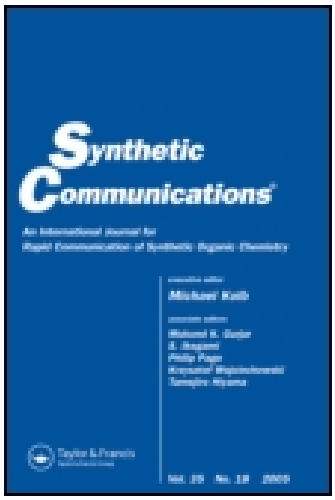


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Facile Synthesis of Racemic 2-Aminomethyl-4-oxo-piperidine Intermediates

Daniel D. Holsworth [a c], Farid Bakir [a], Roy T. Uyeda [a], Yu Ge [a], Jesper Lau [b], Thomas K. Hansen [b] & Henrik Sune Andersen [b]

[a] Ontogen Corporation, Department of Chemistry, Carlsbad, California, USA

[b] MedChem. Research I# and IV‡, Novo Nordisk A/S, Denmark

[c] Pfizer Global Research and Development, Department of Chemistry, 2800 Plymouth Road, Ann Arbor, MI 48105, USA Fax: E-mail:

Published online: 17 Aug 2006.

To cite this article: Daniel D. Holsworth, Farid Bakir, Roy T. Uyeda, Yu Ge, Jesper Lau, Thomas K. Hansen & Henrik Sune Andersen (2003) A Facile Synthesis of Racemic 2-Aminomethyl-4-oxo-piperidine Intermediates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:10, 1789-1795, DOI: 10.1081/SCC-120018941

To link to this article: http://dx.doi.org/10.1081/SCC-120018941

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 10, pp. 1789–1795, 2003

A Facile Synthesis of Racemic 2-Aminomethyl-4-oxo-piperidine Intermediates

Daniel D. Holsworth,[1,*] Farid Bakir,[1] Roy T. Uyeda,[1] Yu Ge,[1] Jesper Lau,[2,#] Thomas K. Hansen,[2,‡] and Henrik Sune Andersen[2,#]

[1]Ontogen Corporation, Department of Chemistry, Carlsbad, California, USA
[2]MedChem. Research I[#] and IV,[‡] Novo Nordisk A/S, Denmark

ABSTRACT

Facile access to the 2-substituted piperidine nucleus was achieved by a 3-component hetero Diels-Alder reaction. The use of an appropriately functionalized imine allowed the installation of a protecting group for both the piperidine and 2-position side chain nitrogens in one step. Also, by employing 2-trimethylsiloxy-1,3-butadiene, a reduction step was avoided, thus providing rapid entry into the piperidine core structure. This protocol led to the synthesis of

*Correspondence: Daniel D. Holsworth, Pfizer Global Research and Development, Department of Chemistry, 2800 Plymouth Road, Ann Arbor, MI 48105, USA; Fax: 734-622-3107; E-mail: Daniel.holsworth@pfizer.com.

DOI: 10.1081/SCC-120018941 0039-7911 (Print); 1532-2432 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

some racemic 2-aminomethyl-4-oxo-piperidines; intermediates that were synthesized in multigram quantities.

Key Words: Hetero Diels-Alder; 2-Aminomethyl 1-4-oxo-piperidine.

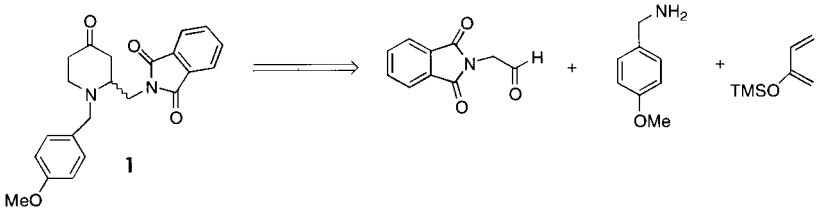
INTRODUCTION

The piperidine nucleus serves as an essential core for a variety of natural products as well as a scaffold for drug candidates.[1] During our research activities, we required a ''masked'' 2-aminomethyl-4-oxo-piperidine skeleton **(1)**. In an effort to synthesize the desired scaffold **(1)** in an expeditious fashion, it was envisioned that a hetero Diels-Alder reaction with a functionalized imine moiety would provide rapid entry into the desired piperidine ring system. This approach also provides a starting structure with appropriate nitrogen protecting groups present as well as the desired regiochemistry set in one step[2] (Sch. 1).

