Srinivas et al. Sustainable Chemical Processes 2014, 2:2
http://www.sustainablechemicalprocesses.com/content/2/1/2

SUSTAINABLE CHEMICAL PROCESSES

RESEARCH ARTICLE Open Access

Improved one-pot synthesis of N, N-diisopropyl-3-(2-Hydroxy-5-methylphenyl)-3-phenyl propanamide; a key intermediate for the preparation of racemic Tolterodine

Garaga Srinivas[1,2*], Ambati V Raghava Reddy[1], Koilpillai Joseph Prabahar[1], Korrapati venkata vara Prasada Rao[1], Paul Douglas Sanasi[2] and Raghubabu Korupolu[2]

Abstract

An improved, cost effective process for the synthesis of *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide; a key intermediate for the preparation of Tolterodine and its related substances were described. The process features one pot synthesis employing inexpensive reagents.

Keywords: Coumarin, Diisopropylamine, Aceticacid, Amidation, Tolterodine

Introduction

Tolterodine is chemically known as (R)-N,N-disiopropyl-3-(2-hydroxy-5-methyl phenyl)-3-phenyl propyl amine. Tolterodine acts as a muscarinic receptor antagonist. It is useful in the treatment of urinary incontinence [1]. Tolterodine tartrate acts by relaxing the smooth muscle tissues in the walls of the bladder by blocking cholinergic receptors [2]. Tolterodine tartrate [3] is marketed by Pharmacia & Upjohn in the brand name of Destrol®.

The present invention relates to a novel process for the preparation of *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (**4**); a key intermediate for the preparation of Tolterodine (**1**). Some different approaches have been published [4-8] for the preparation of *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (**4**). These methods involve multistep synthesis using hazardous, expensive reagents and some of the methods [6] involve activators like Grignard reagents, LDA, n-butyl lithium, Lewis acids. Hence there is a need to develop an alternative, plant friendly procedure for the preparation of *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (**4**) from 3,4-dihydro-6-methyl-4-phenylcoumarin (**2**) (Figure 1).

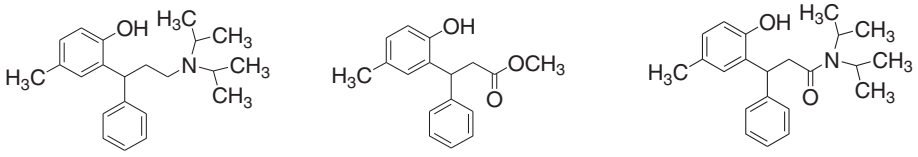
Results and discussion

Ring opening reactions of dihydrocoumarins are well known in literature [9-11]. But in the present invention, we have described a new methodology (Scheme 1 & Scheme 2) for the preparation of *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (**4**) by using inexpensive and commercially vailable starting materials like 3, 4-dihydro-6-methyl 4-phenylcoumarin (**2**), which was synthesized from p-cresol and trans-cinnamic acid [12].

3,4-Dihyhydro-6-methyl 4-phenylcoumarin (**2**) reacts with diisopropylamine (**6**) in presence of acetic acid gives *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (**4**) at room temperature. This process of compound **4** is very useful for commercialization of Tolterodine **1** in plant.

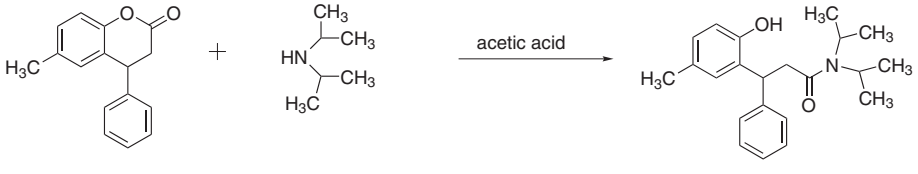
In order to optimize the yields, this reaction was studied in different solvents like Dichloromethane, Tetrahydrofuran, Acetonitrile, Toluene, Ethanol, Methanol and Diisopropylether. The reaction parameters are tabulated in Table 1. In methanol, methyl 3-(2-hydroxy-5-methylphenyl)-3-phenylpropanoate (**3**) was observed as an intermediate, which is not completely converted to amide (**4**). Hence the yield was found low. Among, diisopropylether was found to be the best suitable solvent for the preparation of

