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Highly Diastereoselective Three-Component Vinylogous Mannich Reaction between Isoquinolines, Acyl/Sulfonyl Chlorides, and Silyloxyfurans

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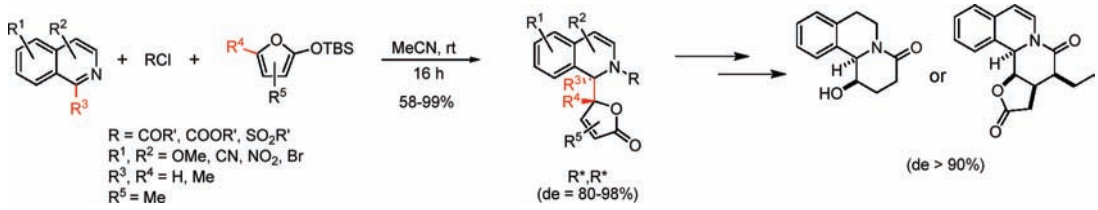
ABSTRACT



Reaction of an isoquinoline, a silyloxyfuran, and an acyl or sulfonyl chloride provides easy access to a wide variety of isoquinolinobutyrolactones with excellent yields and diastereoselectivites (*R*,R isomer), even in the case of formation of quaternary centers (i.e., R^3 or R^4 = Me). Moreover, the use of a chiral auxiliary allowed formation of a single stereoisomer in 96% yield. This represents the first examples of asymmetric vinylogous Mannich reactions on isoquinolinium salts.**

Tetrahydroisoquinolines (THIQ) and the closely related 1,2-dihydroisoquinolines represent a central unit of a wide variety of both alkaloids and pharmaceutical products.[1] These moieties are very often observed with a substituent at the C-1 stereogenic position, and various procedures have been described in the past to access optically pure C-1-substituted derivatives.[2,3] In this context, the Mannich reaction represents a very powerful tool for the formation of C−C bonds[4] and although this reaction is more difficult in the case of cyclic vs noncyclic imines,[3h,5] it has been successfully applied to both 3,4-dihydroisoquinolines and isoquinolines for this purpose in both racemic[6] and asymmetric[3g,h,7] versions. In the last case, the use of chiral auxiliaries attached to the nitrogen atom has been exploited,[7a,8] while more recently, Jacobsen and co-workers[9] have employed chiral thioureas as organocatalysts for the enantioselective addition of silyl enol ethers to *N*-acylisoquinolines with excellent results. Compared to the simple Mannich reaction, the vinylogous version would allow introduction of greater chemical complexity at C-1 of the heterocycle with the possibility of generating two contiguous stereogenic centers in the case of a nonterminal double bond on the starting silyl enol ether.[10] In this regard, butyrolactones and lactams are particularly useful reagents for vinylogous Mannich reactions since their silyl enol ethers are easily prepared and are available with a variety of substituents on the ring.[11] While very few examples of the addition of silyloxyfurans to cyclic

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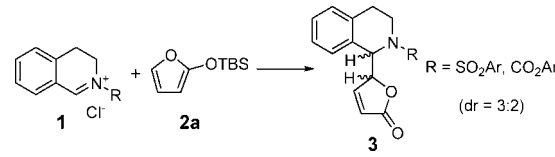
imines have been reported,[12] we described the first vinylogous Mannich reaction of 2-trialkylsilyloxyfurans with 3,4-dihydroisoquinolinium salts.[13] Thus, addition of 1-(*tert*-butyldimethylsilyloxy)furan **2a** to 3,4-dihydroisoquinolinium salts **1** derived from acyl or sulfonyl chlorides afforded the 1-isoquinolinyl-5-butyrolactone **3** in high yields but with very poor diastereoselectivities, typically in the 3:2 range (Scheme 1). In this paper, we describe the extension of this procedure to completely aromatic isoquinoline derivatives and show that, using a variety of cyclic silyl enol ethers and acylating/sulfonylating agents, this vinylogous Mannich reaction is high yielding and in most cases almost entirely diastereoselective in the absence of a chiral environment while in the presence of a chiral environment, essentially only one of the four possible stereoisomers is formed.

