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Tetrahedron Letters 45 (2004) 9277–9280
Tetrahedron Letters

A complementary method to obtain *N*-acyl enamides using the Heck reaction: extending the substrate scope for asymmetric hydrogenation

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Received 19 August 2004; revised 7 October 2004; accepted 12 October 2004
Available online 22 October 2004

Abstract—A method to prepare *N*-acyl enamides is reported that is complementary to the existing protocols. Heck reaction of a variety of aryl trifluoromethanesulfonates with commercially available *N*-vinylacetamide occurred in a highly regioselective fashion to provide these valuable synthetic intermediates. This method permits the formation of *N*-acyl enamides containing functionality that would not be tolerated by the existing methods. Asymmetric hydrogenation using [diphosphine RhCOD]BF_4 complexes provided optically active protected amines in up to 99% ee. De-acylation occurs without affecting the amine enantiopurity.

Enantiomerically pure amines are valuable building blocks for organic synthesis and serve as resolving agents, chiral auxiliaries and ligands for many useful transformations. Consequently, methods to obtain amines of high enantiomeric purity are of considerable interest. Although there has been considerable progress in the enantioselective reduction of imines,[1] the asymmetric hydrogenation of *N*-acyl enamides to produce amines of high enantiopurity is still widely practiced. This indirect method to obtain optically active amines is favoured by a number of factors such as a range of preparative methods for forming *N*-acyl enamides,[2] substrate stability and the tolerance of *E*/*Z* mixtures in highly efficient catalytic asymmetric hydrogenations.[3] Although there are several efficient methods for the formation of *N*-acyl enamides (Fig. 1), they suffer from harsh reaction conditions or the use of reagents and substrates that preclude the incorporation of certain functional

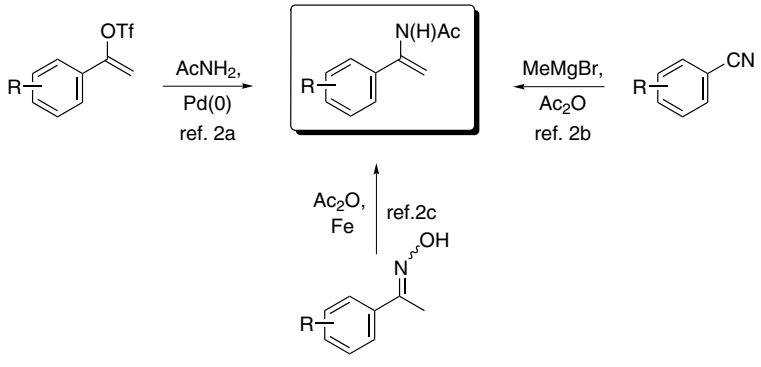

Figure 1. Existing methods to prepare aryl *N*-acyl enamides.

Keywords: *N*-Acyl enamides; Heck reaction; Asymmetric hydrogenation.
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doi:10.1016/j.tetlet.2004.10.063

groups such as ketones, esters and nitriles. We herein report a complementary method for producing *N*-acyl enamides. Furthermore, we also describe the asymmetric hydrogenation of these substrates.

The existing methods to obtain aryl *N*-acyl enamides rely on the presence of functionality that is converted into the enamide unit. An alternative approach to construct this class of compound is based on the functionalisation of a pre-existing *N*-acyl enamide (Fig. 2). This approach involves the regioselective coupling of the *N*-acyl enamide unit to an activated aryl species.

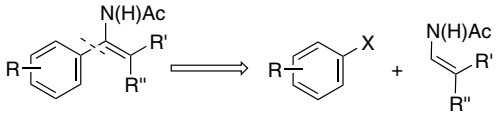
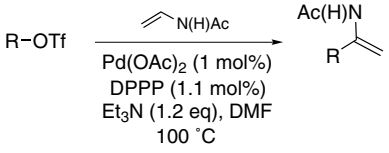
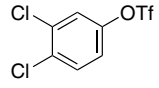
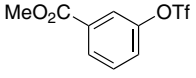
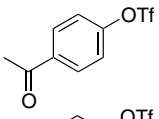
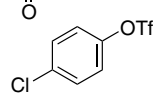
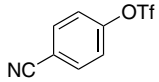
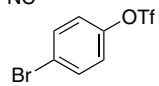
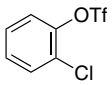


Figure 2. Approach to *N*-acyl enamides.

