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

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Dinesh S. Bhalerao [a], Golla China Mala Kondaiah [a], Namrata Dwivedi [a], Ravi Kumar Mylavarappu [a], Lekkala Amarnath Reddy [a], Arnab Roy [a], Gudimalla Nagaraju [a], Padi Pratap Reddy [a], Apurba Bhattacharya [a] & Rakeshwar Bandichhor [a]

[a] Center of Excellence, Dr. Reddy's Laboratories Ltd., Bachupally, Qutubullapur, India

Available online: 13 Sep 2010

To cite this article: Dinesh S. Bhalerao, Golla China Mala Kondaiah, Namrata Dwivedi, Ravi Kumar Mylavarappu, Lekkala Amarnath Reddy, Arnab Roy, Gudimalla Nagaraju, Padi Pratap Reddy, Apurba Bhattacharya & Rakeshwar Bandichhor (2010): Novel Approach to the Synthesis of Omeprazole: An Antipeptic Ulcer Agent, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:20, 2983-2987

To link to this article: http://dx.doi.org/10.1080/00397910903341171

Synthetic Communications®, 40: 2983–2987, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903341171

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NOVEL APPROACH TO THE SYNTHESIS OF OMEPRAZOLE: AN ANTIPEPTIC ULCER AGENT

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Center of Excellence, Dr. Reddy's Laboratories Ltd., Bachupally, Qutubullapur, India

A novel approach for the synthesis of omeprazole, a potent antiulcer drug, is described. The synthetic procedure involved the formation of an ester of the 5-methoxy thiobenzimidazole followed by coupling of the ester with the Grignard reagent of 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine.

Keywords: Esterification; Grignard reagent; oxidation; peptic ulcer

INTRODUCTION

Tricoordinated sulfur compounds and sulfoxides have attracted researchers for the past few decades.[1] Many biologically active molecules[2] have stereogenic sulfur and sulfenyl atoms in their structure.[3] Prominent examples are the sulfenyl-substituted benzimidazoles, which are proton pump inhibitors (PPI),[4] a powerful class of antiulcer agents.[5] The leading member of this family, omeprazole **1**, was the world's best-selling drug in 1997. The enantiomerically pure isomer esomeprazole (**2**) was introduced into the market later and was the seventh-best-selling drug in 2003. Omeprazole **1** had been previously synthesized by a linear reaction sequence involving the nucleophilic substitution reaction between 5-methoxy thiobenzimidazole **7** and 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine **8**, resulting in pyrmetazole, which was subjected to oxidation with peroxides such as *m*-chloroperbenzoic acid (*m*-CPBA) or H_2O_2[6] to furnish the omeprazole **1**. A major drawback of this methodology was the incomplete oxidation of pyrmetazole as well as overoxidation to sulfone and formation of sulfone N-oxide.

Herein, we report a novel convergent approach to the synthesis of omeprazole, comprising an ester and unprecedented Grignard fragments. This methodology

Received June 13, 2009.

Address correspondence to Rakeshwar Bandichhor, Center of Excellence, Innovation Plaza, IPDO, Research and Development, Dr. Reddy's Laboratories Ltd., Survey Nos. 42, 45, 46, and 54, Bachupally, Qutubullapur, R. R. Dist.-500073, AP, India. E-mail: rakeshwarb@drreddys.com