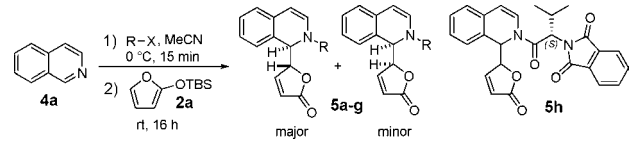
We first studied the reaction of **2a** with isoquinolinium salts derived from various acid chlorides. Thus, treatment

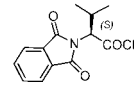
Scheme 1



of isoquinoline **4a** with 2 equiv of acetyl chloride in acetonitrile at 0 °C for 15 min followed by addition of 1.1 equiv of silyl enol ether **2a** afforded product **5a** in 80% yield and with dr = 92:8 (Table 1, entry 1). An even better result

Table 1. Variation of the Electrophile



entry	R-X	product	yield (%)	diastereoisomeric ratio[a]
1	AcCl	**5a**	80	92:8
2	$PhCH_2COCl$	**5b**	82	98:2
3	MeOCOCl	**5c**	87	>99:1
4	CbzCl	**5d**	76	92:8
5	MsCl	**5e**	89	99:1
6	TsCl	**5f**	58	93:7
7	MeI	**5g**	0	
8[b,c]		**5h**	99	96:3:<1:<1

[a] Measured by HPLC. [b] 1.1 equiv of R-X, 2 equiv of **2a**, CH_2Cl_2, −78 °C→ rt, 18 h. [c] See the Supporting Information for further examples.

was obtained using phenylacetyl chloride as acylating agent, compound **5b** being formed in 82% yield and dr = 98:2 (entry 2). With methyl chloroformate, the formation of only one diastereomer of **5c**, obtained in 87% yield, could be observed by HPLC (entry 3), while benzyl chloroformate provided compound **5d** in 76% yield and dr = 92:8 (entry 4). Reaction of **2a** with the isoquinolinium salt derived from methylsulfonyl chloride provided an excellent yield (89%) and high dr (>99:1) of the corresponding *N*-methylsulfonyl reaction product **5e** (entry 5). Use instead of *p*-toluenesulfonyl chloride gave a lower product yield (**5f**, 58%) though a satisfactory diastereoselectivity (dr = 93:7) was maintained (entry 6). No reaction of **2a** with the alkylisoquinolinium salt derived from methyl iodide (entry 7) was observed, indicating that an electron-withdrawing substituent on the quaternary nitrogen atom is necessary for the reaction to proceed.

The relative configuration of the major diastereoisomer of compound **5a** was determined to be (*R**,*R**) by X-ray crystallography (see the Supporting Information).[14] We also investigated the possibility of developing an asymmetric

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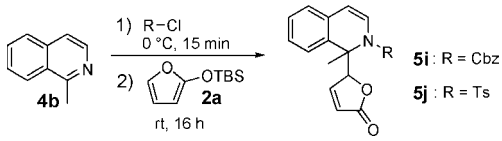
version of this reaction using an (*S*)-valine-based chiral auxiliary developed by Ohsawa[7a] for the asymmetric addition of silyl enol ethers to the C-1 position of isoquinolines. Thus, when the acid chloride derived from *N*-phthaloylvaline was used as the electrophile in the vinylogous Mannich reaction of **4a** with **2a**, one of the four possible isomers of **5h** was formed in 96% yield (entry 8).[15]

We then studied the behavior of substituted isoquinoline derivatives in the vinylogous Mannich reaction with **2a**. In the case of the *N*-Cbz salt derived from 1-methylisoquinoline **4b**, reaction with **2a** under the same reaction conditions as previously afforded only a low yield (10%) of the expected 1′-methyl-1′-(5-butyrolactone) product **5i** though a high diastereoselectivity was maintained (dr >95:5, Table 2, entry 1).[16] The yield of product **5i** could be increased to 76% without affecting the dr by diminishing the quantity of acylating agent to 1.1 equiv and increasing the quantity of silyloxyfuran **2a** to 2 equiv (entry 2). Replacement, in this last reaction, of the solvent (acetonitrile) by diethyl ether or THF led to considerably lower yields (41% and 36%, respectively) (entries 3 and 4), while dichloromethane provided a satisfactory yield (71%) of **5i** (entry 5).

Table 2. Optimization of Reaction Conditions

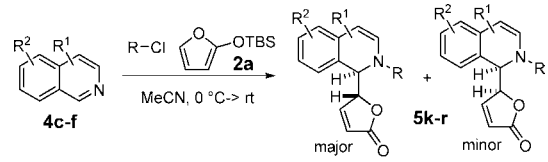


entry	solvent	R-Cl	**2a** (equiv)	yield (%)	dr[a]
1	MeCN	CbzCl, 2 equiv	1.1	10	>95:5
2	MeCN	CbzCl, 1.1 equiv	2	76	>95:5
3	Et_2O	CbzCl, 1.1 equiv	2	41	>95:5
4	THF	CbzCl, 1.1 equiv	2	36	>95:5
5	CH_2Cl_2	CbzCl, 1.1 equiv	2	71	>95:5
6[b]	MeCN	CbzCl, 1.1 equiv	2	89	>95:5
7[b]	MeCN	TsCl, 1.1 equiv	2	0	

[a] Measured by ^{1}H NMR. [b] The three components were mixed together at the same time.