Catalysts for the hetero Diels-Alder reaction (Table 1, Entries 1–5) were chosen from published work,[3] where hetero Diels-Alder reactions between electron deficient imines and electron rich dienes were successful. Of primary concern was the electronically rich nature of both the diene as well as the in-situ generated dienophile (Sch. 2). From the selection of published catalysts, only BF_3–OEt_2 (Entry 1) led to low yields of the desired product **(1)**.

Interestingly, aluminum chloride (Table 1, Entry 6) proved to be the best catalyst for the preparation of **1**, providing the piperidine framework in 37% yield.

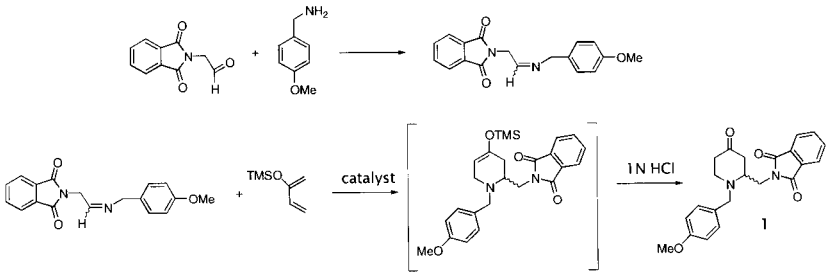
A modest amount (~11%) of crude trimethylsilyl enol ether (intermediate, Sch. 2) was observed during work-up and after purification. Exposing the reaction mixture to 1 N HCl for longer periods of



Scheme 1. Retrosynthetic analysis of racemic 2-aminomethyl-4-oxo-piperidine.

Table 1. Conditions explored for hetero Diels-Alder reaction. Entry 6 was found to be the best catalyst/conditions investigated.

Entry #	Catalyst	Temperature (°C)	Solvent	% Yield of **1**
1	BF_3–OEt_2	0	CH_2Cl_2	8
2	$Yb(OTf)_3$	0 to rt	CH_3CN	0
3	$Yb(OTf)_3$	0	CH_2Cl_2	0
4	BF_3–OEt_2	−20	CH_2Cl_2	0
5	ZnI_2	−40	CH_3CN	0
6	$AlCl_3$	−78 to rt	CH_2Cl_2	37

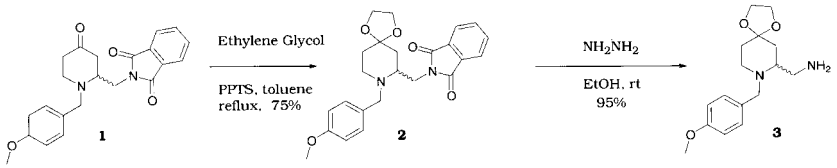


Scheme 2. Hetero Diels-Alder reaction for 4-oxo-2-substituted piperidine synthesis **(1)**.

time (>2 h) during work-up did not improve hydrolysis. Therefore, after isolation, additional 1 N hydrochloric acid was needed to convert the silyl intermediate to the 4-oxo-piperidine framework.

We have conducted the hetero Diels-Alder reaction on 15 g scale and obtained isolated yields of compound **1** in the 33–38% range (see Experimental Section). Once a reliable and efficient synthesis of compound **1** was in hand, transformation of the 4-keto moiety into the 1,3-dioxolane provided the fully protected 2-aminomethyl-4-oxo-piperidine compound **2** (Sch. 3). Liberation of the primary amine with hydrazine produced another useful 2-aminomethyl-4-oxo-piperidine building block (compound **3**).

In conclusion, the useful 2-substituted-4-oxo-piperidine scaffold can be rapidly obtained in racemic form in a single step via a hetero Diels-Alder reaction between an appropriately substituted imine and 2-trimethylsilyl-1,4-butadiene. The utility of this methodology has been demonstrated in our laboratories by the production of useful synthetic intermediates for drug discovery.



