Tetrahedron Letters 55 (2014) 6354–6358

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of enantiopure β-amino amides via a practical reductive amination of the corresponding β-keto amides

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ARTICLE INFO

Article history:
Received 7 June 2014
Revised 28 August 2014
Accepted 24 September 2014
Available online 2 October 2014

Keywords:
β-Keto esters
β-Keto amides
Reductive amination
β-Amino amides
Microwave

ABSTRACT

A convenient and efficient reductive amination for the preparation of chiral β-amino amides is developed utilizing microwave heating. A variety of chiral β-keto amides react with ammonium acetate and sodium cyanoborohydride to afford the desired functionalized amines in good yields. This improved procedure takes advantage of microwave heating to significantly accelerate the reaction and offers a convenient and effective method to access some interesting molecules containing primary amine functionalities.

Amino- and amido-functionalized organic compounds are very common in Nature. Their biological importance[1] has led to extensive studies of their structural and physicochemical properties.

In addition to their relevance in biochemistry and pharmaceutical chemistry, amines and amides are attractive building blocks in supramolecular chemistry.[2] Depending on the solution pH, amine-based ligands can act as both cation and anion chelators.[3]

Amide-containing receptors also exhibit dual cation/anion binding properties. They have emerged as attractive building blocks for a variety of anion receptors due to their relatively strong hydrogen bond donor N–H groups.[3] In addition, they contain oxygen and nitrogen heteroatoms that can coordinate with metal ions.[4]

On the other hand, β-amino amide subunits are found in numerous pharmaceuticals and are often found as constituents of important building blocks of many natural products that express potent biological activity.[5]

Prominent examples of amino amides have recently emerged, underscoring their importance in medicinal chemistry.[6] Among them are saxagliptin and compounds **2a** and **2b**[7] (Fig. 1). Furthermore, a series of β-amino amides bearing triazolopiperazines has been prepared and evaluated as potent, selective, orally active dipeptidyl peptidase IV (DPP-4) inhibitors for the treatment of type 2 diabetes, with Januvia™ (sitagliptin phosphate) (**1**) as an example)[6a,8] (Fig. 1).

Bestatin (**3**) is a prototypical member of a growing family of peptidyl α-hydroxy-β-amino amide natural products isolated from bacterial cultures that demonstrate potent inhibition of aminopeptidases and prolyl endopeptidases.[9]

Due to their roles in various key industries, useful synthetic approaches have been reported[10] for the synthesis of this class of compounds. Most have involved coupling of tetrahydrotriazolopyrazine with β-amino acids,[11] acylation of amines with (3*R*)-*N*-Boc-β-amino acids using a coupling reagent such as TsCl with *N*-methylimidazole,[6b] or acid-catalysed hydrolysis of the resulting

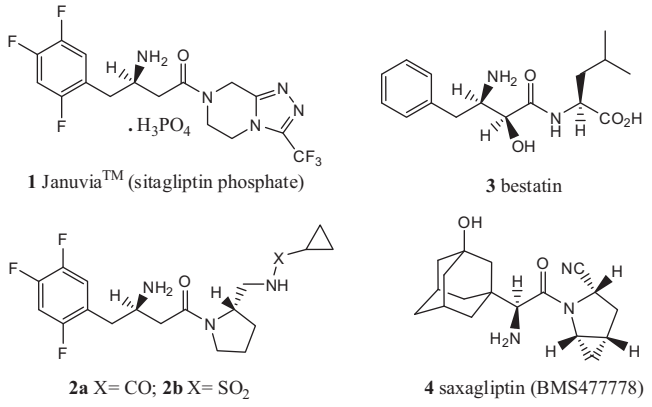

Figure 1. Representative examples of biologically active α- and β-amino amide derivatives.

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http://dx.doi.org/10.1016/j.tetlet.2014.09.111
0040-4039/

β-amino esters, HOBt/EDC-mediated coupling with the triazolopyrazine fragment, and hydrogenolysis.[12]

In addition, the Passerini reaction of N-protected amino aldehydes, isonitriles, and TFA using pyridine-type bases proceeds under mild conditions and affords directly α-hydroxy-β-amino amide derivatives in moderate to high yields.[13]

Recently, the conjugate addition of *O*-benzylhydroxylamine to a 3,5-dimethylpyrazole-derived enoate has been disclosed in good yield using a catalytic amount of a chiral Lewis acid.[10b]

However, no attention has been given to the stereoselective reductive amination of chiral β-keto amide derivatives. Hence, in continuation of our research aimed toward the preparation of natural and non-natural compounds of biomedical importance,[14] and in connection with ongoing investigations on the synthesis and reactivity of β-keto esters,[15] we report herein an efficient and simple methodology for the synthesis of the novel chiral β-amino amides **8** via reductive amination of the previously[16] synthesized β-keto amides **7** (Scheme 1).

