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Traceless solid-phase synthesis of N-substituted 3,5-bis(substituted-idene)piperidin-4-one derivatives

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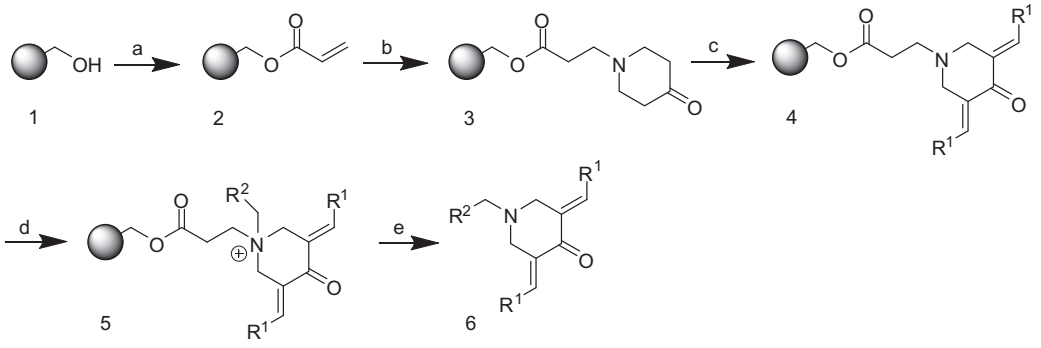
ABSTRACT

A series of N-substituted 3,5-bis(substituted-idene)piperidin-4-ones have been prepared using solid-phase organic synthesis. The synthesis starts with a Michael addition with piperidin-4-one serving as the donor and REM resin as the acceptor. Various aldehydes were then utilized through a Knoevenagel condensation to afford the 3,5-bis(substituted-idene)piperidin-4-ones on the solid support. The final products were removed from the support and a second diversity position was introduced through a Hofmann elimination using different alkyl bromides.

Solid-phase organic synthesis (SPOS) is a powerful technique for the rapid generation of structurally diverse compounds for the drug discovery community.[1] Solid-phase synthesis of heterocyclic compounds has received special attention because of their broad range of biological activities.[2] As a result, an increasing number of pharmaceutically useful heterocyclic compounds have been prepared recently using solid-phase methodology.[3]

The N-substituted 3,5-bis(substituted-idene)piperidin-4-one is an attractive drug template because of its cytotoxic properties and potential in cancer therapy.[4] Therefore, the facile preparation of diverse N-substituted 3,5-bis(substituted-idene)piperidin-4-ones for lead discovery is highly desirable. Although many solution-phase methods have been explored for the synthesis of this useful scaffold, very few solid-phase synthetic approaches have been reported.[5] Herein, we present an efficient solid-phase synthetic approach for the synthesis of N-substituted bis(substituted-idene)piperidin-4-ones. The linkage strategy involves the use of REM resin which has been widely used in the synthesis of tertiary amines and involves a final Hofmann elimination step to release the target products.

REM resin[6] **2** was prepared by treating hydroxyl resin **1** with acryloyl chloride in the presence of DIEA (diisopropylethylamine).[7] After piperidin-4-one was tethered to resin **2** by Michael addition, the afforded tertiary amine **3** was then condensed, respectively, with various aldehydes under TMCl-promoted Knoevenagel reaction condition.[8] The resulting tertiary amines **4** were quaternized with different alkyl bromides in DMF at 65 °C overnight to give the corresponding ammonium salts **5**, which were then released from the resin by Hofmann elimination. After purifying by preparative HPLC, pure N-substituted 3,5-bis(substituted-idene)piperidin-4-one products were obtained in good yields (Scheme 1).[9]



Scheme 1. Regents and conditions: (a) acryloyl chloride, DIEA, DCM, rt, overnight; (b) 4-piperidinone hydrate hydrochloride, DIEA, DMF, rt, 48 h; (c) aldehyde, TMSCl, DMF, 80 °C, 48 h; (d) alkyl bromide, DMF, 65 °C, overnight; (e) DIEA, acetonitrile, 65 °C, overnight.