Finally, it was found that mixing the three reagents together in one-pot fashion instead of sequentially gave the highest yield of **5i** (89%) with no deleterious effect on the diastereoselectivity (entry 6). However, use of tosyl chloride instead of Cbz chloride under these same one-pot conditions did not give the expected addition product **5j** (entry 7). These optimal one-pot reaction conditions were then applied to isoquinoline derivatives substituted on positions other than C-1 and using either CbzCl or TsCl as the electrophile (Table 3). Thus, while reaction of 3-cyanoisoquinoline **4c**, CbzCl, and silyloxyfuran **2a** provided a good yield (58%) and high dr (>99:1) of the expected product **5k** (entry 1), no reaction was observed in the presence of TsCl (entry 2), a result similar to that observed with 1-methylisoquinoline **4b** (Table 2, entry 7), suggesting that steric factors inhibit the reaction in both cases. In support of this, use of the less sterically hindered 4-bromoisoquinoline **4d** as the substrate provided high yields in the presence of CbzCl (**5m**, 94%) or of TsCl (**5n**, 95%) with dr = 92:8 and dr = 90:10, respectively (entries 3 and 4). Similarly, 5-nitroisoquinoline **4e** and 6,7-dimethoxyisoquinoline **4f** reacted with **2a** in the presence of either electrophile to give 80−90% yields of the corresponding products **5o**−**r** with consistently high diastereoselectivities (entries 5−8). Taken together, these results indicate that while steric factors can negatively affect the outcome of these vinylogous Mannich reactions, the electronic character of the substituents on the isoquinoline nucleus has little influence, high yields and dr's being obtained whether these are electron-withdrawing or -donating.

Table 3. Variation of the Isoquinoline Substrate



entry	isoquinoline	R-Cl	product	yield (%)	dr[a]
1	3-cyano **4c**	CbzCl	**5k**	58	>99:1
2		TsCl	**5l**	0	
3	4-bromo **4d**	CbzCl	**5m**	94	92:8
4		TsCl	**5n**	95	90:10
5	5-nitro **4e**	CbzCl	**5o**	90	>96:4
6		TsCl	**5p**	88	87:13
7	6,7-dimethoxy **4f**	CbzCl	**5q**	80	89:11
8		TsCl	**5r**	81	91:9

[a] Measured by HPLC.

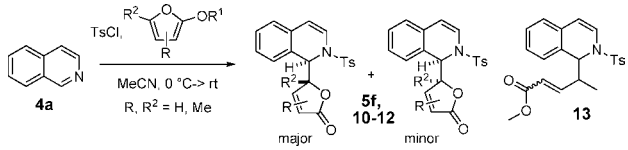
The scope of the reaction with respect this time to the nature of the vinylogous silyl enol ether was then studied using isoquinoline **4a** and TsCl as components and the same conditions. As shown in Table 4, no difference in yield (89%, 90%) and dr (93:7) was seen in the formation of product **5f** whether the TBS or TMS ethers **2a** or **2b**, respectively, were used (entries 1 and 2), while a slight decrease in yield of **5f** (81%) was observed using the TIPS ether **2c** but with no change in dr (93:7, entry 3). While a methyl group at C_3 of

(14) The X-ray crystal structure determination of the major isomers of compounds **5a**, **12**, **14**, **15** (see the Supporting Information) and of **10** (unpublished results) showed that these correspond to the *R**,*R** diastereoisomers. This allowed correlation to ^{1}H NMR data in which the difference in $H_{1'}$ and H_5 ppm values ($\Delta(\delta)$) for the major diastereomers was consistenly larger than for the minor diastereomers, while inversely, the $H_{1'}$, H_5 coupling constants for the major diastereomers were smaller (usually in the 4.8−5.8 Hz range) than for the minor diastereomer (typically in the 6.5−8.0 Hz range). The same trends were observed in the vinylogous Mannich products for which X-ray crystal structures are not available, thereby allowing attribution of their relative stereochemistry.

(15) While the absolute configuration of the major isomer of compound **5h** has not yet been determined with certainty, the observation by Ohsawa (ref 7a) that the (*S*)-valine-derived chiral auxiliary gives the Mannich product having the *R* configuration at C_1 of isoquinoline combined with our observation that the major product formed in the vinylogous Mannich reaction has the *R**,*R** configuration strongly suggests that **5h** therefore has the *R*,*R* configuration.

(16) The absence of a proton at $C_{1'}$ of **5i** precludes use of the technique of ref 15 for attribution of the relative configuration.