The starting β-keto esters **6** were prepared from the commercially available acetophenone derivatives **5** in the presence of sodium hydride and dimethyl carbonate, as previously described[15] (Scheme 1).

The β-keto amides **7** were synthesized by reacting β-keto esters **6** with different commercially available chiral amines in refluxing non-polar solvents such as toluene. The resulting products were obtained in excellent yields and interestingly, the stereogenic center did not undergo any racemization. A single crystal X-ray crystal structure[17] was obtained for 3-(4-fluorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide (**7a**) (Fig. 2).

The conversion of β-keto amides **7** into the corresponding β-amino derivatives **8** was accomplished by means of diastereoselective reductive amination utilizing microwave heating (Scheme 2).

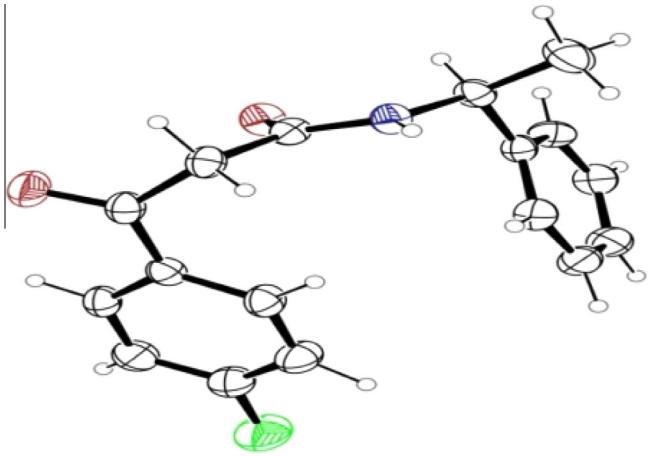
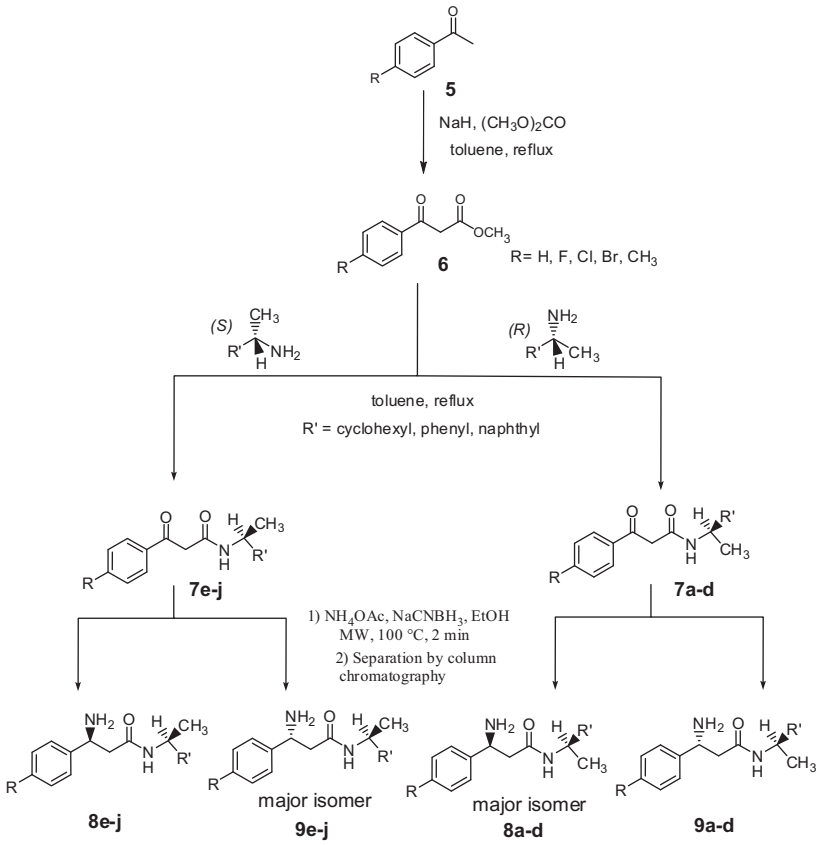


Figure 2. ORTEP representation of 3-(4-fluorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide (**7a**). Thermal ellipsoids are drawn at 50% probability.