* Correspondence: srinivasgaraga@yahoo.com
[1]Chemical Research and Development Department, Aurobindo Pharma Ltd, Survey No:71&72, Indrakaran Village, Sangareddy Mandal, Medak district, Hyderabad 502329, Andhra Pradesh, India
[2]Engineering Chemistry Department, AU college of Engineering, Andhra University, Visakhapatnam 530003, Andhra Pradesh, India



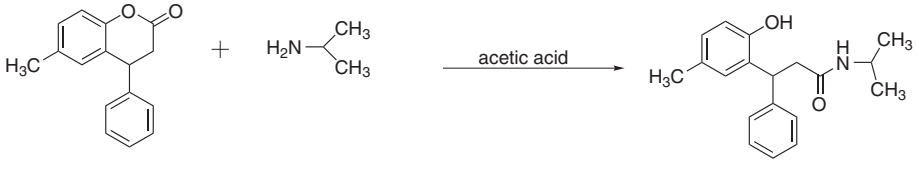
1 3 4

Figure 1 Tolterodine (1), Methyl 3-(2-hydroxy-5-methylphenyl)-3-phenylpropanoate (3) and *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (4).



2 6 4

Scheme 1 *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide 4.



2 7 5

Scheme 2 *N*-Isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide 5.

Table 1 Screening of solvent for the synthesis of compound 4

Entry	Coumarin	Amine	Solvent	Temparature	Yield (%)[c]
1.	2	DIPA[a]	DCM	Reflux	No reaction
2.	2	DIPA	THF	Reflux	No reaction
3.	2	DIPA	ACN	Reflux	No reaction
4.	2	DIPA	ACN	Sealed tube[b]	15
5.	2	DIPA	Methanol	25-30°C	15
6.	2	DIPA	Methanol	Reflux	15
7.	2	DIPA	Ethanol	Reflux	10
8.	2	DIPA	Toluene	Reflux	30
9.	2	DIPA	Diisopropylether	25-30°C	53

[a]N.N-diisopropylamine (DIPA), for all the above reactions 5 mole equivalents of DIPA used. [b]pressure reaction performed at 110°C. [c]isolated yields.

N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide (**4**), which results maximum yields of 53%.

In our continuous research, this reaction was further studied with acetic acid as a catalyst in diisopropylether. The experiments details are tabulated in Table 2. Based on the results, we observed the yield of compound **4** was increased to 75%, when 4 mole equivalents of acetic acid was used. But our attempts to increase the yield of compound **4** further by adding more equivalents of acetic

Table 2 Screening of catalyst for the synthesis of compound 4

Entry	Coumarin	Catalyst	Moles	Temparature	Yield (%)[a]
1.	2	Acetic acid	1	25-30°C	50
2.	2	Acetic acid	2	25-30°C	55
3.	2	Acetic acid	3	25-30°C	57
4.	2	Acetic acid	4	25-30°C	75
5.	2	Acetic acid	5	25-30°C	75

[a]isolated yields.

acid were not successful. With lesser equivalents of acetic acid, we observed lower yields of compound **4**.

Compound 4 is known in literature [4-12]. Compounds 4a-4c and 5-5c are novel. These compounds upon reduction [4-12] with $LiAlH_4$, Vitride, Sodium borohydride gives corresponding amines, which are useful in the synthesis of Tolterodine and its related compounds.

Conclusion

An efficient, synthesis of *N,N*-diisopropyl-3-(2-hydroxy-6-methylphenyl)-3-phenylpropanamide was achieved by one pot synthesis between 3,4-dihydro-6-methyl-4-phenylcoumarin and diisopropylamine.

Experimental

Solvents and reagents were obtained from commercial source and used without purification. The IR spectra (ϑmax, cm^{-1}) were recorded in solid state KBr dispersion using Perkin Elmer FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-Avance 300 MHz spectrometer. The chemical shifts were reported in δ/ ppm relative to TMS. The mass spectra were recorded on API 2000 Perkin Elmer PE-Sciex mass spectrometer. The reactions were monitored by Thin–layer chromatography (TLC). Melting points were determined by polman melting point apparatus (Model No MP96), open capillary method and are uncorrected.