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Table 1
N-substituted 3,5-bis(substituted-idene)piperidin-4-ones

Compound	R1	R2	Yield[a] (%)	M_W[b]
6a	4-Flourophenyl	Methyl	78	340.4 (M+1)
6b	4-Flourophenyl	2-Hydroxymethyl	67	356.4 (M+1)
6c	4-Flourophenyl	2-Phenoxyl methyl	73	432.5 (M+1)
6d	4-Flourophenyl	3,4-Difluorophenyl	81	438.4 (M+1)
6e	4-Methoxyphenyl	Methyl	76	364.5 (M+1)
6f	4-Methoxyphenyl	2-Hydroxymethyl	58	380.5 (M+1)
6g	4-Methoxyphenyl	2-Phenoxyl methyl	64	456.5 (M+1)
6h	4-Methoxyphenyl	3,4-Difluorophenyl	86	462.5 (M+1)
6i	Benzyl	Methyl	43	332.5 (M+1)
6j	Benzyl	2-Hydroxymethyl	45	348.5 (M+1)
6k	Benzyl	2-Phenoxyl methyl	52	424.6 (M+1)
6l	Benzyl	3,4-Difluorophenyl	60	430.5 (M+1)

[a] Yields are based on the weight of purified product and relative to the initial loading of the resin (1.1 mmol/g).
[b] Determined by ESI-MS.

To illustrate the versatility of this chemistry, a library of 12 compounds (**6a**–**i**) was prepared (Table 1). Three different aldehydes and four different alkyl bromides were employed in the synthesis of this library. For most of the compounds (**6a**–**h**), a single configuration (most likely *E*,*E*) product was detected by LCMS after the cleavage, although trace amounts of isomeric product (most likely *E*,*Z*-configuration) were detected in some crude products (**6i**–**l**). In all cases, pure (*E*,*E*) N-substituted 3,5-bis(substituted-idene)piperidin-4-one products were obtained in moderate yields after the HPLC purification. This is in agreement with reports that the known 3,5-bis(substituted-idene) piperidin-4-ones are isolated as thermodynamically more stable *E*,*E*-isomers.[4a]

In summary, we have developed an efficient traceless solid-phase synthetic approach for the synthesis of N-substituted 3,5-bis(substituted-idene)piperidin-4-one derivatives. The methodology is of value for high throughput synthesis of these potentially bioactive molecules.

Acknowledgments

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9. General procedure for the synthesis of N-substituted 3,5-bis(substituted-idene) piperid-4-one derivatives: 100 mg of benzyl alcohol resin (loading: 1.2 mmol/g) was sealed within a polypropylene mesh packet. Reactions were carried out in polyethylene bottles. REM resin was prepared following the protocol from the literature.[6] 4-Piperidinone hydrate hydrochloride (6 equiv) was tethered to the resin in the presence of DIEA (6 equiv) with DMF as solvent at room temperature for 48 h. After washing with DMF (three times), DCM (three times), and air dried, the resin-bound tertiary amine was reacted with aldehyde (10 equiv) in DMF using TMCl (1 equiv) as a catalyst at 80 °C for 48 h. The resin was then washed with DMF (three times), 5% DIEA/DCM (three times), DCM (three times), and MeOH (three times). The afforded resin was treated with alkyl bromide (6 equiv) in DMF at 65 °C overnight and then washed with DMF (three times) and DCM (three times). The crude product was released from the resin by heating at 65 °C overnight in acetonitrile with DIEA (2 equiv) as a base. The crude product was purified by preparative HPLC[10] and characterized by LC–MS under ESI positive mode and ^{1}H NMR. ESI-MS (*m*/*z*) of **6a**: 340.4 (M+H); ^{1}H NMR of **6a**: (500 MHz, DMSO-d_6): δ 1.24 (3H, t, *J* = 7.0 Hz), 2.70 (2H, q, *J* = 7.0 Hz), 3.63 (4H, s), 6.98 (4H, d, *J* = 7.6 Hz), 7.61 (2H, s), 8.23 (4H, d, *J* = 7.6 Hz).
10. The column used was a Phenomenex (Luna 5u C18(2) 100 Å AX, 150 × 21.20 mm 5 μm). A 5–95% gradient of water (0.1% Formic) and ACN (0.1% Formic) was used at 15 ml/min for 30 min, the fractions were monitored using a Shimadzu LCMS 2010 ESI positive mode.