Scheme 3. Simple transformation of compound **1** to racemic 2-aminomethyl-4-oxo-piperidine building blocks **2** and **3**.

EXPERIMENTAL SECTION

All reagents were purchased from Aldrich and used without further purification. Solvents used were of HPLC grade and used without further purification. NMR spectra were recorded on a Varian 400 MHz spectrometer and referenced to the solvent. Melting point values are uncorrected.

2-[1-(4-Methoxy-benzyl)-4-oxo-piperidin-2-yl-methyl]-isoindole-1,3-dione (1)

Phthalimidoacetaldehyde diethyl acetal (100 g, 0.38 mol), THF (600 mL) and 1 N HCl (300 mL) were heated to 80°C for 18 h, then cooled and the solvent evaporated in vacuo. The semi-solid was diluted with dichloromethane (600 mL) and the solids filtered (*Keep solid*!). The filtrate was washed with saturated sodium bicarbonate (2×), brine (2×) and dried over magnesium sulfate. Removal of solvent gave a solid, that was washed with *n*-butylchloride to produce 22.0 g of (1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetaldehyde as a white solid. To the solid that was put aside, add THF (600 mL), magnesium sulfate and activated carbon (~5 g each). The mixture was stirred at rt for 2 h, filtered through a pad of celite and evaporated in-vacuo to give a brown oil. *N*-Butylchloride was added to the oil and triturated to form a brown solid. *N*-Butylchloride (500 mL) was added again to the solid and the solids collected via suction filtration. 49.64 g of beige solid was obtained. The 49.6 g of beige solid was partially dissolved in 600 mL of chloroform and stirred 5 min. The insolubles were filtered off and the mother liquor evaporated under reduced pressure to obtain 41.20 g of (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetaldehyde as a white solid. Total amount of

(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetaldehyde isolated: 63.20 g (88%). M.p. = 112–114°C (lit. value: 114°C; Ref.[4]); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (s, 1H), 7.87 (dd, $J = 5.6$, 2.4, 2H), 7.75 (dd, $J = 5.2$, 2.8, 2H), 4.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 47.6, 123.9, 132.1, 134.5, 167.7, 193.7; Anal. calcd for $C_{10}H_7NO_3$ (%): C, 63.49; H, 3.73; N, 7.40; found: C, 63.09; H, 3.73; N, 7.15; MS (APCI) m/z 190.0 (M + 1).

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetaldehyde (17.3 g, 0.092 moles), 150 mL of dry dichloromethane, molecular sieves (15 g, 4 Å), and 4-methoxybenzylamine (11.9 mL, 0.092 moles) were stirred at rt, under nitrogen for 1 h. The reaction mixture was filtered and the solution (imine in dichloromethane) added to an addition funnel containing 2-trimethylsilyloxy-1,3-butadiene (20.9 mL, 0.12 moles). The resultant mixture was added slowly to a solution of aluminum chloride (14.64 g, 0.11 moles) in dichloromethane (100 mL) previously cooled to −78°C. Once the addition was complete the mixture was allowed to stir for 18 h, slowly warming to rt. The reaction mixture was cooled to 0°C and 1 N HCl (100 mL) was added slowly. Once the addition completed, the reaction mixture was stirred for 2 h. Water was added (0.5 L) and the product extracted with dichloromethane (Keep aqueous layer). The aqueous layer was basified with sodium carbonate and extracted with dichloromethane. The organic fractions were combined, washed with brine (2×) and dried over anhydrous magnesium sulfate. The solvent was removed in-vacuo to yield a brown solid (35 g). The solid was subjected to flash chromatography (60:40 hexanes/ethyl acetate) to produce 11.8 g of 2-[1-(4-methoxy-benzyl)-4-oxo-piperidin-2-yl methyl]-isoindole-1,3-dione (**1** ($R_f = 0.4$)) as a yellow solid. Also obtained was 4.6 g of crude TMS enol ether product ($R_f = 0.87$, 60 hexanes/40 ethyl acetate). The crude enol ether was subjected to 1 N HCl for 2 h. The solution was basified with sodium carbonate and extracted with dichloromethane. The organic layer was washed with brine and subjected to flash chromatography to yield 1.0 g of additional **1**. Total amount of compound **1** isolated: 12.8 g (37%). M.p. = 97–99°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, $J = 4.8$, 2.8, 2H), 7.69 (dd, $J = 5.6$, 2.8, 2H), 6.97 (d, $J = 8.8$, 2H), 6.54 (d, $J = 8.8$, 2H), 3.88 (q, $J = 4.4$, 1H), 3.76 (q, $J = 19.2$, 2H), 3.68 (s, 3H), 3.52−3.44 (m, 2H), 3.38 (ddd, $J = 14$, 10, 3.6, 1H), 2.89 (dt, $J = 10$, 4.8, 1H), 2.61 (ddd, $J = 15$, 6, 1.2, 1H), 2.47 (dddd, $J = 15$, 14, 10, 6, 1H), 2.26 (m, 1H), 2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.0, 39.5, 41.6, 47.7, 55.3, 56.7, 58.2, 113.8, 123.4, 129.7, 130.9, 132.2, 134.1, 158.9, 168.2, 208.7; Anal. calcd for $C_{22}H_{22}N_2O_4$ (%): C, 69.77; H, 5.86; N, 7.26; found: C, 69.83; H, 5.86; N, 7.40; MS (APCI) m/z 379.3 (M + 1).