Table 4. Variation of the Silyl Enol Ether



entry	silyl enol ether	product	yield (%)	dr[a]
1	**2a**	**5f**	90	93:7
2	OTMS **2b**	**5f**	89	93:7
3	OTIPS **2c**	**5f**	81	93:7
4	OTBS **6**	**10**	88	93:7
5	OTBS **7**	**11**	54	60:40
6	OTBS **8**	**12**[b]	77	76:24
7	OTBS (E)(Z) **9**	**13**	48	13:9:12:63

[a] Measured by ^{1}H NMR. [b] Confirmed by X-ray crystallography (see the Supporting Information).

the furan ring (**6**) maintained a high product yield (88%) and dr (93:7) (entry 4), the presence of the same group at C_4 (**7**) or C_5 (**8**) resulted in both lower yields (54% and 77%) and dr's (60:40 and 76:24) of the corresponding products **11** and **12**, respectively (entries 5 and 6). Finally, when the reaction was conducted with the acyclic vinylogous enol ether **9**, an inseparable mixture of at least four diastereoisomers of the expected vinylogous Mannich products was obtained (**13**, entry 7).

In order to explain the origin of the observed high diastereoselectivity, the transition-state structures (TS) of the reaction of silyloxyfuran with *N*-tosylisoquinolinium and *N*-tosyldihydroisoquinolinium were located and optimized using a semiempirical orbital molecular method at the RHF/AM1 level.[17,18]

HOMO and LUMO coefficients analysis for favored TS revealed favorable orbital overlaps between the silyloxyfuran and the $C_{3'}-C_{4'}$ double bond of *N*-tosylisoquinolinium which is not present in the *N*-tosyldihydroisoquinolinium TS (see the Supporting Information). These stabilizing interactions seem to be responsible for the observed high dr in the case of the fully aromatic isoquinolinium salts (Figure 1).

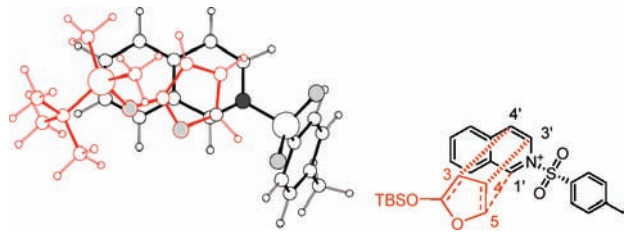
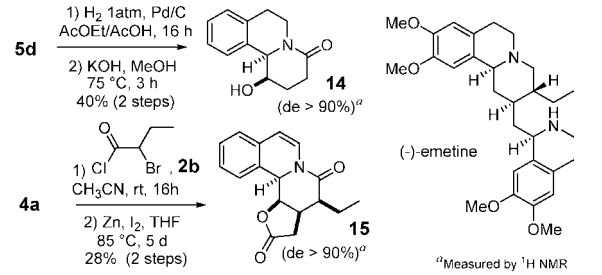


Figure 1. Calculated preferential transition state for silyloxyfuran attack on *N*-tosylisoquinolinium.

The introduction of a butyrolactone moiety at C_1 of the isoquinoline ring system allows for considerable synthetic opportunities. An example is that illustrated in Scheme 2

Scheme 2. Applications



wherein adduct **5d** was efficiently converted into the benzo[*a*]quinazoline **14**.[19] Thus, palladium/carbon-catalyzed hydrogenation of **5d** in ethyl acetate/acetic acid resulted in simultaneous reduction of the 3,4-double bonds of the isoquinoline and lactone moieties and hydrogenolytic cleavage of the Cbz group in 64% yield. Treatment of the product with KOH in refluxing methanol then led to the cyclized product **14** in 62% yield. Alternatively, reaction of isoquinoline, 2-bromobutanoyl chloride, and **2b** in acetonitrile followed by treatment with zinc/iodine provided compound **15**, the core structure of emetine, an antitumor alkaloid.[3j,20] The structures of both **14** and **15** were confirmed by X-ray crystallographic studies (see the Supporting Information).

In conclusion, we have discovered that the three-component vinylogous Mannich reaction of silyl enol ethers derived from butyrolactones and of isoquinolines in the presence of an acylating or sulfonylating agent is high yielding and highly diastereoselective even in the case of the formation of a chiral quaternary center. Use of a chiral acylating agent such as the acid chloride derived from *N*-phthaloylvaline then allows almost complete stereoselectivity with formation of essentially a single stereoisomer. The transformation of these substrates into a variety of isoquinoline-based alkaloid natural products is an objective which is presently being pursued.

Supporting Information Available: Experimental details, characterization data, and spectra (^{1}H and ^{13}C NMR) for new compounds, crystallographic data for compounds **5a**, **12**, **14**, and **15**, and HPLC chromatograms for compounds **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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