European Journal of Medicinal Chemistry 44 (2009) 3350–3355

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Preliminary communication

Synthesis and antitubercular screening of imidazole derivatives☆

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ARTICLE INFO

Article history:
Received 7 June 2008
Received in revised form
29 January 2009
Accepted 12 February 2009
Available online 20 February 2009

Keywords:
Tuberculosis
Imidazoles
Glycosyl amino ester
C-alkylation
C-Allyl imidazoles

ABSTRACT

A series of imidazole based compounds were synthesized by reacting simple imidazoles with alkyl halides or alkyl halocarboxylate in presence of tetrabutylammonium bromide (TBAB). The compounds bearing carbethoxy group undergo amidation with different amines in the presence of DBU to give respective carboxamides. The synthesized compounds were screened against *Mycobacterium tuberculosis* where compound **17** exhibited very good in vitro antitubercular activity and may serve as a lead for further optimization.

1. Introduction

An increase in the global burden of tuberculosis with the worldwide mortality rate of 23% is a major concern in the socio-economic and health sectors [1–5]. The synergy of this disease with HIV infection and the emergence of multi drug resistance and extensively drug resistance tuberculosis (MDRTB and XDRTB) pose a threatening global challenge [6–8]. Although a number of lead molecules exist today to develop new drugs, no new chemical entity has emerged for clinical use for over the last 45 years in the treatment of this disease [9,10]. Therefore, there is an urgent need to develop new drugs, acting through a novel mechanism of action for the chemotherapy of tuberculosis.

Recently certain imidazole based compounds were reported to possess antimicrobial activities [11]. It is believed that aryl–azolyl–ethane moiety, present in many azole antifungal drugs serve as pharmacophore in compounds having *Mycobacterium* killing activity [12,13]. Many azole derivatives have also displayed interesting antimycobacterial activity in addition to antifungal activity [14–16]. It is established that these compounds target the sterol demethylase, a mixed-function oxidase involved in sterol synthesis in eukaryotic organisms [17]. The unraveling of *Mycobacterium* genome sequence has revealed that a protein having homology to one of the above mixed oxidase function is present in *Mycobacterium tuberculosis* [18]. Nitroimidazole derivative such as nitroimidazopyran is in advanced stage of clinical trial for the treatment of tuberculosis and it has been speculated that this compound is active against both the replicating and the latent *Mycobacterium* [19]. Keeping in mind the above facts, we were interested to see the antitubercular potential in simple imidazole derivatives.

2. Results and discussion

Compounds **3**–**5** and **15**–**18** were synthesized starting from simple imidazoles by reacting them with different alkyl halides (viz. 3,4-dichlorobenzyl bromide, ethyl bromoacetate, ethyl bromopropionate, 1,3-dibrompropane and 1,5-dibromopentane) in the presence of NaH/TBAB (tetrabutylammonium bromide) in anhydrous DMF or THF (Table 1). Although few such alkylation methods for the synthesis of 1-alkyl-, aralkyl imidazoles and bis-imidazolyl alkanes were reported earlier [32–35], however our method of alkylation of imidazole and 2-propylimidazole in the presence of TBAB offers advantages over previous ones in terms of mild reaction conditions along with shorter reaction time and better yield of the products.

☆ CDRI communication number: 7398.

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doi:10.1016/j.ejmech.2009.02.013

Table 1
Synthesis of substituted imidazoles and benzimidazoles (**3**–**18**).

Compound No.	Physical state	M.p. (°C)	Known m.p. (°C) [Ref]	% Yield
3	Yellow semi solid	–	–	65
4	White solid	120–124	124 [32]	70
5	Light brown solid	165–168	–	70
6	Viscous mass	–	–	78
7	Yellow semi solid	–	[33]	78
8	Yellow solid	74–76	–	80
9	Pale yellow semi solid	–	–	78
10	Colorless solid	37–39	36–40 [34]	46
11	Viscous mass	–	–	80
13	Pale yellow solid	116–118	–	70
14	Yellow solid	138–140	–	75
15	Yellow oil	–	[35]	68
16	Viscous mass	–	–	70
17	Colorless oil	–	–	55
18	Colorless oil	–	–	45

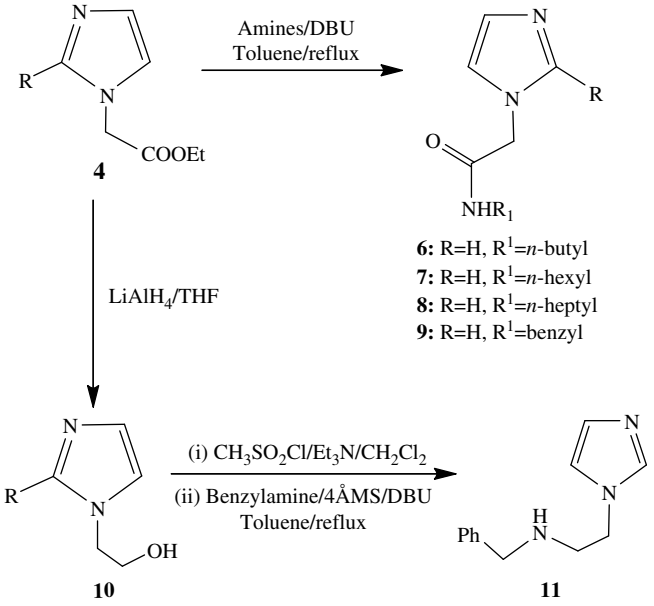
Thus, reaction of imidazole (**1**) with 3,4-dichlorobenzyl bromide, ethyl bromoacetate and ethyl bromopropionate separately in THF in the presence of NaH/TBAB gave 1-(3,4-dichlorobenzyl)-1*H*-imidazole (**3**), imidazol-1-yl-acetic acid ethyl ester (**4**) and 3-imidazol-1-yl-propionic acid ethyl ester (**5**) respectively in quantitative yield (Scheme 1).