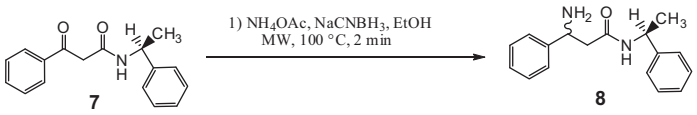
Because of the added attraction of a concise approach amenable to a one-pot protocol,[18] we explored a variety of reaction conditions to find the optimum conditions. The initial screening of the reaction conditions is summarized in Table 1.

Reaction of 3-oxo-3-phenyl-*N*-[(*R*)-1-phenylethyl]propanamide (**7d**) with 15 equiv of NH_4OAc and 1.2 equiv of $NaCNBH_3$ in methanol at 90 °C for 2 min failed to give any significant quantities of the anticipated product, affording mostly recovered starting material (entry 1).

Increasing the reaction time to 5–10 min did not improve the conversion (entries 2 and 3). Using ethanol as the solvent allowed



Scheme 1.



Scheme 2.

Table 1
Microwave-accelerated reductive amination of 3-oxo-3-phenyl-*N*-[(*R*)-1-phenylethyl]propanamide (**7d**)[a]

Entry	Procedure	NH_4OAc (equiv)	Solvent	Temp (°C)	Time (min)	Yield[c] (%)	de (%)[d] (3*S*), *N*-(*R*)/(3*R*), *N*-(*R*)[e]
1	MW[b] heating	15	MeOH	90	2	7	—
2	MW heating	15	MeOH	90	5	10	—
3	MW heating	15	MeOH	90	10	14	—
4	MW heating	15	EtOH	90	2	64	12
5	MW heating	15	EtOH	100	2	72	12
6	MW heating	10	EtOH	100	2	61	12
7	conventional heating	15	EtOH	90	10 (h)	40	10

[a] $NaCNBH_3$ (1.2 equiv), solvent (10 mL), β-keto amide (1 equiv).
[b] Irradiation was carried out using a Milestone Ethos microwave apparatus with an internal temperature sensor, a 640–260 terminal with easy control software installed and a Pro 24/16 high throughput rotor. The emitted power was monitored (between 15 and 1000 W) to maintain a constant temperature.
[c] Isolated yield based on the starting β-keto amide.
[d] Determined by ^1H NMR spectroscopy of the crude reaction mixture.
[e] The absolute configuration of the major isomer [3*S*,*N*-(*R*)] was assigned by comparing the sign of the observed specific rotations with that obtained after asymmetric hydrogenation of 3-oxo-3-phenyl-*N*-[(*R*)-1-phenylethyl]propanamide at atmospheric pressure by using in situ generated {$RuBr_2$[(*R*)-BINAP]} and Mitsunobu amination reaction of the corresponding β-hydroxy amide. We assumed that asymmetric hydrogenation follows the same stereochemical outcome as above according to the stereochemical model proposed for the hydrogenation of β-keto amides with ruthenium-arylphosphine catalysts.[16]

