http://dx.doi.org/10.5935/0103-5053.20130177

J. Braz. Chem. Soc., Vol. 24, No. 9, 1396-1402, 2013.
Printed in Brazil - ©2013 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

A Straightforward and Efficient Method for the Synthesis of Diversely Substituted β-Aminoketones and γ-Aminoalcohols from 3-(*N*,*N*-Dimethylamino)propiophenones as Starting Materials

Rodrigo Abonia,* Danny Arteaga, Juan Castillo, Braulio Insuasty, Jairo Quiroga and Alejandro Ortíz

Research Group of Heterocyclic Compounds, Department of Chemistry, Universidad del Valle, A. A. 25360, Cali, Colombia

Bibliotecas de novos β-aminocetonas e γ-aminoálcoois que mostram uma grande diversidade estrutural foram facilmente obtidas a partir de uma abordagem simple, utilizando os derivados da 3-(*N*,*N*-dimetilamino)propiofenona como material de partida chave. O procedimento envolveu inicialmente a *N*-alquilação de benzilaminas secundárias com derivados de propiofenona produzindo as desejadas β-aminocetonas. A redução química ou catalítica dos grupos carbonilo atinge a obtenção dos γ-aminoálcoois em bons rendimentos. Este protocolo mostrou ser uma via alternativa conveniente para a síntese do anestésico local Falicain® e para a droga tópica antifúngica Naftifina®.

Libraries of novel β-aminoketones and γ-aminoalcohols showing a wide structural diversity were easily obtained from a simple approach, using 3-(*N*,*N*-dimethylamino)propiophenone derivatives as key starting material. The procedure involved initially an *N*-alkylation of secondary benzylamines with propiophenone salts yielding the desired β-aminoketones. Chemical or catalytic reduction of their carbonyl groups provided the final γ-aminoalcohols in good yields. This protocol proved to be convenient as an alternative route for the synthesis of the local anesthetic Falicain® and for the topic antifungal drug Naftifine®.

Keywords: benzylamines, propiophenones, β-aminoketones, γ-aminoalcohols, Mannich type reaction

Introduction

Amino-ketones and aminoalcohols are compounds with superior importance not only for their practical applications displayed by themselves but also because they have been found forming part of the structure of synthetic and naturally occurring compounds of diverse practical interest.[1] Thus, Falicain® (a local anesthetic and bronchomotor),[2] compound BE-2254 (antihypertensive and very selective α_1-adrenoceptor antagonist, precursor of the 3-^{125}I-derivative),[3] Moban (a neuroleptic)[4] and the benzylamine derivative **1** (a potent Jak3 kinase inhibitor),[5] are representative examples of this large family of amino-compounds (Figure 1), as well as the naturally occurring aminoalcohols Anisomycin (a potent activator of stress-activated protein kinases (JNK/SAPK) and p38 MAP kinase)[6] and Castanospermine (a potent inhibitor of α- and β-glucosidases inhibits HIV syncytium formation and replication),[7] the synthetic aminoalcohols Salbutamol (a non-selective β-adrenergic agonist, more potent for β_2 than β_1 receptors)[8] and the phenyl/thienyl-γ-aminoalcohols **2** (direct precursors for the synthesis of Fluoxetine (Ar = Ph) and Duloxetine (Ar = 2-thyenyl), selective serotonin reuptake inhibitors).[9]

Particularly, Guarna *et al.*[10] reported the synthesis of new γ-aminoalcohols **7** as potential ^{125}I-radioligands for dopamine and serotonin receptors. The synthesis of these compounds was achieved in a four-step sequence as described in Scheme 1. Continuing with our studies toward the synthesis and functionalization of benzylamine derivatives,[11-13] herein, we report our results on alternative and simple approaches for the synthesis of new β-aminoketones **10** and their subsequent reduction to the corresponding γ-aminoalcohols **11**, structurally

*e-mail: rodrigo.abonia@correounivalle.edu.co

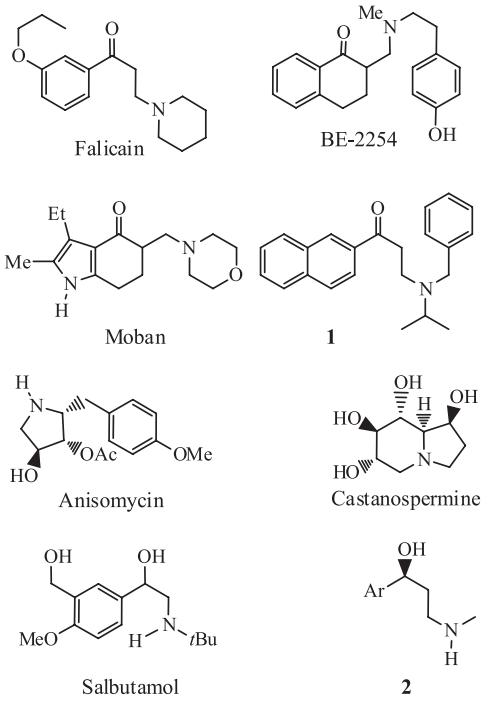


Figure 1. Some amino-ketones and aminoalcohols of biological interest.