2-[8-(4-Methoxy-benzyl)-1,4-dioxa-8-aza-spiro[4.5]dec-7-yl methyl]-isoindole-1,3-dione (2)

A 500 mL flask, equipped with a reflux condensor and Dean-Stark trap was charged with compound **1** (3.0 g, 7.9 mmol), toluene (210 mL), ethylene glycol (3.62 mL, 20 equiv.), pyridinum *p*-toluenesulfonate (1.22 g, 4.8 mmol), and molecular sieves (4 Å, 1.5 g). The reaction mixture was heated to 140°C for 18 h. The reaction mixture was cooled to rt, diluted in ethyl acetate (500 mL) and washed with saturated sodium bicarbonate (3×100 mL), and brine (3×100 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in-vacuo to yield an oil. The oil was subjected to column chromatography (80% ethyl acetate/20% hexanes) to yield 2.51 g (75%) of 2-[8-(4-methoxy-benzyl)-1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl]-isoindole-1,3-dione **(2)** as an orange semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (dd, $J = 5.6$, 3.2, 2H), 7.66 (dd, $J = 5.6$, 3.2, 2H), 6.98 (dd, $J = 6.8$, 2, 2H), 6.52 (dd, $J = 6.4$, 1.6, 2H), 4.23 (dd, $J = 14$, 8.6, 1H), 3.93 (dddd, $J = 9.6$, 7.2, 6, 4.4, 2H), 3.87 (dddd, $J = 9.6$, 7.6, 6.4, 4.4, 2H), 3.81 (d, $J = 13.6$, 1H), 3.66 (s, 3H), 3.48 (ddd, $J = 19.6$, 14, 5.6, 2H), 3.15 (dddd, $J = 17.2$, 13.2, 9.2, 3.6, 1H), 3.06 (dddd, $J = 18.8$, 13.6, 10.4, 5.2, 1H), 2.50 (dddd, $J = 13.2$, 10.4, 6.4, 4, 1H), 1.85 (dddd, $J = 13.6$, 6.4, 5.2, 1.2, 1H), 1.69–1.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.8, 34.6, 40.1, 46.7, 55.3, 56.3, 56.6, 64.6, 107.6, 113.6, 123.3, 129.8, 131.8, 132.5, 133.9, 158.6, 168.5; Anal. calcd for $C_{24}H_{26}N_2O_5 \cdot 1.5\,H_2O$ (%): C, 64.13; H, 6.50; N, 6.23; found: C, 64.25; H, 5.75; N, 6.14; MS (APCI) m/z 423.1 (M + 1).