Compounds (**6**–**9**) were prepared by reaction of compound **4** with different amines viz. *n*-butyl, *n*-hexyl, *n*-heptylamine, and benzylamine under refluxing condition. $LiAlH_4$ reduction of the above compound **4** gave respective 1-(2-hydroxy ethyl)-1*H*-imidazole (**10**) in good yield. The latter, on mesylation with methanesulphonyl chloride followed by reaction with benzyl amine in presence of DBU and 4 Å molecular sieve gave 1-(2-benzyl amino ethyl)-1*H*-imidazole (**11**) in quantitative yield (Scheme 2).

The structures of all the synthesized compounds were established on the basis of spectroscopic data and analysis. The IR data for compound **3** exhibited C=N and C=C stretching frequency at υ_{max} 1730 and 1642 cm^{-1}, respectively. In the ^1H NMR spectrum of compound **3**, appearance of a multiplet in the range of δ 7.56–6.89 corresponds to three imidazole and three phenyl protons and a singlet at δ 5.09 corresponds to methylene protons. In the ^{13}C NMR spectrum, peaks at δ 142.7, 137.6, 136.8, 136.4, 134.5, 134.1, 132.2, 128.2 and 124.6 showed the presence of imidazole carbons and aromatic carbons whereas peak at δ 54.3 showed the presence of methylene carbon. Finally, molecular ion peak at *m*/*z* 228 $(M+H)^+$ in MS spectrum confirms the structure of compound **3**.

Similarly, compounds **13** and **14** were prepared by benzylation of benzimidazole (**12**) with benzyl bromide and 3,4-dichlorbenzyl bromide respectively (Scheme 3) and the structures were established on the basis of spectroscopic data and analysis.

Compounds **15**–**18** were prepared by the reaction of imidazole (**1** or **2**) with dibromoalkanes in presence of NaH and TBAB in THF (Scheme 4). The reaction of 2 eq. of imidazole with 1 eq. of 1,3-dibromopropane and 1,5-1,5-dibromopentane separately led to

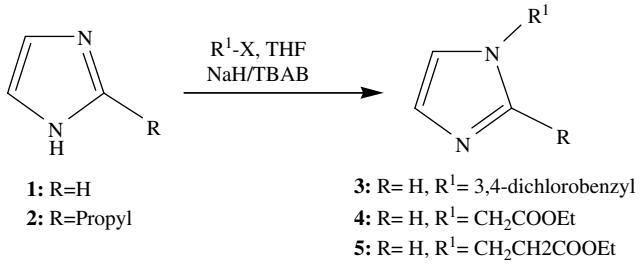


Scheme 2. Synthesis of imidazole derivatives.

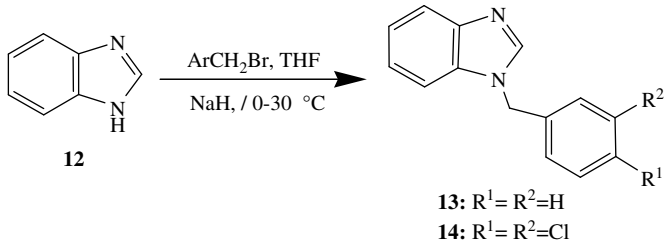
the formation of compounds **15** and **16** respectively in good yields. However, reacting 2 eq. of 2-propylimidazole with 1 eq. of 1,3-dibromopropane gave the expected 1,3-bis-(2-propylimidazol-1-yl)-propane (**17**) as major product along with another unusual minor product, 1-(4-allyl-2-propylimidazol-1-yl)-3-(2-propylimidazol-1-yl)-propane (**18**) (Scheme 4). Formation of compound **18** is speculated via electrophilic attack of carbocation generated from allyl bromide which in turn formed via rearrangement of 1,3-dibromopropane. However, exact mechanism is yet to be established.

Since glycosyl amino ester derivatives and other glycoconjugates bearing alkyl substitutents at the nitrogen atom [20–24] have been found to possess antitubercular activity, we were prompted to see the effect of imidazole ring at the C-5 of sugar moiety on antitubercular activity profiles. Synthesis of imidazolyl glycosyl uronoates (**19**–**22**, Fig. 1) in moderate yields was carried out by us as reported earlier [25].

The imidazole derivatives (**3**–**22**) were screened for their antitubercular efficacy against *M. tuberculosis* using different test models [26–29] and the results are shown in Table 2. The antitubercular efficacy of these compounds were tested against avirulent strain *M. tuberculosis* $H_{37}Ra$ and virulent strain *M. tuberculosis* H37Rv at different concentrations ranging from 50 μg/ml to 3.25 μg/ml. As evident from Table 2 that most of the compounds displayed antitubercular activity with MIC ranging from 25 to >12.5 μg/ml against either the avirulent strain *M. tuberculosis* H37Ra or the virulent strain *M. tuberculosis* H37Rv. The only compound **17** showed MIC 6.25 μg/ml against virulent strain



Scheme 1. Synthesis of *N*-alkyl(aralkyl) imidazoles.



Scheme 3. Synthesis of benzimidazole derivatives.