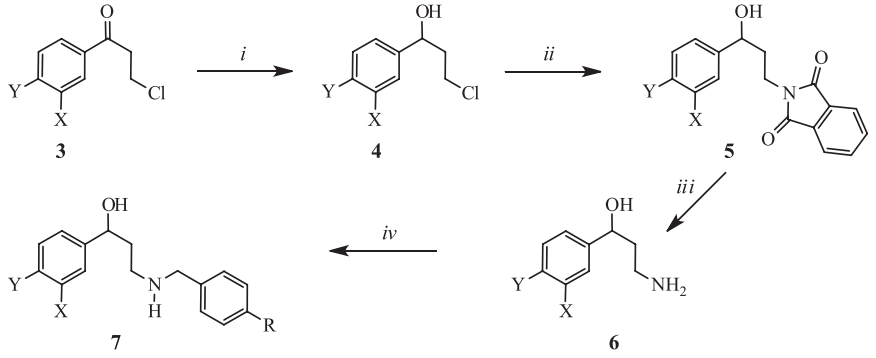
related to the active compounds **1**, **2** and **7**, from secondary benzylamines and 3-(*N*,*N*-dimethylamino)propiophenone derivatives, as easily accessible starting materials (Scheme 2).

Experimental

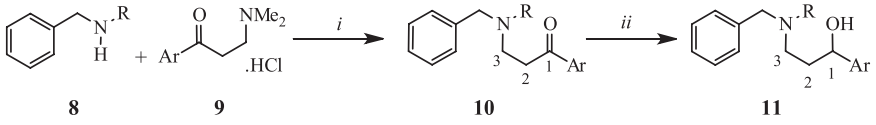
Melting points were determined on a Büchi B-450 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR 8400 spectrophotometer in KBr disks and films. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal standard for ^{1}H NMR. Mass spectra were run on a Shimadzu 2010-DI-2010 GC-MS apparatus (equipped with a direct inlet probe) operating at 70 eV. Microanalyses were performed on an Agilent elemental analyzer and the results are within ± 0.4% of the theoretical values. Silica gel plates (Merck 60 F_{254}) were used for analytical TLC. The starting amines **8a-d** and **8f-h** (Figure 2) were purchased from Aldrich, Fluka and Acros and were used without further purification. Owing that benzylamine **8e** is commercially unavailable, it was synthesized by a reductive amination from benzylamine and 3,4,5-trimethoxybenzaldehyde, following a similar procedure as described previously.[11,12] The 3-(*N*,*N*-dimethylamino) propiophenone hydrochlorides **9a-d** were synthesized from their respective acetophenones by following a procedure similar to that described in the literature.[14]

General procedure for the synthesis of the β-aminoketones (**10**)

A mixture of amine **8** (500 mg) and the corresponding 3-(*N*,*N*-dimethylamino)propiophenone hydrochloride **9** (1 mmol) was dissolved in a mixture of 1,4-dioxane (5 mL) and triethylamine (TEA, 1 mL). The solution was stirred at reflux for 0.5-2 h until the starting materials were not further detected by TLC. After cooling, the solvent was removed under reduced pressure and the crude was purified by column chromatography on silica gel, using a mixture of CH_2Cl_2:AcOEt (5:1) as eluent.



Scheme 1. Four-step synthesis of the ^{125}I-radioligands **7** for dopamine and serotonin receptors (X, Y = H, F, Br, I); (*i*) $NaBH_4$, MeOH, 0 °C; (*ii*) phthalimide, KF, DMF, 120 °C, 8 h; (*iii*) $H_2N–NH_2$, H_2O-MeOH-HCl, reflux, 3 h; (*iv*) 4-R-C_6H_4CHO (R = H, F), $NaBH_3CN$, MeOH, 24 h, temperature. Adapted from reference 10.



Scheme 2. Proposed sequence for the synthesis of β-aminoketones (**10**) and γ-aminoalcohols (**11**) from the benzylmethylamine derivatives (**8**).