A series of aryl trifluoromethanesulfonates containing a variety of pendant functional groups were prepared from commercially available phenols under standard conditions.[4] Purification was achieved by distillation or solvent slurry. Highly regioselective Heck reactions with tertiary *N*-vinylacetamides have been reported by Cabri et al.[5] and Larhed and co-workers.[6] The conditions described by Cabri et al. were extended to commercially available *N*-vinylacetamide (Table 1), allowing access to non-alkyl substituted primary amines after a simple deprotection.

Table 1. Heck reactions to provide *N*-acyl enamides



Entry	R-OTf	Yield[a] (%)
1		62
2		69
3		40
4		64
5		55
6		24
7		63

[a] Isolated yield.

Consistent with the original report on the Heck reaction of aryl trifluoromethanesulfonates with unsymmetrical olefins, high regioselectivity was observed.[5] Analysis of the crude reaction products by ^{1}H NMR spectroscopy indicated >19:1 ratio of regioisomers in the majority of cases and the minor regioisomer could be easily removed by flash column chromatography or solvent slurry. Replacement of DPPP with triphenylphosphine did not result in any observable Heck reaction, which is consistent with the previous results.[5]

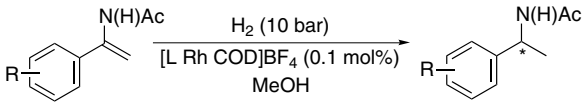
This method works well for the preparation of aryl-*N*-acyl enamides, which are obtained in moderate to good yields. No optimisation was carried-out and all the Heck reactions were performed under the originally reported conditions. The low yield observed with the *para*-bromo substituted trifluoromethanesulfonate can be understood in terms of the similar reactivity of the bromide and trifluoromethanesulfonate functionalities towards palladium insertion (entry 6).[7] Recent improvements in the field of palladium catalysed cross-coupling reactions of aryl chlorides[8] renders the chloro-substituted products particularly useful (entries 4 and 7). Although not examined in this study, further functionalisation of the *N*-acyl enamides obtained could be envisaged.

The limitations of this method were demonstrated by the lack of reaction observed under these conditions with a number of substrates. The enol trifluoromethanesulfonates derived from ethyl acetoacetate decomposed under the reaction conditions whilst reaction with methyl 3-acetylaminoacrylate only resulted in isomerisation of the olefin geometry. Aryl trifluoromethanesulfonates containing nitro groups in the *meta* or *para* positions were not reactive under the conditions employed.

The asymmetric hydrogenation of the *N*-acyl enamides obtained was examined using a selection of [diphosphine RhCOD]BF_4 complexes and the catalyst providing the highest enantioselectivity for each substrate was identified (Table 2). The diphosphines studied were Me-DuPhos, Et-DuPhos, Me-BPE, Et-BPE and Ph-BPE. These initial reactions were performed using 0.1 mol% of the rhodium complex.

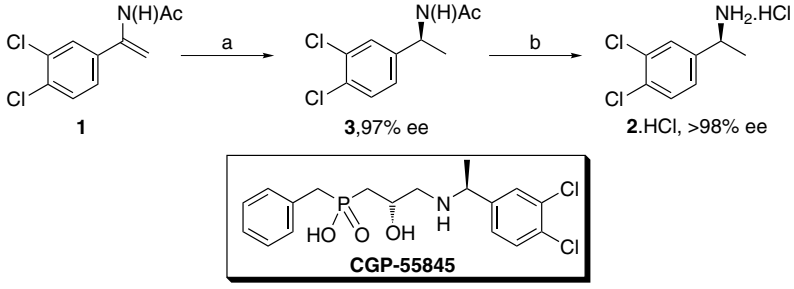
In all cases, with the exception of the *ortho*-chloro substituted aryl *N*-acyl enamide (entry 7), excellent conversions and enantioselectivities were observed. The absolute stereochemistry of the amines obtained has been tentatively assigned based upon the well-documented behaviour of the DuPhos and BPE ligand family.[3] For substrates containing a ketone, the Lewis acidic catalysts can promote ketal formation and the addition of water as a co-solvent is necessary in order to prevent the formation of this by-product (entry 3). It is notable that in many cases the recently introduced Ph-BPE[9] was identified as the optimal ligand and with several of the substrates this provided far superior results compared to the alternatives examined.

