Tetrahedron Letters 51 (2010) 2983–2985

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Ugi reaction for the synthesis of 4-aminopiperidine-4-carboxylic acid derivatives. Application to the synthesis of carfentanil and remifentanil

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ARTICLE INFO

Article history:
Received 15 February 2010
Revised 24 March 2010
Accepted 30 March 2010
Available online 3 April 2010

Keywords:
Ugi reaction
Remifentanil
Carfentanil
Mumm rearrangement

ABSTRACT

A two-step sequence involving an Ugi four-component reaction was developed for the preparation of 4-aminopiperidine-4-carboxylic acid derivatives. This strategy has led to the successful preparation of two drugs carfentanil and remifentanil in shorter times and better yields than previously described methods.

In the last two decades, multicomponent reactions (MCR) have demonstrated themselves to be very powerful in the synthesis of natural products, as well as in combinatorial chemistry.[1] The combination of three or more different series of reagents allows the straightforward construction of large libraries while accepting a broad variety of chemical functionality.[2–4] By far, most applications of MCRs described are in the area of drug discovery where it is often crucial to access rapidly and efficiently a large diversity of structures.[5] Indeed, the ease of performance, the time-saving aspect, the versatility, the diversity of obtained scaffolds, and the very large chemical space explored have urged medicinal chemists to use MCRs. The Ugi four-component condensation (Ugi-4CC) represents a powerful method to quickly assemble in one-pot *N*-acyl amino acid amides from a primary amine, a carbonyl compound, a carboxylic acid, and an isocyanide as starting reagents.[6]

Several potent μ-opioid agonists display a common 4-phenylaminopiperidine-4-carboxylic acid methyl ester substructure (Fig. 1). Remifentanil is a potent ultra short-acting analgesic drug and carfentanil is one of the most potent opioids used in veterinary medicine.[7] The standard synthesis of these drugs consists of eight steps among which is the preparation of a key α-aminonitrile via Strecker reaction. This α-substituted nitrile must be hydrated and the obtained amide hydrolyzed, the aniline acylated and finally the acylaminoacid must be methylated. This reaction sequence is not very powerful because α-substituted nitriles are known to be resistant to hydration.[8]

Also N-acylation is particularly difficult in the case of gem disubstituted piperazines. Optimized methods for the N-acylation and esterification steps were published for remifentanil.[9] Recently, a more efficient four-step synthesis involving a Stecker reaction was described. However the yield of the synthesis does not exceed 25%.[10]

In this Letter, we show that the Ugi reaction can be a good alternative method that uses the same ketone precursors for the synthesis of 4-aminopiperidine-4-carboxylic acid derivatives. Ketones can be indeed involved in a Ugi MCR which is synthetically

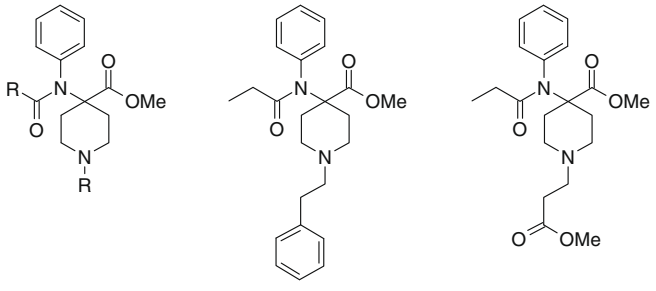

Figure 1. Piperidine amino acid μ-agonists.

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doi:10.1016/j.tetlet.2010.03.120

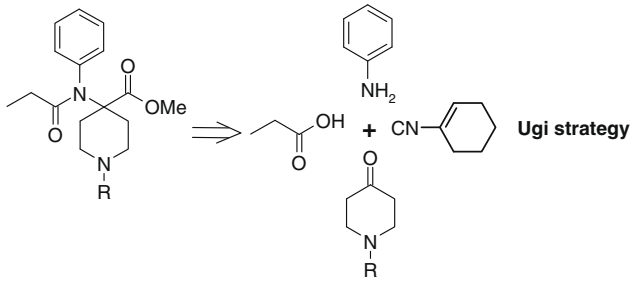
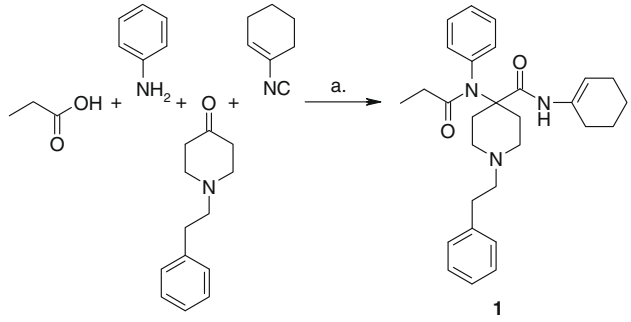


Figure 2. Synthetic strategy.