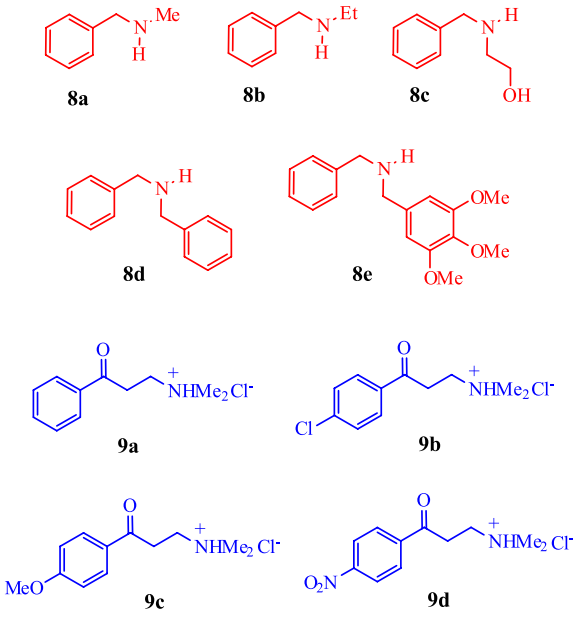


Figure 2. Diversity of benzylamines (**8**) and propiophenones (**9**) employed as reagents for the synthesis of products **10** and **11**.

General procedure for the synthesis of γ-aminoalcohols (**11**)

Approach A: Raney-nickel was added (100 mg) to a sample of aminoketone **10** (300 mg) dissolved in ethanol (15 mL), and then was stirred for 3-4 h at room temperature under hydrogen pressure (50 psi) in a Parr apparatus. When the starting material was not detected by TLC and by the IR spectrum, the catalyst was filtered off, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, using a mixture of CH_2Cl_2:MeOH (20:1) as eluent.

Approach B: Solid $NaBH_4$ (2 mmol) was added portionwise to a sample of aminoketone **10** (300 mg, 1 mmol) dissolved in methanol (5 mL), and then was stirred for 0.5-1 h at room temperature. When the starting material **10** was not further detected by TLC, the volume of the reaction mixture was reduced to 1 mL under reduced pressure, and water (5 mL) was added. The aqueous solution was extracted with ethyl acetate (2 × 5 mL), and the combined organic extracts were dried with Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel, using a mixture of CH_2Cl_2:MeOH (20:1) as eluent.

Results and Discussion

Initially, a mixture of benzylmethylamine **8a** (R = Me, 1 mmol) and *N*,*N*-dimethylaminopropiophenone hydrochloride **9a** (Ar = Ph, 1 mmol)[14] was subjected to reflux for 4 h in ethanol (step *i*, Scheme 2). This (approach 1) provided the corresponding β-aminoketone **10a** (R = Me, Ar = Ph) as a pale yellow oily material in only 30% isolated yield. Repeating the same reaction but using a 4:1 ethanol:TEA mixture (approach 2), afforded **10a** in 68% isolated yield, after 2 h of heating. Pursuing to improve the efficiency of the formation of ketone **10a**, the reaction was repeated but using a 5:1 v/v mixture of 1,4-dioxane:TEA (approach 3). After heating for 1 h and verifying complete consumption of the starting materials (TLC control), product **10a** was obtained in 88% isolated yield.

Once established the better reaction conditions and in order to determine its scope and general character, the approach 3 was extended to the benzylamine chemset **8a-e** and propiophenone chemset **9a-d** (Figure 2). To our satisfaction, the corresponding β-aminoketones **10a-k** were fairly obtained in 0.5-2 h reaction times and 62-90% isolated yields, as shown in Table 1. The IR spectra of compounds **10** showed absorption bands corresponding to the C=O moiety in the range of 1671-1696 cm^{-1}. In the case of **10f**, an additional hydroxyl broad band was observed at 3426 cm^{-1} corresponding to the OH group. The main signals in the ^1H NMR spectra corresponded to a triplet integrating for 2H in the range of 2.70-3.01 ppm, assigned to the H-2 protons, a triplet for 2H in the range of 3.08-3.22 ppm, assigned to the H-3 protons, and a singlet for 2H (or 4H) in the range of 3.56-3.98 ppm, assigned to the benzylic protons. The more relevant features in the ^{13}C NMR spectra of compounds **10** corresponded to signals in the ranges 36.4-36.9, 48.5-52.4, 58.2-62.5 and 197.9-199.6 ppm, which were assigned to the C-2 carbon atoms, the C-3 carbons, the methylene carbon atom of the benzyl functionality and the C=O carbon atoms, respectively.