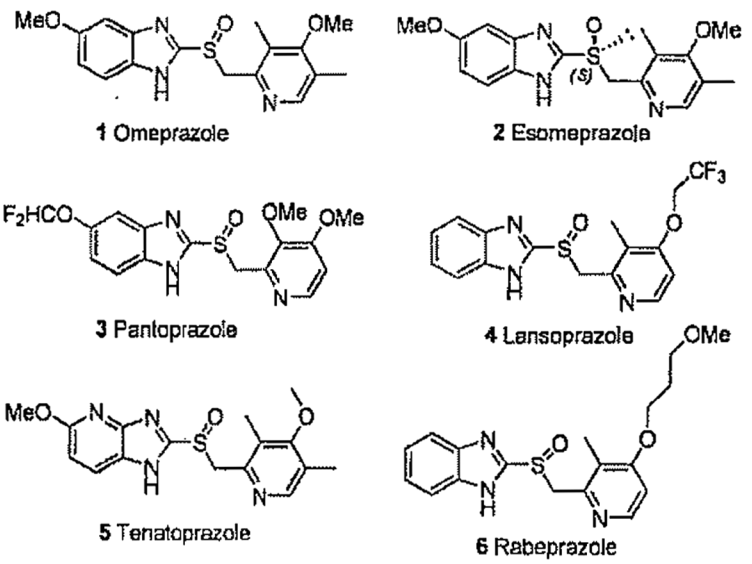


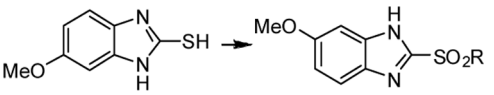
Figure 1. Structures of proton pump inhibitors.

provides a generalized entry to various prazoles, which have similar kinds of molecular architecture (**1–6**), as shown in Fig. 1.

RESULT AND DISCUSSION

The ester component was prepared according to the literature procedure by the treatment of **7** with various alcohols in the presence of 30% aq. H_2O_2,[7] and the results are summarized in Table 1. Simple alcohols such as methyl, ethyl, and benzyl alcohols formed the corresponding esters (Table 1), whereas the chiral alcohols such as menthol and diacetonide glucose failed to result in the respective chiral esters.

Table 1. Formation of ester of 5-methoxythiobenzimidazole



7 **9**(a-e)

R = CH_3 (**9a**) , C_2H_5 (**9b**), Bn (**9c**)

Entry	H_2O_2 eq.	Conditions	Yield (%) of **9a–e**
1	5.0	Methanol, −10 °C	35
2	5.0	Ethanol, −10 °C	42
3	1.5	Benzyl alcohol, −10 °C	75
4	5.0	Menthol, −10 °C	—
5	5.0	Diacetonide glucose, −10 °C	—

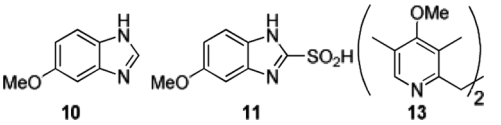
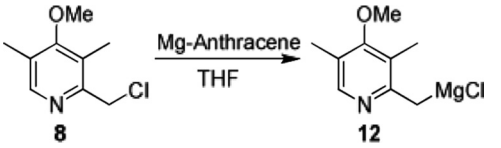


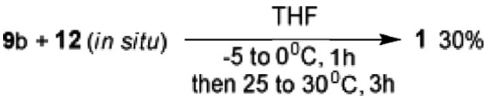
Figure 2. Structure of side products **10**, **11**, and **13**.

We anticipate that the bulky nature of the alcohol plays a pivotal role in the ester formation. In this reaction, the major by-product formed with MeOH, EtOH, and BnOH was the benzimidaziole **10**, whereas with menthol and diacetonide glucose, compound **11** was the only product formed, as shown in Fig. 2. The synthesis of the Grignard fragment was a difficult task. The conventional method of generating the Grignard reagent using magnesium turnings and organic halides was not possible in this instance because of the formation of benzylic and allylic radicals, which are susceptible to migration from metal surface, yielding Wurtz coupled products.[8] Moreover, the synthesis of polyfunctional Grignard reagents was a problem because the insertion of magnesium metal to aryl (or heteroaryl) halides bearing electron-withdrawing groups is inhibited by the presence of these functional groups either inside or outside of the aromatic ring. These problems were addressed by utilizing the magnesium–anthracene complex in tetrahydrofuran (THF).[9] The 1:1 orange-colored crystalline magnesium–anthracene complex was prepared by activating magnesium with a catalytic amount of ethyl bromide, followed by addition of anthracene in THF at 40 °C under an inert atmosphere. 2-Chloromethyl-4-methoxy-3,5-dimethyl-pyridine was added to this magnesium–anthracene complex, furnishing the pyridyl Grignard reagent **12** as shown in Scheme 1. The ester fragment **9b** was added to the Grignard reagent **12** at 0 °C to furnish omeprazole **1** in moderate yield (Scheme 2). Along with the required product, dimer **13** of the 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine and some unreacted starting material were recovered.