Scheme 1. Formation of piperidine derivative **1** via Ugi-4CC. Reagents and conditions: (a) MeOH, room temp or 55 °C, 24 h.

simpler and more efficient than the Strecker reaction. The Ugi reaction is especially interesting because it can be completed fast and without side-products. This is attributed to the high energy content of the isocyanide and to the stability of the product formed which contains two amide bonds. Due to subsequent irreversibility of this isocyanide addition reaction there is no asymmetric version of the Ugi reaction.[3] This can be an issue when the target compound is a chiral α amino-acid derivative. In these conditions, the asymmetric versions of the Strecker reaction remain the route of choice.[11] However in the case of symmetrical 4,4-disubtituted piperidines the Ugi reaction will demonstrate its superiority, as described hereafter.

Our approach to synthesize carfentanil and remifentanil, in only two steps and high yield, involves the Ugi four-component reaction driven by 1-cyclohexenyl isocyanide (Fig. 2).[12]

The first step of the synthesis of carfentanil is the Ugi reaction between propionic acid, aniline, 4-phenylethylpiperidone, and 1-cyclohexenyl isocyanide (Scheme 1) in methanol for 24 h.

We designed a set of screening conditions to determine the factors that have a significant effect on the yield of the reaction: concentration, stoichiometry of amine and ketone, and temperature. The results are shown in Table 1.

Excess of aniline or ketone failed to deliver good conversions (entries 2–5 vs 1). Increasing concentration to 0.2 M allowed reaching 50% yield at room temperature (entry 7 vs 1 and 6). Increasing temperature to 55 °C allowed excellent yields (entries 8 and 9). Precursor **1** was thus obtained in 82% yield in one step.

The mechanism for the Ugi reaction with piperidone is depicted in Scheme 2. The 4-anilino group at the piperidine quaternary carbon is particularly unreactive.[13] However, in this particular situation, the acylated isoamide readily undergoes cyclization to form the spiro[4.5]bicyclic intermediate of the Mumm rearrangement to give the desired product **1** in mild conditions with an excellent yield.

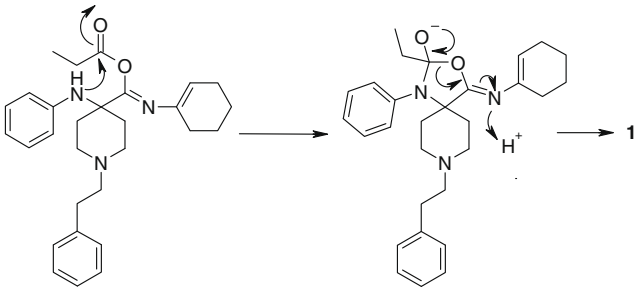
N-Cyclohexenyl amides are known in the literature to be convertible: Rosendahl and Ugi[14] found that hydrolysis of *N*-acylamino amides arising from 1-cyclohexenyl isocyanide leads to the formation of primary amides. Then Keating and Armstrong demonstrated that carboxylic acid or esters could be obtained from *N*-acylaminoamides via the formation of münchones with water or alcohol as nucleophile.[12] The synthesis of carfentanil **2** was achieved by methanolysis of **1** in 10% AcCl in MeOH[15] at room temperature for 24 h (Scheme 3), in an excellent 70% overall yield after purification.[16]

We explored the utility of this procedure for the synthesis of remifentanil (Scheme 4). The optimized conditions were applied for the condensation of propionic acid, aniline, 3-(4-oxo-piperidine-1-yl)-propionic acid methyl ester and 1-cyclohexenyl isocyanide. 3-(4-oxo-piperidine-1-yl)-propionic acid methyl ester was synthesized in one step from the piperidone. The piperidone can be synthesized from β-alanine methyl ester and 8,8-dimethyl-3-oxo-8-azonia-bicyclo[3.2.1]octane iodide 'IDABO'[17] or by Michael addition of methylacrylate on piperidone.[10]

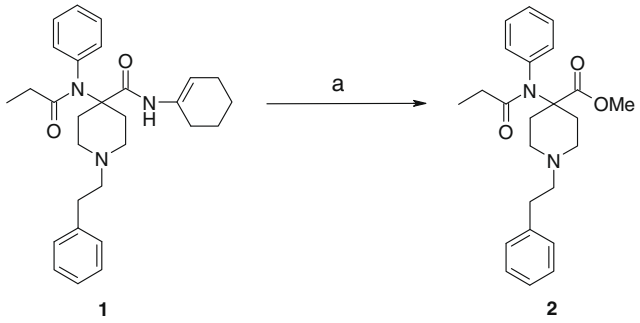
The α-acylamino amide **3** was successfully obtained. The methanolysis of **3** was achieved and gave remifentanil **4** in quantitative yield.[18] Remifentanil was thus obtained in 67% overall yield (76% from piperidone) as compared to 25% previously reported.