Most of the mass spectra of compounds **10** are characterized by low-intensity peaks for their molecular ions and base peaks at *m/z* 91, corresponding to the tropylium ion resulting from the benzyl functionality. In the case of structures **10j** and **10k**, which possess two possible tropylium ions, the base peak appears at *m/z* 181 due to the higher stability of its trimethoxy analogue than the proper tropylium ion.

Once the β-aminoketones **10** were efficiently obtained, reduction of their carbonyl groups was undertaken (step *ii*, Scheme 2). Recently, Cho and Kang[15] reported an efficient chemical reduction of carbonyl derivatives by grinding a mixture of the respective carbonyl compound and $NaBH_4$ in the presence of benzoic acid in a mortar. Unfortunately, the extension of this procedure to β-aminoketone **10a** was unsuccessful and no product **11a** was formed. Moreover, this reaction was difficult to handle. In a second approach, compound **10a** was dissolved in methanol and subjected to a catalytic hydrogenation at room temperature in a Parr

Table 1. Synthesis of the β-aminoketones (**10a-k**) and γ-aminoalcohols (**11a-k**)

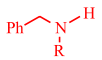
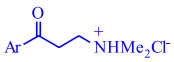
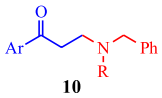
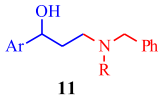
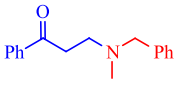
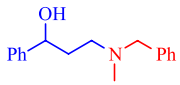
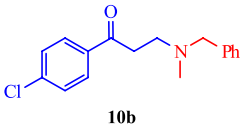
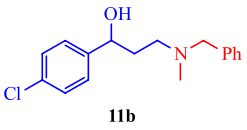
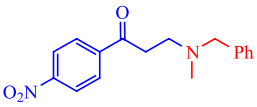
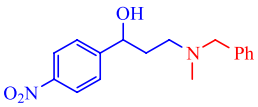
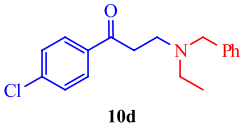
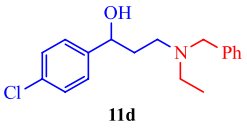
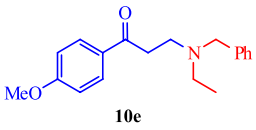
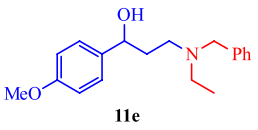
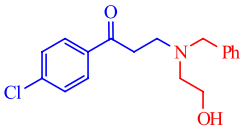
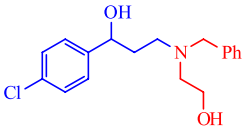
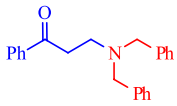
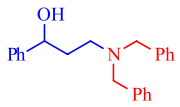
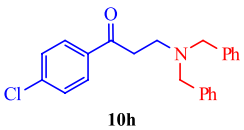
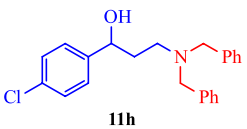
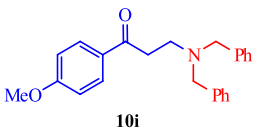
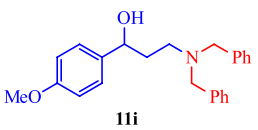
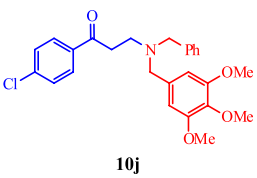
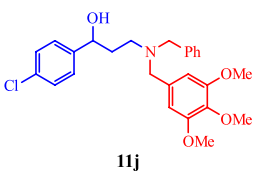
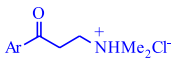
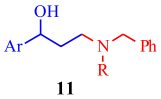
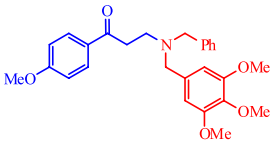
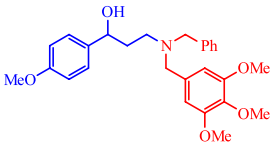
Entry	 **8**	 **9**	 **10**	 **11**	Yield / % **10** / **11**[a,b]
1	**8a**	**9a**	 **10a**	 **11a**	88[c,d] / (84)82[d]
2	**8a**	**9b**	 **10b**	 **11b**	78[e] / (86)96
3	**8a**	**9d**	 **10c**	 **11c**	62[f] / 57[g]
4	**8b**	**9b**	 **10d**	 **11d**	74 / (93)83
5	**8b**	**9c**	 **10e**	 **11e**	90 / (78)89
6	**8c**	**9b**	 **10f**	 **11f**	65 / (72)61
7	**8d**	**9a**	 **10g**	 **11g**	68[h] / (81)85[i]
8	**8d**	**9b**	 **10h**	 **11h**	77[j] / (85)92
9	**8d**	**9c**	 **10i**	 **11i**	69[j,k] / (81)93
10	**8e**	**9b**	 **10j**	 **11j**	79/(88)91