The ^{1}H NMR, IR, and mass spectra of the synthesized compound **1** were in complete agreement with the reported values. In summary, we have described a novel synthesis for omeprazole **1** using Grignard reagent and sulfinic ester.



Scheme 1. Preparation of Grignard reagent **12**.



Scheme 2. Synthesis of omeprazole **1**.

CONCLUSION

We have successfully demonstrated an unprecedented coupling of sulfinic ester (**9b**) and Grignard reagent (**12**) to synthesize omeprazole, which can be utilized for synthesis of the other members of the prazole class of molecules. Efforts are under way to synthesize chiral esters (e.g., entries 4 and 5; Table 1) in high yields, which would result in an enamtiomercally pure isomer of not only esomeprazole but also the other members of this type (Fig. 1).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 400 and 200 MHz respectively with a Varian Gemini FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to tetramethylsilane (TMS). The Fourier transform (FT)–IR spectra were recorded using a Perkin-Elmer 16650 FT-IR spectrometer. Mass spectra (70 eV) were recorded on a HP-5989A LC-MS spectrometer. The melting points were determined by using the capillary method on a Polmon (model MP-96) melting-point apparatus and are uncorrected. The solvents and reagents were used without further purification. Optical rotations were measured with a Jasco DIP-370 digital polarimeter at 25 °C. A microwave reactor specifically designed for holding reactions at a set temperature (Discover, CEM Corporation) was used. All reactions were performed in flame-dried glassware under nitrogen. Tetrahydrofuran (THF) and Et_2O were dried and distilled from Na/benzophenone. Benzene and CH_2Cl_2 were dried and distilled from CaH_2. Hexane and ethyl acetate were freshly distilled from CaH_2. Thin-layer chromatography (TLC) was performed on silica-gel 60 F254 precoated plates (250-μm layers). All retention factors (R_f) are on silica-gel TLC plates unless otherwise noted. TLC visualizations were performed with 5% phosphomolybdic acid [0.2 M in 2.5% conc. H_2SO_4/EtOH (v/v)], I_2 vapor, or ultraviolet (UV) light. Commercial reagents were used without further purification unless specifically noted. Column chromatography was performed using 100–700 times excess 32- to 64-μm silica gel. Products separated by chromatography are specified in elution order. In some cases, the yields of products containing residual amounts of solvent were corrected for the solvent peak integration in ^{1}H NMR spectra and specified individually in the data sections. The purity of reaction products was estimated to be at least 90–95% by TLC and NMR analyses unless specified otherwise.

Synthesis of Omeprazole 1

Ethyl bromide (0.01 mL) was added to a stirred solution of Mg (1 g, 0.041 mol) in THF (2 mL) and heated to 40–45 °C. Anthracene (4 g) in THF (20 mL) was added and stirred at 45–50 °C after 6 h, resulting in an orange complex of [Mg(antracene)$(THF)_3$]. The magnesium–antharacene complex was cooled between −5 and 0 °C, followed by the addition of **8** (3.8 g, 0.028 mol), resulting in Grignard reagent **12**. Ester fragment **9b** (2.5 g, 0.010 mol) in THF (5 mL) was added, and the reaction mixture was maintained for 1 h at this temeperature and allowed to stir to room temperature for another 3 h. After completion of the reaction (TLC monitoring), THF was distilled under reduced pressure to result in a crude oil. Water (30 mL) was