Table 1

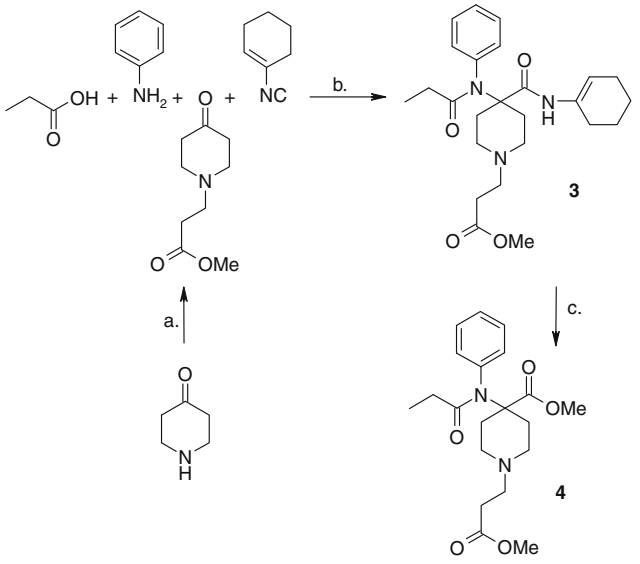
Entry	Concn (M)	Aniline (equiv)	Ketone (equiv)	Temp (°C)	Yield (%)
1	0.125	1	1	25	27
2	0.125	1.25	1	25	26
3	0.125	2	1	25	22
4	0.125	1	1.25	25	25
5	0.125	1	2	25	24
6	0.05	1	1	25	10
7	0.2	1	1	25	50
8	0.125	1	1	55	67
9	0.2	1	1	55	82



Scheme 2. Mumm rearrangement for piperidone derivative.



Scheme 3. Formation of carfentanil **2** via methanolysis. Reagents and conditions: (a) AcCl 10%/MeOH, 24 h.



Scheme 4. Formation of remifentanil **4** via Ugi-4CC and methanolysis. Reagents and conditions: (a) K_2CO_3, methyl acrylate, MeOH; (b) MeOH, 55 °C, 24 h; (c) AcCl 10%/MeOH, 24 h.

In summary, we have developed an efficient and original procedure for the synthesis of carfentanil and remifentanil using the Ugi reaction. This strategy in mild conditions is suitable for the synthesis of novel structurally varied μ-opioid agonists and should prove valuable in library synthesis. As well, being straightforward, rapid and efficient it could be used for the synthesis of radiolabeled fluoroalkyl derivatives of carfentanil or remifentanil.[19]

Acknowledgements

We are grateful to the institutions that support our laboratory (Inserm, Université de Lille2, Institut Pasteur de Lille). We thank also the following institutions or companies: CAMPLP and Waters.inc for technical support. This project was supported by Conseil Régional Nord-Pas de Calais, DRRT PRIM 2008-07 PRIM-SP.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.120.

