A One-Pot Synthesis of Omarigliptin and its Analogues via Stabilized *beta*-Amino Ketone Intermediate

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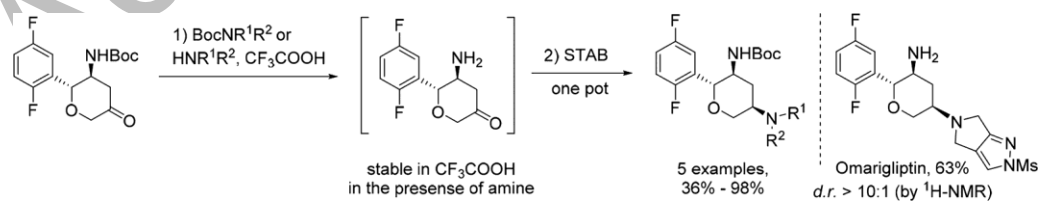
Abstract

We have discovered a unique stabilization condition for *beta*-amino ketone **7**. With compound **7** as an unprecedented intermediate, Omarigliptin **1** could be prepared in a highly efficient one-pot procedure with good yield. Also with this intermediate **7**, some analogues of Omarigliptin **1** were readily prepared for the first time.

Graphical Abstract



KEYWORDS: omarigliptin, *beta*-amino ketone, reductive amination, one pot synthesis, stabilization effect

1. INTRODUCTION

Among different therapeutic targets against type 2 diabetic mellitus, DPPIV (DiPeptidyl Peptidase IV) has proved highly successful, and attracted much attention from drug design community through process chemists. Being one of the latest DPPIV inhibitors, Omarigliptin **1** [1] features a unique *C*-glycoside scaffold, and efficient preparation of this compound is challenging. To date, all reported methods to **1** started from pyrazole **2** and ketone **3**.[1,2] In a proprietary process,[2b,c] the Boc-protection on compound **2** was removed with benzene sulfonic acid to yield salt **4**, which underwent reductive amination with ketone **3** to yield the intermediate **5**, and a subsequent Boc-deprotection gave compound **1**. Recently, Merck disclosed another route[2d] to compound **1**. In this work, the Boc-protection on compound **2** was removed with trifluoacetic acid and the following reductive amination to compound **5** was carried out in one pot without separating the intermediate **6**. Thus, compound **1** was prepared more efficiently, also avoiding using sulfonic acid which might introduce genetoxic impurities (Scheme 1).

It seems that the two step sequence, namely reductive amination and subsequent removal of Boc-protection, is too simple to be further optimized. Nevertheless, we found that the

order of reductive amination and Boc-deprotection can be exchanged, and the inverted two-step sequence can be further telescoped into a one-pot conversion. Consequently, the production of Omarigliptin **1** and its analogues could be greatly simplified. The results will be described herein.

2. DISCUSSION

From pyrazole **2** and ketone **3**, the original two-step sequence is the most straightforward route to Omarigliptin **1**. If Boc-deprotection was done in prior to reductive amination, the imaginary intermediate **7**, a *beta*-amino ketone, must be a very unstable species[3] and will pose problems in the synthetic process. As described in Scheme 2, when ketone **3** was treated with trifluoroacetic acid at 0 ^{o}C, degradation of intermediate was observed by TLC in 1-2 h.[4] Alternatively, ketone **3** underwent simultaneous dithiolane protection and Boc-deprotection to give a stable free amine **9**.[2e,5] When the reaction time was kept short, intermediate **8** could be isolated, too. Compound **9** was subjected to oxidative deprotection of dithiolane, and rapid decomposition was again recorded.[6] Thus, we experimentally demonstrated that *beta*-amino ketone **7** as an unstable species under different conditions (Scheme 2).

Unexpectedly, when pyrazole **2** and ketone **3** were dissolved into trifluoroacetic acid at the same time, a stabilization effect was observed: *beta*-amino ketone **7** remained

unchanged for more than 24 h at RT, according to TLC and NMR. Furthermore, when DMAC, TEA, and STAB were added into this solution, direct reductive amination was achieved between intermediate **6** and **7**, giving Omarigliptin **1** in one pot with a yield of 63%, and a diastereoselectivity greater than 10:1 according to ^{1}H-NMR. Similarly, sulfonic acid salt **4** could react with ketone **3** in one pot, and produce Omarigliptin **1** with a slightly lower yield of 57%, and a similar diastereoselectivity greater than 10:1 according to ^{1}H-NMR (Scheme 3). In all cases, no products derived from self-condensation of compound **7** could be isolated.