Table 2
Reactions of various β-keto amides **7**

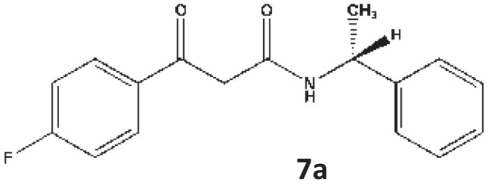
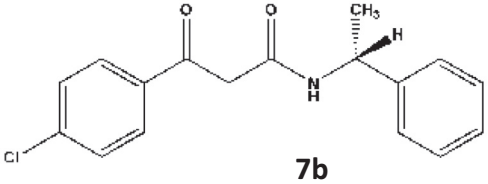
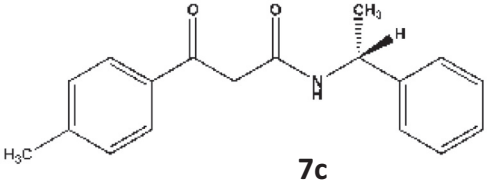
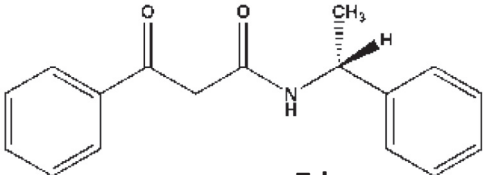
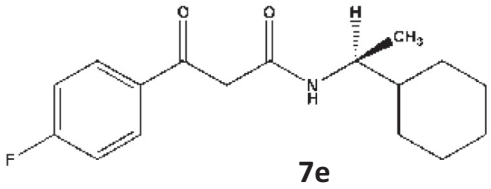
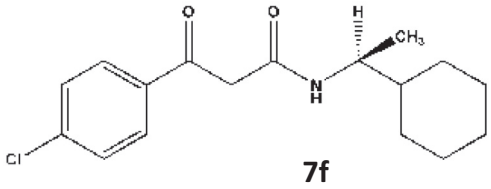
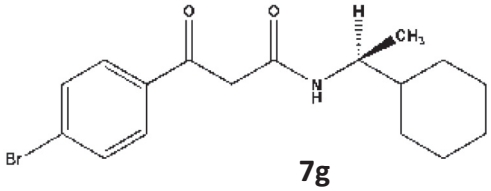
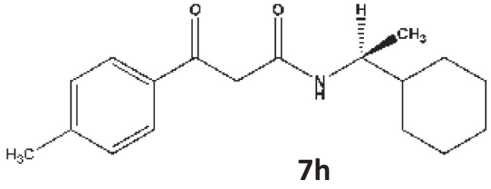
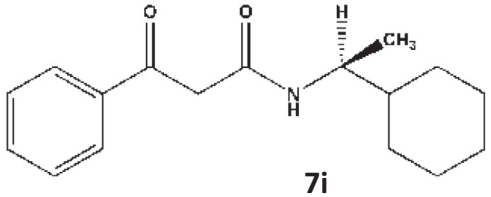
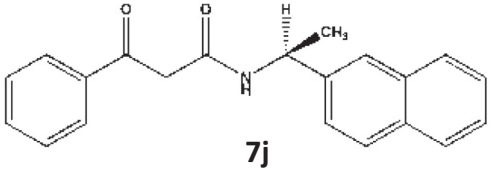
Entry	Substrate	Yield of **8** (%)	de (%)[a] (conf.)[b]
1	 **7a**	84	10 (3*S*), *N*-(*R*)
2	 **7b**	79	9 (3*S*), *N*-(*R*)
3	 **7c**	67	6 (3*S*), *N*-(*R*)
4	 **7d**	63	12 (3*S*), *N*-(*R*)

Table 2 (*continued*)

Entry	Substrate	Yield of **8** (%)	de (%)[a] (conf.)[b]
5	 **7e**	86	5 (3*R*), *N*-(*S*)
6	 **7f**	84	4 (3*R*), *N*-(*S*)
7	 **7g**	71	9 (3*R*), *N*-(*S*)
8	 **7h**	64	8 (3*R*), *N*-(*S*)
9	 **7i**	62	14 (3*R*), *N*-(*S*)
10	 **7j**	68	11 (3*R*), *N*-(*S*)

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[b] Configuration of the major corresponding amino amide product eluted first by column chromatography.

us to explore how higher temperatures would affect the reaction. At 100 °C, the reaction proceeded smoothly to give a 72% yield of the desired amino amide in only 2 min (entry 5). Encouraged by this result, a lower amount of NH_4OAc (10 equiv) and short reaction time (2 min) was investigated. Unfortunately, the reaction yield suffered in this case (entry 6).

In order to check the possible intervention of specific non-purely thermal MW effects,[19] conventional thermal conditions were compared to microwave heating. When the reaction was heated for 10 hours in a sealed tube at 90 °C using a controlled oil bath, we obtained only a 40% isolated yield of a separable mixture of **8d** (entry 7) with complete consumption of the β-keto amide **7d**, however, only moderate diastereoselectivity was observed (de = 10%).

Under similar temperature conditions, it was found that the reaction under microwave irradiation proceeded with a considerably higher yield (64%) in a very short reaction time (2 min, entry 4), demonstrating that the effect of microwave irradiation was evidently not only purely thermal.