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16. *Procedure for preparing* **1**: 1-cyclohexenyl isocyanide (47 mg, 50.2 μL, 0.44 mmol) was added to a solution of propionic acid (33 mg, 32.9 μL, 0.44 mmol), aniline (41 mg, 40.1 μL, 0.44 mmol), 4-phenylethylpiperidone (90 mg, 0.44 mmol) in MeOH (2.2 mL) at room temperature and the solution was heated at 55 °C and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (5 mL). The organic solution was washed with satd aq $NaHCO_3$ (2 × 2.5 mL) and brine (2.5 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified either via HPLC/MS preparative with gradient starting from 10% MeOH/90% H_2O/0.1% ammonia reaching 100% MeOH/0.1% ammonia. The product was obtained in 82% yield (165 mg). [(M+H)] = 460 (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (t, J = 7.4 Hz, 3H), 1.20 (t, J = 6.6 Hz, 2H), 1.65 (dd, J = 32.8/5.6 Hz, 4H), 2.05 (m, 2H), 1.99–2.20 (m, 5H), 2.52–2.90 (m, 7H), 3.04 (d, J = 12 Hz, 2H), 3.68 (q, J = 7.0 Hz, 1H), 6.08 (s, 1H), 7.15–7.38 (m, 9H), 8.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.33, 18.41, 21.85, 22.56, 24.23, 28.28, 30.31, 32.07, 32.78, 50.14, 59.30, 64.15, 114.09, 126.53, 128.33, 128.60, 128.63, 128.92, 129.04, 129.54, 130.28, 130.60, 132.73, 138.52, 139.41, 170.15, 176.27. Procedure for preparing **2**: Acetyl chloride (133.5 mg, 121 μL, 1.7 mmol) was added to a solution of the compound **1** (77 mg, 0.17 mmol) in MeOH (2.8 mL) at room temperature and the solution was heated at 55 °C and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (5 mL). The organic solution was washed with satd aq $NaHCO_3$ (2 × 2.5 mL) and brine (2.5 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified either via HPLC/MS preparative with gradient starting from 10% MeOH/90% H_2O/0.1% ammonia reaching 100% MeOH/0.1% ammonia. The product was obtained in 86% yield (59 mg). [(M+H)] = 395 (100%): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, J = 7.4 Hz, 3H), 1.89 (m, 4H), 2.35 (d, J = 12 Hz, 2H), 2.80 (m, 6H), 3.07 (d, J = 12 Hz, 2H), 3.80 (s, 3H), 7.13–7.42 (m, 8H), 7.43 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.13, 29.11, 31.93, 49.25, 52.39, 59.12, 61.64, 126.54, 128.61, 128.65, 129.05, 129.55, 130.41, 138.83, 173.53, 174.41.
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18. *Procedure for preparing* **3**: 1-cyclohexenyl isocyanide (117 mg, 124.9 μL, 1.0 mmol) was added to a solution of propionic acid (74 mg, 74.8 μL, 1.0 mmol), aniline (93 mg, 91.2 μL, 1.0 mmol), 3-(4-oxo-piperidine-1-yl)-propionic acid methyl ester (186 mg, 1.0 mmol) in MeOH (5 mL) at room temperature and the solution was heated at 55 °C and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (10 mL). The organic solution was washed with satd aq $NaHCO_3$ (2 × 5 mL) and brine (5 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified either via HPLC/MS preparative with gradient starting from 10% MeOH/90% H_2O/0.1% ammonia reaching 100% MeOH/0.1% ammonia. The product was obtained in 86% yield (379 mg). [(M+H)] = 442 (100%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, J = 7.5 Hz, 3H), 1.62 (d, J = 5.4 Hz, 2H), 1.72 (d, J = 7.2 Hz, 2H), 1.91 (q, J = 7.2 Hz, 4H), 2.17 (m, 4H), 2.55 (m, 6H), 2.78 (m, 4H), 3.67 (s, 3H), 6.10 (s, 1H), 7.22 (m, 2H), 7.40 (m, 3H), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.36, 21.97, 22.51, 24.06, 28.16, 30.24, 31.05, 33.24, 50.01, 51.87, 52.63, 64.37, 113.89, 128.81, 129.43, 130.35, 132.74, 139.54, 170.13, 172.16, 176.16. Procedure for preparing **4**: acetyl chloride (26 mg, 233 μL, 3.3 mmol) was added to a solution of the compound **3** (147 mg, 0.33 mmol) in MeOH (5.5 mL) at room temperature and the solution was heated at 55 °C and stirred for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (10 mL). The organic solution was washed with satd aq $NaHCO_3$ (2 × 5 mL) and brine (5 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified either via HPLC/MS preparative with gradient starting from 10% MeOH/90% H_2O/0.1% ammonia reaching 100% MeOH/0.1% ammonia. The product was obtained in 88% yield (94 mg). [(M+H)] = 377 (100%) ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.81 (t, J = 7.2 Hz, 3H), 1.47 (m, 2H), 1.76 (q, J = 7.2 Hz, 2H), 2.05 (d, J = 13.2 Hz, 2H), 2.25 (t, J = 10.2 Hz, 2H), 2.36 (m, 2H), 2.45 (m, 2H), 3.53 (s, 3H), 3.64 (s, 3H), 7.35 (m, 2H), 7.47 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 9.59, 28.81, 32.06, 33.28, 49.52, 51.73, 52.24, 53.28, 62.28, 129.11, 129.86, 130.99, 139.54, 172.83, 173.27, 173.53.
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