Table 2. Asymmetric hydrogenation of aryl *N*-acyl enamides



Entry	R	L	Temp (°C)	Conv. (%)[a]	ee (%)[b,c]
1	3,4-Cl_2	(*S*,*S*)-Et-DuPhos	40	>98	98 (*S*)
2	3-CO_2Me	(*S*,*S*)-Ph-BPE	40	>98	98 (*R*)
3[d]	4-COMe	(*S*,*S*)-Et-DuPhos	30	>98	97 (*S*)
4	4-Cl	(*S*,*S*)-Ph-BPE	40	>98	99 (*R*)
5	4-CN	(*S*,*S*)-Ph-BPE	40	>98	99 (*R*)
6	4-Br	(*S*,*S*)-Ph-BPE	40	>98	99 (*R*)
7	2-Cl	(*S*,*S*)-Et-BPE	40	86	85 (*S*)

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by HPLC or GC (for details see supplementary data).
[c] Absolute stereochemistry tentatively assigned (see text).
[d] Water used as co-solvent (10% v/v).



Scheme 1. Synthesis of **2**·HCl, a potential intermediate to CGP-55845. Reagents and conditions: (a) [(*S*,*S*)-Et-DuPhos RhCOD]BF_4 (0.02 mol%), H_2 (10 bar), MeOH, 40 °C; (b) 6 M HCl, EtOH, 100 °C, 86% overall.

In order to evaluate the synthetic potential of this methodology and encouraged by the screening results obtained, the enantioselective hydrogenation of the *N*-acyl enamide **1** leading to (*S*)-1-(3,4-dichlorophenyl)ethylamine **2** was examined in more detail (Scheme 1). This amine is a potential intermediate to CGP-55845, a GABA-B antagonist that is under investigation by Novartis as a potential treatment for epilepsy.[10] Although we determined that the highest enantioselectivity was provided by a catalyst containing (*S*,*S*)-Et-DuPhos (Table 2, entry 1), there was little distinction between the enantioselectivity associated with this ligand and the others examined for this substrate. However, determination of the relative rates of hydrogenation indicated that the catalyst containing (*S*,*S*)-Et-DuPhos was by far the most active of those examined. The asymmetric hydrogenation was therefore scaled-up and **3** was obtained in a quantitative fashion with 97% ee when performed using 0.02 mol% of [(*S*,*S*)-Et-DuPhos RhCOD]BF_4. At a hydrogen pressure of 10 bar, a temperature of 40 °C and concentration of 0.3 M, the hydrogenation was complete within 80 min.

Treatment of **3** with 6 M hydrochloric acid in refluxing ethanol provided the hydrochloride salt of **2** in 86% overall yield from the *N*-acyl enamide **1**.[11] The enantiopurity was determined to be >98% ee, indicating that although these deprotection conditions are relatively harsh, no racemisation occurs. Formation of the salt **2**·HCl resulted in a small increase in the enantiopurity.

In summary, we have reported a method for producing *N*-acyl enamides that is complementary to the existing methods. This method is compatible with the presence of functional groups such as ketones, esters and nitriles that are not tolerated by the existing methods illustrated in Figure 1. This method introduces substituted phenols as an alternative source of functionalised *N*-acyl enamides. Asymmetric hydrogenation using [diphosphine RhCOD]BF_4 complexes provided optically active amines in up to 99% ee. In many cases the optimal diphosphine was demonstrated to be the recently introduced Ph-BPE. The value of this chemistry was demonstrated by the synthesis of an intermediate to a potential drug candidate. Asymmetric hydrogenation catalysed by [(*S*,*S*)-Et-DuPhos RhCOD]BF_4 proceeded with excellent enantioselectivity (97% ee) and was followed by acetate hydrolysis, which occurred with no detectable effect upon the enantiopurity. The combination of *N*-acyl enamide formation and asymmetric hydrogenation offers a powerful way to access a wide variety of highly enantiomerically enriched amines.