To understand this unique stabilization effect for *beta*-amino ketone **7**, we performed preliminary NMR study. Pyrazole **2** (sample 1), ketone **3** (sample 2), as well as an equimolar mixture of **2** and **3** (sample 3), were dissolved in deuterated trifluoroacetic acid, reacted at RT for 5-10 min, and subjected to ^{1}H-NMR and ^{13}C-NMR analysis. According to Figure 1 and 2, no significant differences could be identified when sample 3 was compared with sample 1 or 2. Thus, the formation of long half-life intermediates, including aminal and imine, could be excluded. As pyrazole **6** was the only factor that could stabilize intermediate **7**, pyrazole **6** and ketone **7** must undergo rapid on- off contact.

The only side product from this Boc-deprotection step was isobutene. According to ^{1}H-NMR, side products from above 3 NMR samples are all isobutene,[7] which could not have stabilizing effect for intermediate **7**.

With the unprecedented *beta*-amino ketone intermediate **7** and the new synthetic method, Omarigliptin **1** could be prepared conveniently from ketone **3** in one pot. It is also of great interest to explore the substrate scope of the amine component for this conversion. Thus, amines **10a-f** were used as substrates for the investigation. As demonstrated in Table 1, in the first Boc-deprotection step, stabilization effect for *beta*-amino ketone **7** could still be observed with most of the amine substrates, except for compound **10d**, which actually accelerated the decomposition of ketone **7**.

In the next reductive amination step, aryl amines **10a**, **b**, **c** could yield the desired products **11**, **12**, and **13** respectively, with moderate to excellent yields. Benzylamine **10e** did not react with ketone **3** probably due to the low nucleophilicity caused by *N*-protonation. Interestingly, Boc-protected proline derivative **10f** could be incorporated into this reaction and produce compound **14** of certain complexity with 59% yield. At the current reaction scale performed for these conversions,[5] the diastereoselectvity was generally good, as no diastereomers could be isolated by flash chromatography or identified by NMR.

3. CONCLUSION

In summary, we have discovered a unique stabilization condition for *beta*-amino ketone **7**, most probably due to its interaction with various amines in trifuoroacetic acid. With ketone **7** as an unprecedented intermediate, Omarigliptin **1** could be prepared in a highly efficient one-pot procedure with good yield and diastereoselectivity. Also with this intermediate, some analogues of Omarigliptin **1** were readily prepared for the first time and could be interesting to further biological study.

4. EXPERIMENTAL

4.1. A Typical One-Pot Preparation Of Omarigliptin 1

Compound **3**[2d] (598 mg, 1.83 mmol) and compound **2**[2d] (500 mg, 1.74 mmol) were dissolved in trifluoroacetic acid (2.6 mL, 35.0 mmol) at 0 ^{o}C and stirred at 0 ^{o}C for 1 h. To the resulting solution, DMAC (7.1 mL, 76 .3mmol) and TEA (2.4 mL, 17.3 mmol) were added slowly and the internal temperature was maintained below 15 ^{o}C. The mixture was then cooled to 0 ^{o}C, treated with STAB (516.3 mg, 2.43 mmol), and stirred at 0-2 ^{o}C for 5 h. Eventually the pH of the reaction was brought to 9 with conc. aq. NH_3, and the resulting suspension was filtered. The filtrate was diluted with water (60 mL), extracted ethyl acetate for several times. Combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column

chromatography (SiO_2, DCM: MeOH = 20:1) to yield the product **1** (white powder, 436 mg, 1.10 mmol, 63 % based on compound **2**, dr = 10:1). Analytical data was parallel to literature report.[1]

4.2. General Procedure For The Preprations Of Compounds 11-14

Compound **3** (101 mg, 0.31 mmol) and amines **10a-f** (0.32 mmol) were dissolved in trifluoroacetic acid (0.45 mL, 6.1 mmol) at 0 ^oC and stirred at 0 ^oC for 1 h. To the resulting solution, DMAC (1.3 mL, 14.0 mmol) and TEA (0.42 mL, 3.0 mmol) were added slowly and the internal temperature was maintained below 15 ^oC. The mixture was then cooled to 0 ^oC, treated with STAB (91 mg, 0.43 mmol), and stirred at 0-2 ^oC for 5 h. Eventually the pH of the reaction was brought to 9 with conc. aq. NH_3, and the resulting suspension was filtered. The filtrate was diluted with water (15 mL), extracted ethyl acetate for several times. Combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, DCM: MeOH = 20:1) to yield the products **11-14**.