General procedure for the synthesis of compounds 4-4c & 5-5c

To a solution of 3,4-dihyhydro-6-methyl 4-phenylcoumarin **2** (10 g, 42 mmol) in diisopropylether (200 mL), *N,N*-diisopropylamine (33.95 g, 336 mmol) and acetic acid (10 g, 168 mmol) were added at room temperature. The suspension was stirred for 16 h at room temperature. The reaction mass was concentrated, the resulting residue was crystallized with D.M.Water (50 mL) and diisopropyl ether (50 mL) mixture to gave *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide **4** (10.6 g, 75% yield).

This methodology was extended to make similar analogues **4-4c** and **5-5c** of compound **4** and **5**. The analogues were summarized in Tables 3 & 4.

Table 3 Novel analogues of compound 4

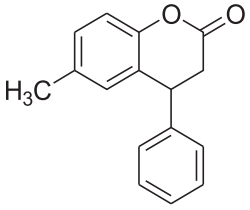
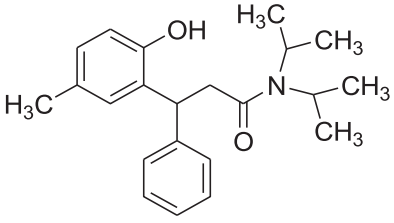
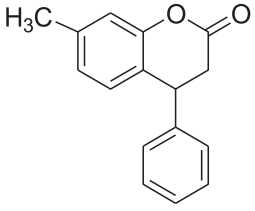
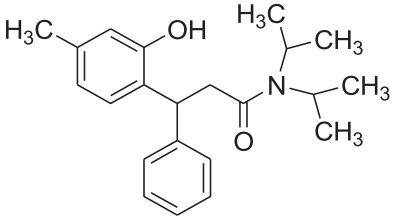
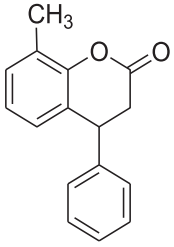
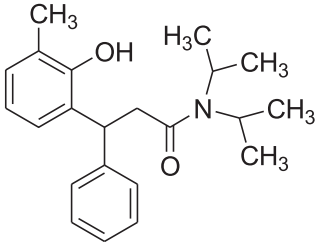
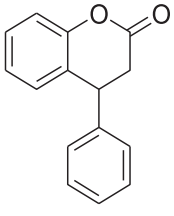
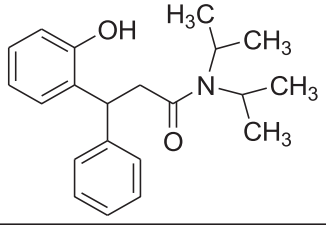
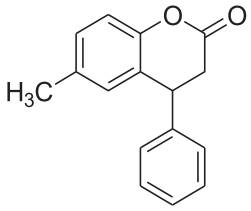
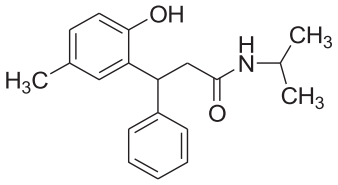
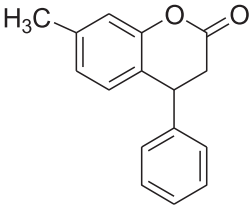
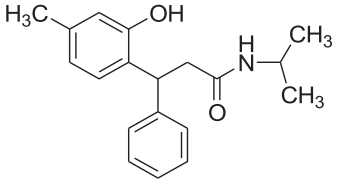
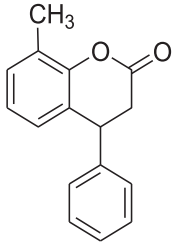
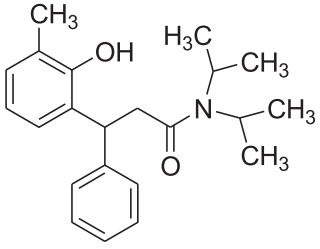
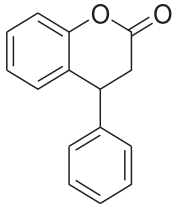
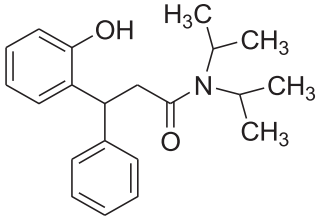
Entrty	Coumarin	Amine	Product	Melting range	Yield
4		DIPA		169- 173°C (literature mp 170-173°C)[7]	75%
4a		DIPA		151-155°C	77%
4b		DIPA		168-172°C	73%
4c		DIPA		169-173°C	75%