Table 1. continuation

Entry	 **8**	 **9**	 **10**	 **11**	Yield / % **10** / **11**[a,b]
11	**8e**	**9c**	 **10k**	 **11k**	62/(80)67

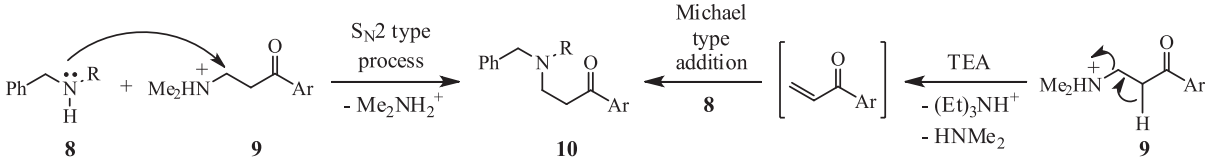
[a]Isolated yields of alcohols from the catalytic hydrogenation between parentheses. [b]Isolated yields of alcohols from chemical reduction with $NaBH_4$. [c]Previously obtained by hydrolysis of an acetylenic derivative; yield not supplied.[17] [d]Previously obtained by $LiAlH_4$ reduction of the amide and carboxymethyl functionalities of the respective perhydrooxazinone; yield not supplied. Also obtained from acetophenone, benzylmethylamine hydrochloride and paraformaldehyde; yield not supplied.[18] [e]Previously obtained from the corresponding phenacyl bromide and benzylmethylamine (63%).[19] [f]Previously obtained from 4-nitroacetophenone, paraformaldehyde and benzylmethylamine hydrochloride (70%).[20] [g]Only chemical reduction is reported; the catalytic hydrogenation afforded a mixture containing the *p*-amino-derivative. [h]Previously obtained from 1,3-dimethyl-imidazoline, acethophenone and dibenzylamine in AcOH (55%).[21] [i]Previously obtained by reduction of **10g** with $NaBH_4$ at 60 °C (72%).[22] [j]Known compound.[23] [k]Previously reported.[24]

apparatus in the presence of Raney nickel as catalyst,[16] affording the corresponding γ-aminoalcohol **11a** as a light oily material in 84% isolated yield. Trying to simplify the reduction procedure, aminoketone **10a** was treated with $NaBH_4$ in methanol at room temperature, affording the γ-aminoalcohol **11a** in 82% isolated yield. At this point, it is worth mentioning that catalytic hydrogenation provided a slightly better yield and an easier work-up than the borohydride-mediated reduction. According to these results, the reduction of the remaining aminoketones **10** either by catalytic hydrogenation or chemical reduction afforded the corresponding γ-aminoalcohols **11** in 72-93 or 57-96% isolated yields, respectively (Table 1).

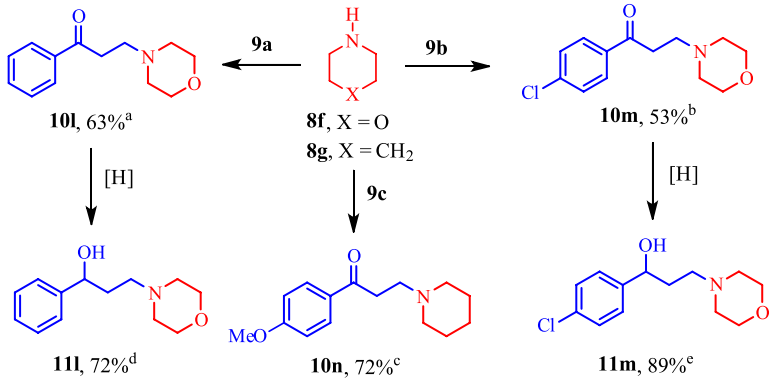
The absence of the C=O absorption bands and the observation of new O–H absorption broad bands in the range of 3218-3409 cm^{-1} were the main features of the IR spectra of compounds **11**. The main signals in the ^1H NMR spectra corresponded to a multiplet integrating for 2H in the range of 1.73-2.04 ppm, assigned to the H-2 protons, a double-double-doublet for 1H in the range of 2.56-2.68 ppm, assigned to a diastereotopic H-3 proton, a double-double-doublet for 1H in the range of 2.69-3.64 ppm, assigned to the other H-3 proton, a pair of doublet (1H each) in the ranges 3.29-3.64 and 3.61-3.88 ppm, assigned to both diastereotopic benzylic methylene protons ($PhCH_2$), and a double-doublet for 1H in the range of 4.71-5.00 ppm assigned to the H-1 proton. Some hydroxyl protons appeared as broad singlets in the range of 5.42-6.46 ppm. Likewise, the more relevant feature in the ^{13}C NMR spectra of compounds **11** was the appearance of a new aliphatic signal in the range of 73.7-75.6 ppm, assigned to the C-1 carbon atom. The disappearance of the C=O signals are also in agreement with the assigned structures. The mass spectra also showed the tropylium ions as base peaks and as the main signals.