Acknowledgements

We thank Dr. Ian Lennon for useful discussions.

Supplementary data

Analytical methods for determination of the enantiopurity of the acylamines are available in the supplementary data accompanying this paper, in the online version, at doi:10.1016/j.tetlet.2004.10.063.

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4. Representative procedure: trifluoromethanesulfonic anhydride (17.1 mL, 101 mmol) was added in a dropwise manner, at a rate such that the temperature did not exceed 15 °C, to a stirred solution of 3,4-dichlorophenol (15.0 g, 92.0 mmol) and triethylamine (15.9 mL, 120 mmol) in dichloromethane (100 mL) under a nitrogen atmosphere. Once the addition was complete the mixture was warmed to room temperature. After 18 h, the mixture was diluted with MTBE (150 mL), sequentially washed with saturated ammonium chloride solution (2×100 mL), 2 M sodium carbonate (2×100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo to provide 3,4-dichloro-1-trifluoromethanesulfonyloxy-benzene as a light yellow liquid (27.8 g), which was used in the next step without further purification. ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.55 (1H, d, J 8 Hz), 7.42 (1H, d, J 2 Hz), 7.17 (1H, dd, J 8 and 2 Hz); ^{19}F NMR δ (376 MHz, $CDCl_3$) −73.
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11. Experimental procedure: the *N*-acyl enamide **1** (6.35 g, 27.6 mmol) and methanol (80 mL) were charged to a glass liner and secured in a 300 mL Parr pressure reactor. The vessel was charged with nitrogen to a pressure of 10 bar, stirred (800 rpm) and after 15 min vented. The mixture was heated to 40 °C and the nitrogen charge-vent cycle repeated twice. Stirring was stopped and a freshly prepared solution of [(*S*,*S*)-Et-DuPhos RhCOD]BF_4 in deoxygenated methanol (5 mL of a 0.0011 M solution, 0.0055 mmol) was then added. The vessel was charged with hydrogen to a pressure of 10 bar and subsequently vented. This hydrogen charge-vent cycle was repeated twice and the vessel was then charged with hydrogen to a pressure of 10 bar and stirring initiated. The hydrogen pressure was maintained between 8.3 and 10 bar and once consumption ceased, the vessel was vented and the mixture concentrated in vacuo to provide the amine **3**, which was used without further purification. Hydrochloric acid (45 mL of a 6 M solution in water, 270 mmol) was added to a solution of the amine **3** in ethanol (15 mL). After heating at reflux for 17 h further hydrochloric acid (15 mL of a 6 M solution in water, 90 mmol) was added and heating was continued for a further 4 h. The mixture was concentrated in vacuo and the residue was redissolved in ethanol (60 mL) and concentrated in vacuo. This procedure was repeated twice and the residue was then slurried in dichloromethane/MTBE (50 mL, 1:3 v/v). Isolation by filtration followed by drying in vacuo (40 °C, 35 mbar) provided **2**·HCl as an off-white solid (5.34 g, 86% overall). ^{1}H NMR δ (400 MHz, DMSO) 8.41 (2H, br s), 7.68 (1H, s), 7.56 (1H, d, J 8 Hz), 7.35 (1H, d, J 8 Hz), 4.28 (1H, q, J 6 Hz) and 1.32 (3H, d, J 6 Hz). **2**·HCl (4 mg) was dissolved in MTBE (2 mL) and washed with 2 M NaOH (2 mL). GC analysis of the MTBE solution indicated >98% ee (Chirasil Dex-CB, Helium (20 psi), 100 °C for 30 min ramped to 200 °C at 5 °C/min, (*S*)-**2**·HCl: 40.5 min, (*R*)-**2**·HCl: 40.4 min).