Table 4 novel analogues of compound 5 (Scheme 2)

Entrty	Coumarin	Amine	Product	Melting range	Yield
5		MIPA[a]		136-139°C	98%
5a		MIPA		132-136°C	88%
5b		MIPA		162-166°C	97%
5c		MIPA		125-128°C	90%

[a]Isopropylamine.

N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide 4

IR (KBr) cm^{-1}: 3024 (Aromatic C-H, str.), 2949, 2904, 2869 (Aliphatic C-H, str.), 1630 (C═O, str.), 1609, 1555, 1510 (C═C, str.), 1469, 1459 (CH_2 bending), 1270 (C-N, str.), 1072 (C-O, str.), 788, 769 (Aromatic CH Out-of-plane bend). ^1H NMR (300 MHz, DMSO-d_6) δ 1.04 (d, 12H), 2.089 (s, 3H), 2.79 (m, 2H), 3.037 (m, 2H), 4.702 (t, 1H), 6.6 (d, 1H), 6.75 (d, 2H), 7.127-7.246 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.39, 20.36, 45.69, 115.33, 125.70, 127.20, 128.15, 130.60, 144.43, 152.23, 173.37. MS *m/z*: 340 $[(M + H)^+]$.

N-Isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide 5

IR (KBr), cm^{-1}: 3030 (Aromatic C-H, str.), 2977, 2932, 2872 (Aliphatic C-H, str.), 1628 (C═O, str.), 1605, 1556, 1509 (C═C, str.), 1496, 1453 (CH_2 bending), 1270 (C-N, str.), 1081 (C-O, str.), 790,753 (Aromatic CH Out-of-plane bend). ^1H NMR (300 MHz, DMSO-d_6) δ 0.9 (m, 6H), 2.16 (s, 3H), 2.69 (m, 2H), 3.69 (m, 1H), 4.74 (t, 1H), 6.6 (d, 1H), 6.76 (d, 2H), 7.08-7.2 (m, 5H), 7.64 (d, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.37, 22.30, 39.17, 39.50, 39.70, 39.90, 40.00, 40.71, 114.98, 125.54, 126.91, 127.11, 127.81, 128.15, 130.11, 144.48, 152.21, 169.38. MS *m/z*: 298 $[(M + H)^+]$.

N,N-diisopropyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropanamide 4a

IR (KBr) cm^{-1}: 3024 (Aromatic C-H, str.), 2984, 2950, 2863 (Aliphatic C-H, str.), 1625 (C═O, str.), 1567, 1493 (C═C, str.), 1470, 1427 (CH_2 bending), 1282 (C-N, str.), 1072 (C-O, str.), 781,762 (Aromatic CH Out-of-plane bend). ^1H NMR (300 MHz, DMSO-d_6) δ 1.04 (d, 12H), 2.089 (s, 3H), 2.79 (m, 2H), 3.037 (m, 2H), 4.702 (t, 1H), 6.6 (d, 1H), 6.75 (d, 2H), 7.127-7.246 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.18, 20.60, 39.0, 39.17, 39.34, 39.50, 39.67, 39.77, 39.84, 40.0, 42.59, 45.22, 116.72,

119.51, 125.41, 127.87, 129.41, 135.58, 145.47, 154.72, 174.71. MS *m/z*: 340 [(M + H)$^+$].