2-[8-(4-Methoxy-benzyl)-1,4-dioxa-8-aza-spiro[4.5]dec-7-yl]-methylamine (3)

2-[8-(4-Methoxy-benzyl)-1,4-dioxa-8-aza-spiro[4.5]dec-7-yl methyl]-isoindole-1,3-dione (**2**, 2.50 g, 5.9 mmol), was dissolved in ethanol (45 mL) and anhydrous hydrazine (0.93 mL, 29.6 mmol) added dropwise. The reaction was complete within 5 h at rt. The reaction mixture was evaporated to dryness under reduced pressure and the resultant solid dissolved in chloroform (40 mL). The solution was filtered to separate insolubles. The filtrate was concentrated, redissolved in chloroform and filtered once again. This procedure was repeated (~5 times) until no precipitate occurred and compound was pure by ^{1}H NMR. 2-[8-(4-methoxy-benzyl)-1,4-dioxa-8-aza-spiro[4.5]dec-7-yl]-methylamine (**3**) was isolated in 95% yield (1.63 g), as a yellow semi-solid. ^{1}H NMR

(400 MHz, $CDCl_3$) δ: 7.22 (d, $J = 8.8$, 2H), 6.84 (d, $J = 8.8$, 2H), 3.94 (dddd, $J = 6.4$, 5.2, 4, 2, 2H), 3.92 (dddd, $J = 9.2$, 6, 4, 1.6, 2H), 3.88 (d, $J = 13.2$, 1H), 3.78 (s, 3H), 3.34 (d, $J = 13.2$, 1H), 3.04 (dd, $J = 13.6$, 5.2, 1H), 2.92 (dd, $J = 13.2$, 5.6, 1H), 2.85 (dddd, $J = 12.8$, 10.4, 6, 4.4, 1H), 2.73 (m, 1H), 2.40 (ddd, $J = 13.2$, 9.6, 4, 1H), 1.76 (m, 2H), 1.65–1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.8, 36.2, 42.9, 47.5, 55.5, 55.9, 59.7, 64.4, 64.5, 107.8, 114.0, 130.1, 131.1, 158.9; Anal. calcd for $C_{16}H_{24}N_2O_3 \cdot 1.0\ H_2O$ (%): C, 61.91; H, 8.44; N, 9.03; found: C, 61.83; H, 7.98; N, 8.77; MS (APCI) m/z 293.2 (M + 1).

REFERENCES

1. (a) For a review on piperidine alkaloids: Plunkett, O.; Sainsbury, M. Rodd's Chem. Carbon Compd. 2nd Ed. **1998**, *4* (Parts F/G), 365–421; (b) Watson, P.S.; Jiang, B.; Scott, B. Organic Lett. **2000**, *2*, 3679–3681; (c) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. Chem. Rev. **1995**, *95*, 1677–1716; (d) Michael, J.P. Nat. Prod. Rep. **1998**, 571–594; (e) Mitchison, A.; Nadin, A. J. Chem. Soc. Perkin Trans I **1999**, 2553–2581.
2. For reviews of the hetero Diels-Alder reaction see: (a) Tietze, L.F.; Kettschau, G. Top. Curr. Chem. **1997**, *189*, 1–120; (b) Weinreb, S.M.; Levin, J.I. Heterocycles **1979**, *12*, 949–975; (c) Weinreb, S.M.; Staib, R.R. Tetrahedron **1982**, *38*, 3087–3128; (d) Waldmann, H. Synthesis **1994**, 535–551.
3. Akiyama, T.; Takaya, J.; Kagoshima, H. Tetrahedron Lett. **1999**, *40*, 7831–7834; (b) Ryan, K.M.; Reamer, R.A.; Volante, R.P.; Shinkai, I. Tetrahedron Lett. **1987**, *28*, 2103–2106; (c) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M.D.; Galvez, J.A. Tetrahedron Lett. **1997**, *38*, 2547–2550; (d) Abraham, H.; Stella, L. Tetrahedron, **1992**, *48*, 9707–9718. (e) Le Coz, L.; Veyrat-Martin, C.; Wartski, L.; Seyden-Penne, J.; Bois, C.; Philoche-Levisalles, M. J. Org. Chem. **1990**, *55*, 4870–4879.
4. Alvarez, M.; Fernandez, D.; Joule, J.A. Tetrahedron Lett. **2001**, *42*, 315–317.

Received in the USA August 16, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016