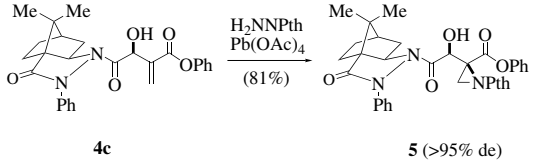


Figure 1. Proposed mechanism of the Baylis–Hillman reaction.



Scheme 2. Further functional group transformation of the Baylis–Hillman adduct **4c**.

phthalimide in the presence of lead tetraacetate, which provides the corresponding *N*-phthalimidoaziridine (**5**) in excellent diastereoselectivity. The structure of **5** was initially assigned by ^{1}H, ^{13}C NMR, and HRMS analyses and further confirmed by single crystal X-ray analysis (Scheme 2).

In summary, the Baylis–Hillman reaction of *N*-glyoxyloyl camphorpyrazolidinone (**2**) with various α,β-unsaturated carbonyls/nitrile proceeds smoothly to give the corresponding 2-hydroxy-3-methylene succinic acid derivative **4** in excellent diastereoselectivity. A preliminary investigation of the 2-hydroxy-3-methylene succinic acid derivative using **4c** has demonstrated its potential as a synthetic scaffold. A multifunctional array of 2-hydroxy-3-methylene succinic acid derivatives can be used for the construction of complex molecular structures. This extends the synthetic application to the versatile and general utility of chiral auxiliary **1**. Further applications of **5** and its derivatives are currently underway.

Acknowledgements

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8. Typical procedure for the preparation of *N*-glyoxyloyl camphorpyrazolidinone (**2**): To a solution of oxalyl chloride (10.0 mL, 117 mmol) in CH_2Cl_2 (50 mL) was added a solution of camphorpyrazolidinone (**1**) (3.0 g, 11.7 mmol) in CH_2Cl_2 dropwise at room temperature. The excess of oxalyl chloride was removed in vacuo after stirring for 10 min and the residue was dried under high vacuum. The residue was dissolved in benzene (20 mL) and Bu_3SnH (3.15 g, 11.7 mmol) was added dropwise at room temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (50 mL × 3). The organic layers were combined and washed (brine), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel, using hexanes/ethyl acetate 2:1 to give *N*-glyoxyloyl camphorpyrazolidinone (3.07 g, 84%).
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10. However, for camphorpyrazolidinone derived glyoxylic oxime ether the *s-trans* conformation favored in the solid state as indicated by single crystal X-ray analysis. Chen, K. Unpublished results.