N-Isopropyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropanamide 5a

IR (KBr) cm^{-1}: 3026 (Aromatic C-H, str.), 2977, 2934, 2874 (Aliphatic C-H, str.), 1627 (C=O, str.), 1610, 1589, 1543 (C=C, str.), 1492, 1449 (CH_2 bending), 1245 (C-N, str.), 1074 (C-O, str.), 780,756 (Aromatic CH Out-of-plane bend). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.9 (m, 6H), 2.16 (s, 3H), 2.69 (m, 2H), 3.69 (m, 1H), 4.74 (t, 1H), 6.6 (d, 1H), 6.76 (d, 2H), 7.08-7.2 (m, 5H), 7.64 (d,1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 0.65, 22.30, 39.17, 39.33, 39.50, 39.67, 39.83, 40.0, 40.74, 115.76, 119.40, 125.51, 127.57, 127.78, 135.95, 144.60, 154.33, 169.42. MS *m/z*: 298 [(M + H)$^+$].

N,N-diisopropyl-3-(2-hydroxy-3-methylphenyl)-3-phenylpropanamide 4b

IR (KBr), cm^{-1}: 3030 (Aromatic C-H, str.), 2952, 2920, 2877 (Aliphatic C-H, str.),1629 (C=O, str.), 1592, 1548, 1495 (C=C, str.), 1466, 1418 (CH_2 bending), 1265 (C-N, str.), 1067.7 (C-O, str.), 780, 769 (Aromatic CH Out-of-plane bend). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (d, 12H), 2.089 (s, 3H), 2.79 (m, 2H), 3.037 (m, 2H), 4.702 (t, 1H), 6.6 (d, 1H), 6.75 (d, 2H), 7.127-7.246 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.6, 16.81, 19.09, 19.14, 40.01, 43.93, 45.64, 118.75, 125.99, 127.66, 128.10, 133.33, 145.66, 153.17, 175.73. MS *m/z*: 340 [(M + H)].

N-Isopropyl-3-(2-hydroxy-3-methylphenyl)-3-phenylpropanamide 5b

IR (KBr): cm^{-1}: 3024 (Aromatic C-H, str.), 2944, 2916, 2895 (Aliphatic C-H, str.), 1627 (C=O, str.), 1592, 1561 (C=C, str.), 1466, 1431 (CH_2 bending), 1274 (C-N, str.), 1080 (C-O, str.), 779.8, 771 (Aromatic CH Out-of-plane bend). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.9 (m, 6H), 2.16 (s, 3H), 2.69 (m, 2H), 3.69 (m, 1H), 4.74 (t, 1H), 6.6 (d, 1H), 6.76 (d, 2H), 7.08-7.2 (m, 5H), 7.64 (d, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.78, 22.25, 39.0, 39.16, 39.33, 39.50, 39.59, 39.66, 39.83, 40.01, 41.04, 119.20, 124.58, 125.21, 125.62, 127.87, 128.36, 131.46, 144.53, 152.21, 169.60. MS *m/z*: 298 [(M + H)$^+$].

N,N-diisopropyl-3-(2-hydroxy phenyl)-3-phenylpropanamide 4c

IR (KBr): cm^{-1}: 3028 (Aromatic C-H, str.), 2944, 2871 (Aliphatic C-H, str.), 1627 (C=O, str.), 1557, 1497 (C=C, str.), 1469, 1452 (CH_2 bending), 1270 (C-N, str.), 1073 (C-O, str.), 780,753 (Aromatic CH Out-of-plane bend). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (d, 12H), 2.089 (s, 3H), 2.79 (m, 2H), 3.037 (m, 2H), 4.702 (t, 1H), 6.6 (d, 1H), 6.75 (d, 2H), 7.127-7.246 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.25, 39.00, 39.17, 39.33, 39.50, 39.67, 39.83, 40.0, 42.53, 45.22, 116.14, 118.75, 125.51, 126.51, 127.97, 132.36, 145.25, 154.92, 174.56. MS *m/z*: 326 [(M + H)$^+$].