According to the results, the formation of the β-aminoketones **10** should proceed via two possible processes, either a S_N2 type reaction or alternatively through a Michael type addition, as shown in Scheme 3.

A S_N2 process is more likely to proceed under neutral or acidic conditions, in which the dimethyl ammonium moiety of the aminoketone salt (**9**) should behave as a good leaving group.[25,26] In this sense, the formation of the product **10a** under approach 1 should be governed mainly by this mechanistic pathway. Meanwhile, when the reaction was carried out in basic media (approaches 2 and 3), a Michael type addition should be the more likely mechanistic pathway, mediated by an arylvinyl ketone (**12**).[27] Formation of this intermediate should be facilitated by the action of TEA via a Hofmann type β-elimination.[26] The detection of this intermediate in the reaction media and some reports of the literature



Scheme 3. Proposed mechanisms for the formation of the β-aminoketones (**10**).

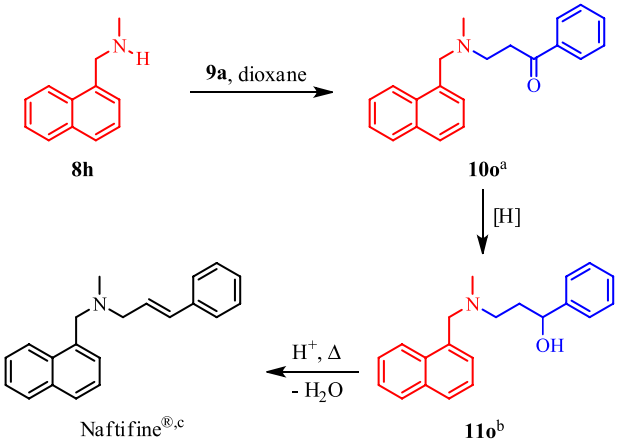


Scheme 4. Synthesis of novel β-aminoketones (**10l**, **10m** and **10n**) and γ-aminoalcohols (**11l** and **11m**) from the reaction of propiophenones (**9a**, **9b** and **9c**) with morpholine (**8f**) and piperidine (**8g**). [a]Previously obtained from acetophenone, paraformaldehyde and morpholine hydrochloride (63%).[28] [b]Yield of the original synthesis not supplied.[29] [c]Previously obtained from 4-methoxyacetophenone, formaldehyde and piperidine (70%).[30] [d]Previously obtained by reduction of **10l** with $NaBH_4$ at 60 °C (84%).[22] [e]Previously obtained by reduction of **10m** with $NaBH_4$ at 60 °C (70%).[22]

support this proposal,[27] which is also reinforced by the relative acidity of the α-hydrogen atoms in **9,** which should be relatively easy to be removed by TEA as the initial step for the elimination process (Scheme 3).

To evaluate the scope of this two-step protocol, the heterocyclic derivatives **11l** and **11m** were efficiently obtained by treatment of propiophenones **9a** and **9b**, respectively, with morpholine **8f** and the subsequent reduction of their carbonyl groups. Likewise, the β-aminoketone **10n** was fairly obtained from the reaction of propiophenone **9c** with piperidine **8g**. Interestingly, the piperidine derivative **10n** is structurally close to the anesthetic Falicain® (Scheme 1); Therefore, this approach could become an alternative synthetic route for Falicain® and derivatives (Scheme 4).