SUPPLEMENTARY MATERIAL

Supporting Information: Full experimental detail, ^1H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGEMENTS

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2. a) Xu, F.; Zacuto, M. J.; Kohmura, Y.; Rosen, J.; Gibb, A.; Alam, M.; Scott, J.; Tschaen, D. *Org. Lett.* **2014**, *16*, 5422-5425; b) Arroyo, I.; Krueger, D.; Chen, P.; Moment, A.; Biftu, T.; Sheen, F.; Zhang, Y. WO2013003249A1, **2013**; c) Zacuto, M. J.; Dunn, R. F.; Moment, A. J.; Janey, J. M.; Lieberman, D.; Sheen, F.; Bremeyer, N.; Scott, J.; Kuethe, J. T.; Tan, L.; Chen, Q. WO2013003250A1, **2013**; d) Chung, J. Y. L.; Scott, J. P.; Anderson, C.; Bishop, B.; Bremeyer, N.; Cao, Y.; Chen, Q.; Dunn, R.; Kassim, A.;

Lieberman, D.; Moment, A. J.; Sheen, F.; Zacuto, M. *Org. Process Res. Dev.* **2015**, *19*, 1760–1768; e) Liu, T.; Hou, J.; Xie, W.; Li, Y.; Ren, H., Liang, J.; Xiong, B., Chen, G., Cheng, M., Zhao, D.; Shen, J.; Chen Y.-L., *Eur. J. Org. Chem.*, DOI: 10.1002/ejoc.201601074.

3. It is known that *b*eta-amino ketones are unstable compounds possibly due to self-condensation or elimination. For example, 4-aminopentan-2-one was found only in 2 patents: a) Young, D. C. US3373177A, **1968**; b) Altman, M. D.; Andresen, B. M.; Arrington, K. L.; Childers, K. K.; Di Francesco, M. E.; Donofrio, A.; Ellis, J. M.; Fischer, C.; Guerin, D. J.; Haidle, A. M.; Kattar, S.; Knowles, S. L.; Li, C.; Lim, J.; Machacek, M. R.; Northrup, A. B.; O'Boyle, B. M.; Otte, R. D.; Petrocchi, A.; Reutershan, M. H.; Romeo, E.; Siu, T.; Taoka, B. M.; Trotter, B. W.; Zhou, H.; Burch, J.; Cote, B.; Dupont-Gaudet, K.; Fournier, J.-F.; Gauthier, J. Y.; Guay, D.; Robichaud, J. S.; Grimm, J.; Maddess, M. L.; Schell, A. J.; Spencer, K. B.; Woo, H. C.; Bhat, S. WO2011075515A1, **2011**. Hindered or *N*-protected *b*eta-amino ketones are more stable: c) Haeseler, P. R., *Org. Synth.* **1926**, *6*, 28-30.

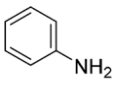
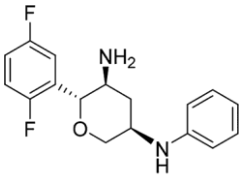
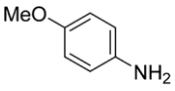
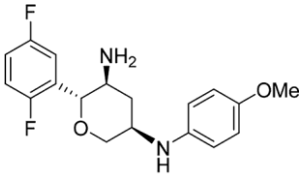
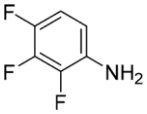
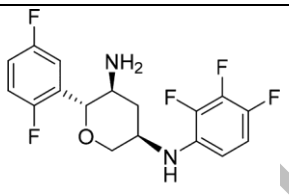
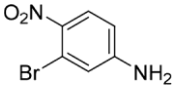
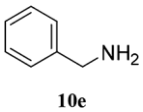
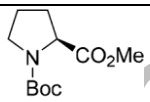
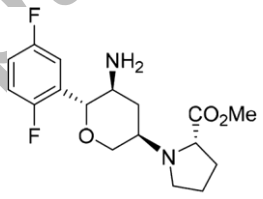
4. Compound **3** (200 mg, 0.611 mmol) was dissolved into trifluoroacetic acid (0.9 mL, 12.2 mmol) at 0 ^{o}C. After 2 h at 0 ^{o}C, starting material disappeared completely and multiple spots were found on TLC.