N-Isopropyl-3-(2-hydroxy phenyl)-3-phenylpropanamide 5c

IR (KBr): cm^{-1}: 3027 (Aromatic C-H, str.), 2933, 2874 (Aliphatic C-H, str.), 1626 (C=O, str.), 1557, 1505 (C=C, str.), 1496, 1456 (CH_2 bending), 1271 (C-N, str.), 1081 (C-O, str.). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.9 (m.6H), 2.16 (s, 3H), 2.69 (m, 2H), 3.69 (m, 1H), 4.74 (t, 1H), 6.6 (d, 1H), 6.76 (d, 2H), 7.08-7.2 (m, 5H), 7.64 (d, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.26, 22.28, 38.99, 39.16, 39.33, 39.50, 39.66, 39.73, 39.83, 39.93, 40.0, 40.65, 115.11, 118.725, 125.60, 126.84, 127.79, 130.47, 144.36, 154.48, 169.36. MS *m/z*: 284 [(M + H)$^+$].

Data of the compounds 4-4c,5-5c

'Additional file 1 complete spectral data. This material can be found via the 'Supplementary Content' section of this article's web page'.

Additional file

Additional file 1: Supporting information for compounds 4-4c, 5-5c.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors read and approved the final manuscript.

Acknowledgements

The authors gratefully acknowledge the management of Aurobindo pharma limited for allowing to us carryout this research work.

Received: 20 October 2013 Accepted: 2 January 2014
Published: 20 January 2014

References

1. Jonas U, Hoefner K, Madersbacher H, Holmdahl TH: *World J Urol* 1997, **15:**144–151.
2. Nilvebrant I, Anderson KE, Gillberg PG, Stahl M, Sparf B: *Eur J Pharmacol* 1997, **327:**195–207.
3. Tolterodine Tartrate (Destrol®): *Physicians Desk Reference*. 66th edition. LLC: Montvale, NJ: PDR Network; 2012:2482–2489.
4. Gianolli E, Giannini E, Bigini L, Piccolo O, Holmberg P, Lundholm T: **Process for the preparation of *N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and its salts.** *PCT Int Appl* 2012, **157:**294728. WO 2012098044 A1 20120726 CAN.
5. Kobayashi K, Nishikata T, Yamamoto Y, Miyaura N: **Stepwise palladium-catalyzed 1,4-addition of arylboronic acids to enones and regioselective Baeyer-Villiger oxidation for enantioselective synthesis of β -diaryl esters and (+)-(R)-tolterodine.** *Bull Chem Soc Jpn* 2008, **81**(8):1019–1025. CAN 149:471296.
6. Wang G, Zhang J, He X, Wang Y: **Process for preparation of Tolterodine and tartrate.** *Faming Zhuanli Shenqing* 2009, **CN 101445462 A 20090603 CAN 151:**77765.
7. Kompella A, Thungathuthy Srinivasa R, Adibhtla Kali S, Bhujanga R, Venkaiah C, Nannapaneni: **Process for the preparation of an intermediate useful in the synthesis of tolterodine.** *Indian Pat Appl* 2005, **IN 2003CH01028 A 20051230 CAN 147:**486225.

8. Razzetti G, Mantegazza S, Rossi R, Allegrini P: **A process for the preparation of tolterodine.** *Eur Pat Appl* 2006, **EP 1693361 A1 20060823 CAN 145:**271484.
9. Kelin L, Tunge JA: *J Org Chem* 2008, **73:**8651–8653.
10. Li K, Tunge JAJ: *J Comb Chem* 2008, **10:**170–174.
11. Bussolari JC, Rehborn DC, Combs DW: *Tetrahedron Lett* 1999, **40:**1241–1244.
12. Jonsson N, Spart BA, Mikiver L, Moses P, Nilverbrant L, Glas G: **U.S. Patent 5,382,600.** 1995.

doi:10.1186/2043-7129-2-2
Cite this article as: Srinivas *et al.*: Improved one-pot synthesis of N, N-diisopropyl-3-(2-Hydroxy-5-methylphenyl)-3-phenyl propanamide; a key intermediate for the preparation of racemic Tolterodine. *Sustainable Chemical Processes* 2014 **2**:2.