added, and the pH was adjusted between 12 and 13 using 10% aq. NaOH (7 mL). Ethyl acetate (2×50 mL) was used to wash the aquoeus layer, and then the pH of aqueous layer was adjusted between 7 and 8 by 3 N HCl solution. The product was extracted from the aqueous layer with dichoromethane (2×50 mL). The dichloromethane layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure at 30–35 °C to result in a oily compound. Acetone (2 mL) was added to it to furnish a white solid omeprazole **1** (1.12 g, 30%).

ACKNOWLEDGMENTS

The authors are thankful to the management of the Dr. Reddy's Laboratories Ltd. for supporting this work and to Dr. R Vijay Anand for the discussions.

REFERENCES

1. (a) Mislow, K.; Simmons, T.; Melillo, J. T.; Ternay, A. L. The hydrogen chloride–catalyzed racemization of sulfoxides. *J. Am. Chem. Soc.* **1964**, *86*, 1452–1453; (b) Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L. Absolute configuration and optical rotatory power of sulfoxides and sulfinate esters. *J. Am. Chem. Soc.* **1965**, *87*, 1958–1976.
2. Kalir, A.; Kalir, H. H. In *The Chemistry of Sulfur Compounds Functional Groups*; S. Patai, Z. Rappoport (Eds.); Wiley: New York, 1993; p. 957.
3. Toru, T.; Watanabe, Y.; Mase, N.; Tsusaka, M.; Hayakawa T.; Ueno Y. Diastereofacial control in the radical addition to chiral α-sulfinyl enones. *Pure Appl. Chem.* **1996**, *68*, 711–714.
4. (a) Tavish, D. M.; Buckley, M. M.; Heel, R. C. Individual and group dose-responses to intravenous omeprazole in the first 24 h: pH-feedback-controlled and fixed-dose infusions. *Drugs* **1991**, *1*, 138–170; (b) Okabe, S.; Shimosako, K. Pharmacological regulation of gastric acid secretion in the apical membrane of parietal cells: A new target for antisecretory drugs. *J. Physiol. Pharmacol.* **2001**, *52*, 639–656; (c) Spencer, C. M.; Faulds, D. Esomeprazole. *Drugs* **2000**, *60*, 321–329; (d) Richardson, P.; Hawkey, C. J.; Stack, W. A. Proton pump inhibitors: Pharmacology and rationale for use in gastrointestinal disorders. *Drugs* **1998**, *56*, 307–335.
5. Shin, J. M.; Cho, M.; Sachs, G. Chemistry of covalent inhibition of the gastric (H^+, K^+)-ATPase by proton pump inhibitors. *J. Am. Chem. Soc.* **2004**, *126*, 7800–7811.
6. (a) McManus, J. W.; Anousis, N.; Banks, B. N.; Liu, H.; Zhou, L. Omerazole process and compositions thereof. US Patent 6,191,148 B1, 2001; (b) Prasad, K. D. Intermediates and an improved process for the preparation of omeprazole employing the said intermediates. US Patent 6,303,787, 2001.
7. Loksha, Y. M.; E1-Barbary, A. A.; E1-Badawi, M. A.; Nielsen, C.; Pedersen, E. B. Synthesis of 2-hydroxymethyl-1H-imidazoles from 1,3-dihydroimidazole-2-thiones. *Synthesis* **2004**, 116–120.
8. Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. Main group-conjugated organic anion chemistry, 3: Application of magnesium–anthracene compounds in the synthesis of Grignard reagents. *J. Org. Chem.* **1988**, *53*, 3134–3140.
9. Bogdanovic, B.; Liao, S.-T.; Mynott, R.; Schlichte, K.; Westeppe, U. Rate of formation and characterization of magnesium anthracene. *Chem. Ber.* **1984**, *117*, 1378–1392.