5. See supporting information for details.

6. Compound **9** (30 mg, 0.099 mmol) was dissolved into a mixture of MeCN and water (4:1, 1 mL) and treated with [bis(trifluoroacetoxy)iodo]benzene (51 mg, 0.119 mmol) at RT. After 30 min at RT, starting material disappeared completely and multiple spots were found on TLC. The same condition was used to convert compound **8** to compound **3** with 79% yield. See Ref. 2e for details.

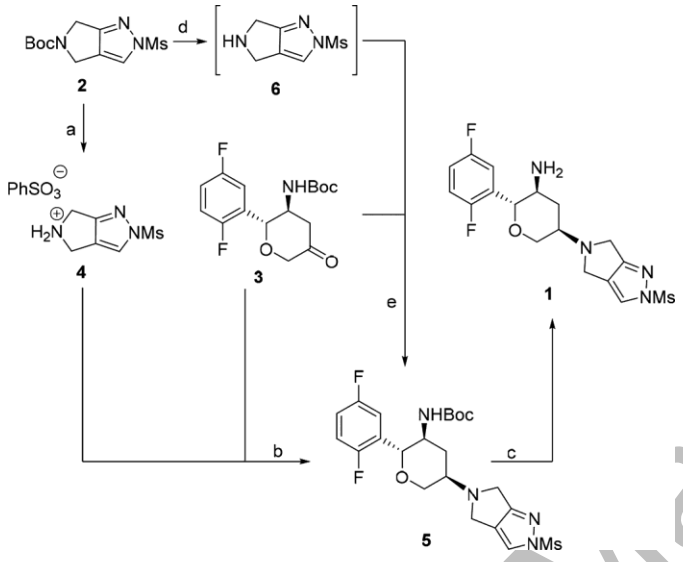
7. ^{1}H-NMRs of isobutene and *tert*-butanol in deuterated trifluoroacetic acid were measured respectively, too. In 3 Boc-deprotection NMR experiments, the proton peak corresponding to *tert*-butanol was not observed.

Table 1. One-pot preparation of analogues of Omarigliptin **1**.[a]

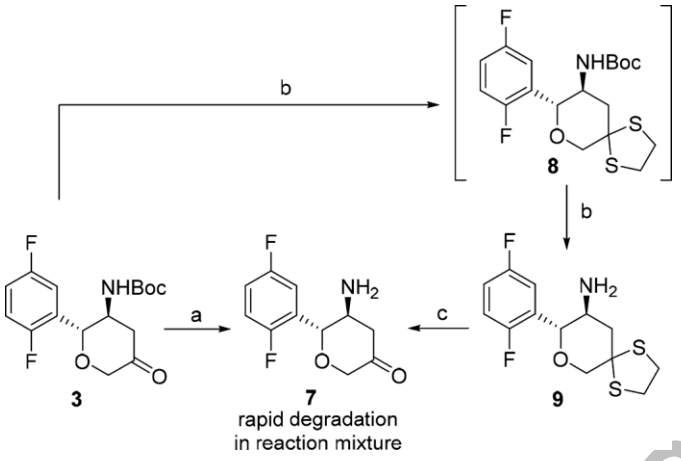
No.	Starting materials	Products
1	 **10a**	 **11** (65% from **10a**)
2	 **10b**	 **12** (98% from **10b**)
3	 **10c**	 **13** (36% from **10c**)
4	 **10d**	rapid decomposition
5	 **10e**	no reaction
6	 **10f**	 **14** (59% from **10f**)

[a] Reaction conditions: Amines **10a**, **b**, **c**, or **f**, CF_3COOH, 0 ^oC. b) DMAC, STAB, and TEA, 0 ^oC.