With optimized conditions in hand,[20] we proceeded to investigate the reductive amination reaction using a variety of β-keto amides **7** and the results are summarized in Table 2. In most cases, good to excellent yields were obtained and the reactions proceeded in the presence of a variety of substituted phenyl rings. The yields were good for substrates with phenyl rings containing chlorine, bromine, or fluorine groups at the *para*-positions (entries 1, 2, 5, 6, and 7), but were lower for unsubstituted phenyl rings (entries 4 and 9). There was little influence imparted by an electron-donating methyl substituent (entries 3 and 8).

The most important specific microwave effect was observed in the case of 3-(4-fluorophenyl)-3-oxo-*N*-[(1*R*)-1-cyclohexylethyl]propanamide (entry 5).

The microwave effects are important and noticeably depend on the nature of the amine substituent, R = phenyl, cyclohexyl, and naphthyl (entries 4, 9, and 10).

In summary, we have described an effective procedure for the diastereoselective synthesis of β-amino amides **8** by means of reductive amination of the corresponding enantiopure β-keto amides **7** utilizing microwave heating. The process works well, is very simple and inexpensive, and easily available starting materials are used. We feel that this new strategy toward β-amino amides will be convenient for the enantioselective synthesis of many biologically interesting molecules containing primary amine functionalities. Further studies along these lines are in progress

Acknowledgments

The authors are grateful to the DGRSRT (Direction Générale de la Recherche Scientifique et de la Rénovation Technologique) of the Tunisian Ministry of Higher Education, Scientific Research and Technology for financial support. We also thank Prof. Abdelhamid Ben Salah, Laboratory Manager of M.E.S.Lab. Faculté des Sciences de Sfax and Dr. Taha Guerfel, Dr. Khaled Walha and Dr. Makki Abdmouleh for their help in the determination of crystal structure.

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17. CCDC 999273 contains crystallographic data for 3-(4-fluorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide (**7a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223336033; e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk). The molecular formula = $C_{17}H_{16}F_1N_1O_2$, belongs to a monoclinic system, space group = P21, parameters of the unit cell are: a = 9.6297 (8) Å, b = 14.6306 (13) Å, c = 10.7151(10) Å, β = 93.789(6)°, Z = 2.
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20. *General procedure for the preparation of β-amino amides*: A mixture of NH_4OAc (513.5 mg, 6.66 mmol) and $NaCNBH_3$ (33.5 mg, 0.533 mmol) was added to a solution of 3-(4-chlorophenyl)-3-oxo-*N*-[(*R*)-1-phenylethyl]propanamide (**7b**) (133 mg, 0.444 mmol) in EtOH (10 mL) in a 100 mL microwave vial. The mixture was stirred and heated at 100 °C for 2 min in a microwave reactor (Milestone Ethos apparatus). The mixture was concentrated to remove most of the EtOH, treated with 2 M NaOH until pH >10, and extracted with EtOAc (2 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give 105 mg (79%) of a mixture of (*R*) and (*S*)-3-amino-3-(4-chlorophenyl)*N*-[(*R*)-1-phenylethyl]propanamide as a white solid, which was separated by column chromatography ($MeOH/CH_2Cl_2$, 5:95). Compound **8b**: mp = 133 °C; ^1H NMR ($CDCl_3$, 300 MHz, 27 °C): δ = 7.25–7.09 (m, 9H), 6.9 (d, J = 7.5 Hz, 1H, NH), 4.95 (q, J = 6.9 Hz, 1H), 4.25 (dd, J = 6.0, 7.2 Hz, 1H), 2.36 (dd, J = 7.5, 1.8 Hz, 2H), 1.79 (s, 2H), 1.36 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): δ = 169.3, 142.8, 142.7, 132.4, 128.2, 128.1, 126.9, 126.7, 125.5, 52.0, 48.1, 45.0, 21.4. IR (KBr): ν = 3355–3313 cm^{-1} (ν_{NH} + ν_{NH2}), 2970 cm^{-1} (ν_{C-H}), 1644 cm^{-1} (ν_{COO}), 1536 cm^{-1} ($\nu_{C=C}$). Anal. Calcd for $C_{17}H_{19}ClN_2O$: C, 67.43; H, 6.32; N, 9.25. Found: C, 67.48; H, 6.25; N, 9.37. MS (CI/NH_3): m/z = 303 (MH^+, 100% (^{35}Cl)), 305 (MH^+, 33% (^{37}Cl)).