To further confirm the practical scope of our two-step protocol, we envisioned the possibility of developing



Scheme 5. Alternative synthetic route for the antifungic Naftifine®. [a]Previously obtained from acetophenone, formaldehyde and *N*-methyl(naphthalen-5-yl)methanamine (55%).[32] [b]Previously obtained by reduction of **10o** with $NaBH_4$ (quant.).[32] [c]Previously obtained by reductive methylation of the respective secondary amine with formaldehyde (94%).[32]

an alternative synthetic route towards Naftifine,® a recognized and highly active antifungal agent.[31] Initially, the commercially available naphthylamine **8h** was treated with propiophenone **9a** to afford the aminoketone **10o** in 89% isolated yield. Then, reduction of **10o** with $NaBH_4$/MeOH at room temperature afforded the aminoalcohol **11o** in 98% isolated yield, which was dehydrated by treatment with refluxing 5 eq-g L^{-1} HCl to afford the expected product in 86% isolated yield (Scheme 5).

Conclusion

In summary, we developed a straightforward, versatile and simple approach for the synthesis of new β-aminoketones (**10**) and their corresponding γ-aminoalcohols (**11**), structurally related to relevant active compounds, by reaction of secondary benzylamines with 3-(*N*,*N*-dimethylamino)propiophenone salts. Several of the obtained compounds **10** and **11** have previously been reported elsewhere; however, under our modified conditions they have been obtained in better or at least comparable yields. Finally, the usefulness of the procedure as an alternative synthesis of biologically active products like Falicain® and Naftifine® was explored.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

Authors thank COLCIENCIAS and Universidad del Valle for financial support.