Scheme 1. Reported Omarigliptin synthesis. Reaction conditions: a) $PhSO_3H$, 92%. b) Dimethylacetamide (DMAC), sodium triacetoxyborohydride (STAB), and TEA, 78%. c) $PhSO_3H$, DMAC, 78%. d) CF_3COOH; e) DMAC, STAB, and TEA, 87% for two steps.



Scheme 2. Attempts at preparation of compound 7. Reaction conditions: a) CF_3COOH; b) $HSCH_2CH_2SH$, BF_3 etherate, DCM, 86%; c) [Bis(trifluoroacetoxy)iodo]benzene, MeCN, water, RT.



Scheme 3. A one-pot deprotection-reductive amination sequence leading to Omarigliptin **1**. Reaction conditions: a) CF_3COOH, 0 ^oC. b) DMAC, STAB, and TEA, 0 ^oC, 63% from compounds **2** and **3**; 57% from compounds **4** and **3**.

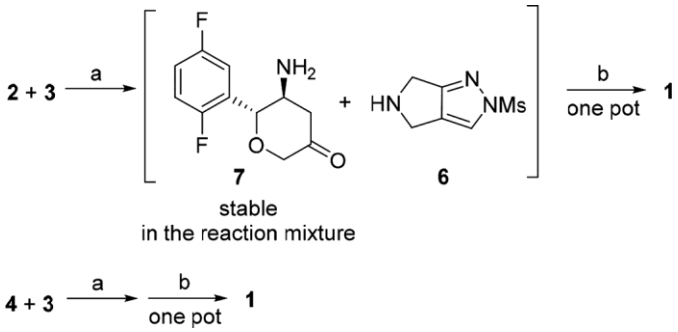


Figure 1. Pyrazole 2 (sample 1), ketone 3 (sample 2), as well as an equimolar mixture of **2** and **3** (sample 3), were dissolved in deuterated trifluoroacetic acid and reacted at RT for 5-10 min. The ^{1}H-NMR was recorded respectively.

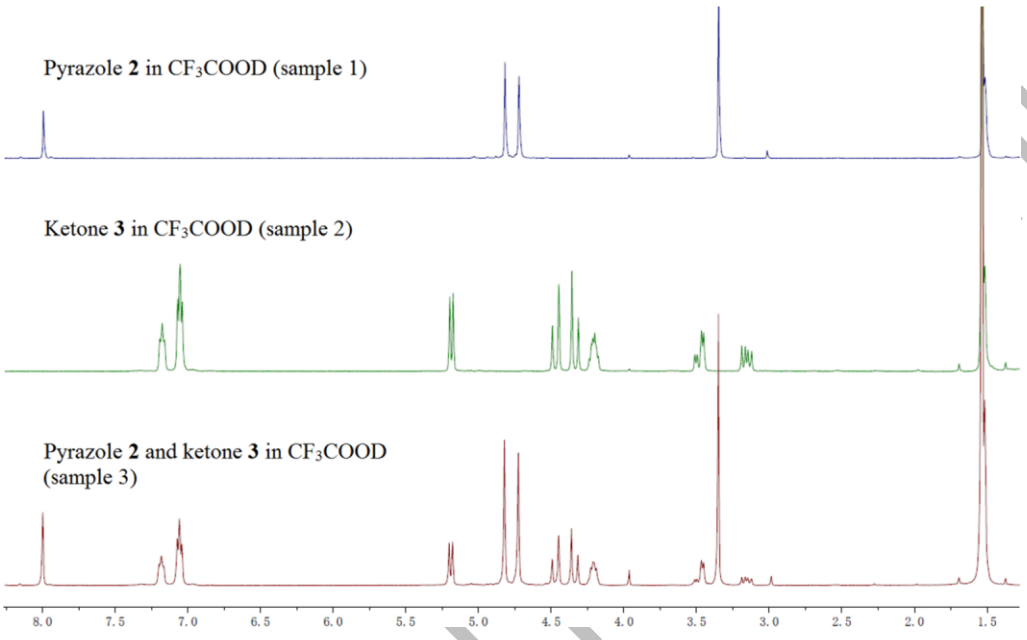


Figure 2. Pyrazole **2** (sample 1), ketone **3** (sample 2), as well as an equimolar mixture of **2** and **3** (sample 3), were dissolved in deuterated trifluoroacetic acid and reacted at RT for 5-10 min. The ^{13}C-NMR was recorded respectively.