References

1. Tanaka, N.; Tamai, T.; Mukaiyama, H.; Hirabayashi, A.; Muranaka, H.; Ishikawa, T.; Akahane, S.; Akahane, M.; *Bioorg. Med. Chem*. **2001**, *9*, 3265; Korošec, T.; Ačimovič, J.; Seliškar, M.; Kocjan, D.; Fon-Tacer, K.; Rozman, D.; Urleb, U.; *Bioorg. Med. Chem*. **2008**, *16*, 209; Roman, G.; Nanu, D.; Comanita, E.; Comanita, B.; *Turk. J. Chem*. **2000**, *24*, 67; Kim, Y.; Ha, H.-J.; Yun, H.; Lee, B. K.; Lee, W. K.; *Tetrahedron* **2006**, *62*, 8844; Bhandari, K.; Srivastava, S.; Shanker, G.; Nath, C.; *Bioorg. Med. Chem*. **2005**, *13*, 1739.
2. Marcus, R.; Gloye, E.; Florance, E.; *Comput. Chem.* **1977**, *1*, 235.
3. Pupo, A.; Uberti, M.; Minneman, K.; *Eur. J. Pharmacol.* **2003**, *462*, 1.
4. Alper, K.; Barry, J.; Balabanov, A.; *Epilepsy Behav.* **2002**, *3*, 13; Szeszko, P.; Bilder, R.; Dunlop, J.; Walder, D.; Lieberman, J.; *Biol. Psychiat.* **1999**, *45*, 680.
5. Brown, B.; Bamford, A.; Bowyer, J.; James, D.; Rankine, N.; Tang, E.; Torr, V.; Culbert, E.; *Bioorg. Med. Chem. Lett.* **2000**, *10*, 575.
6. Kyriakis, J.; Banerjee, P.; Nikolakaki, E.; Dai, T.; Rubie, E.; Ahmad, M.; Avruch, J.; Woodgett, J.; *Nature* **1994**, *369*, 156.
7. Gruters, R.; Neefjes, J.; Tersmette, M.; De Goede, R.; Tulp, A.; Huisman, H.; Miedema, F.; Ploegh, H.; *Nature* **1987**, *330*, 74.
8. Carter, W.; Lynch, M.; *Metabolism* **1994**, *43*, 1119; Uzkeser, H.; Cadirci, E.; Halici, Z.; Odabasoglu, F.; Polat, B.; Yuksel, T.; Ozaltin, S.; Atalay, F.; *Mediat. Inflamm.* **2012**, *2012*, 1.
9. Liu, D.; Gao, W.; Wang, C.; Zhang, X.; *Angew. Chem., Int. Ed.* **2005**, *44*, 1687; Pinder, R. M.; Wieringa, J. H.; *Med. Res. Rev.* **1993**, *13*, 259.
10. Guarna, A.; Menchi, G.; Berti, G.; Cini, N.; Bottoncetti, A.; Raspanti, S.; Politi, A.; Pupi, A.; *Bioorg. Med. Chem*. **2001**, *9*, 3197.
11. Abonia, R.; Castillo, J.; Insuasty, B.; Quiroga, J.; Nogueras, M.; Cobo, J.; *Eur. J. Org. Chem.* **2010**, *33*, 6454.
12. Santacruz, L.; Abonia, R.; Low, J.; Cobo, J.; *Acta Crystallogr.* **2006**, *E62*, 5027.
13. Castillo, J.; Abonia, R.; Cobo, J.; Glidewell, C.; *Acta Crystallogr.* **2009**, *C65*, o303; Abonia, R.; Castillo, J.; Insuasty, B.; Quiroga, J.; Nogueras, M.; Cobo, J.; *ACS Comb. Sci.* **2013**, *15*, 2.
14. Jeffery, G. H.; Bassett, J.; Mendham, J.; Denney, R. C.; *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Longman Inc.: New York, USA, 1978, p. 815.
15. Cho, B. T.; Kang, S. K.; *Tetrahedron* **2005**, *61*, 5725.
16. Rylander, P. N.; *Hydrogenation Methods*; Academic: New York, USA, 1985; Tarasevich, V. A.; Kozlov, N. G.; *Russ. Chem. Rev.* **1999**, *68*, 55.
17. Brooks, J. R.; Harcourt, D. N.; *J. Chem. Soc. C* **1969**, 625.
18. Panunzio, M.; Tamanini, E.; Bandini, E.; Campana, E.; D'Aurizio, A.; Vicennati, P. *Tetrahedron* **2006**, *62*, 12270; Bhandari, K.; Srivastava, S.; Shanker, G.; Nath, C.; *Bioorg. Med. Chem.* **2005**, *13*, 1739.
19. Lutz, R. E.; Allison, R. K.; Ashburn, G.; Bailey, P. S.; Clark, M. T.; Codington, J. F.; Deinet, A. J.; Freek, J. A.; Jordan, R. H.; Leake, N. H.; Martin, T. A.; Nicodemus, K. C.; Rowlett Jr., R. J.; Shearer Jr., N. H.; Smith, J. D.; Wilson III, J. W.; *J. Org. Chem*. **1947**, *12*, 617.
20. Wheatley, W. B.; Fitzgibbon Jr., W. E.; Cheney, L. C.; *J. Am. Chem. Soc*. **1954**, *76*, 4490.
21. Gu, H.; Guo, Y.; Shi, Z.; *Synth. Commun.* **2006**, *36*, 3335.
22. Ueno, S.; Usui, K.; Kuwano, R.; *Synlett* **2011**, 1303.
23. Chaturvedi, S. C.; Patnaik, G. K.; Dhawan, B. N.; Dixit, V. K.; *Indian J. Pharm.* **1985**, *17*, 155.
24. Selvamurugan, V.; Singh-Aidhen, I.; *Synthesis* **2001**, 2239.
25. Aggarwal, V.; Harvey, J.; Robiette, R.; *Angew. Chem., Int. Ed.* **2005**, *44*, 5468.
26. Smith, M.; March, J.; *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Part 2, 6th ed.; John Wiley and Sons, Inc.: New Jersey, USA, 2007; Alunni, S.; Tijskens, P.; *J. Org. Chem.* **1995**, *60*, 8371; Cope, A. C.; Trumbull, E. R.; *Org. React.* **2011**, 317.
27. Shi, M.; Li, C.-Q.; Jiang, J.-K.; *Molecules* **2002**, *7*, 721.
28. Biradar, D. B.; Zhou, S.; Gau, H.-M.; *Org. Lett*. **2009**, *11*, 3386.
29. Weigel, W.; Schiller, S.; Reck, G.; Henning, H.-G.; *Tetrahedron Lett*. **1993**, *34*, 6737.
30. Muthumani, P.; Neckmohammed; Meera, R.; Venkataraman, S.; Chidambaranathan, N.; Devi, P.; Suresh Kumar, C. A.; *Int. J. Pharm. Biomed. Res.* **2010**, *1*, 78.
31. Petranyi, G.; Georgopoulos, A.; Mieth, H.; *Antimicrob. Agents Chemother.* **1981**, *19*, 390; Gupta, A. K; Ryder, J. E.; Cooper, E. A.; *J. Cutan. Med. Surg.* **2008**, *12*, 51; Berney, D.; Schuh, K.; *Helv. Chim. Acta* **1978**, 1262; Petranyi, G.; Ryder, N. S.; Stütz, A.; *Science* **1984**, *224*, 1239.
32. Stütz, A.; Georgopoulos, A.; Granitzer, W.; Petranyi, G.; Berney, D.; *J. Med. Chem.* **1986**, *29*, 112.

Submitted: March 11, 2013
Published online: August 6, 2013