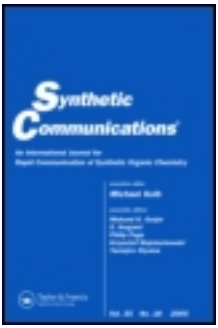

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 24 Sep 2006.

To cite this article: Daniel R. Doerge & Niranjala M. Cooray (1991): Synthesis of N-Substituted Benzimidazole-2-thiones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:17, 1789-1795

To link to this article: http://dx.doi.org/10.1080/00397919108021578

SYNTHETIC COMMUNICATIONS, 21(17), 1789-1795 (1991)

SYNTHESIS OF N-SUBSTITUTED BENZIMIDAZOLE-2-THIONES

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ABSTRACT: General methods were developed for N-substitution of benzimidazoline-2-thione with alkyl, alkenyl, alkynyl and acyl groups using S-tritylation as a protecting reaction.

Benzimidazole-2-thione (MBI) and its N-substituted derivatives inhibit reactions catalyzed by thyroid peroxidase (TPX) and lactoperoxidase (LPX) (1,2). Structurally related compounds such as 1-methyl-imidazole-2-thione and 6-propyl-2-thiouracil are suicide inhibitors of TPX that are used therapeutically to treat hyperthyroidism (3). In order to determine a complete structure-activity relationship for these enzyme inhibitors, it was necessary to develop synthetic methods to introduce nitrogen substituents into the title compound.

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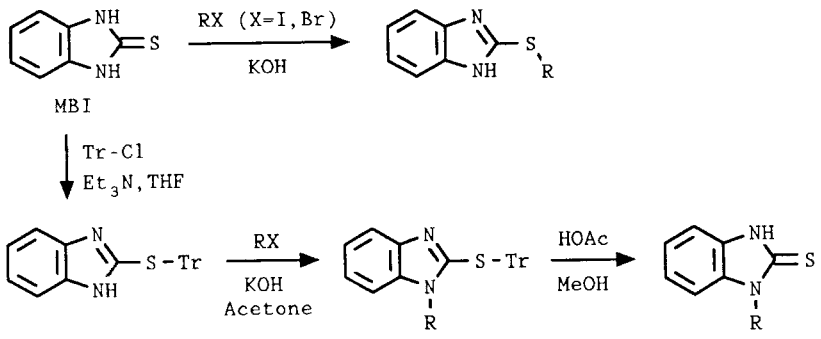
A published method for introduction of N-alkyl groups was previously utilized to synthesize isotopically labelled N-methyl MBI derivatives from 2-chlorobenzimidazole (4).
However, this method proved unsuccessful for introducing reactive alkene and alkyne groups into MBI due to competing side reactions.

Since MBI contains both nucleophilic nitrogen and sulfur, it is a potential ambident nucleophile. It was therefore necessary to consider the differences in reactivity between the "soft" sulfur and "hard" nitrogen centers (5). Since soft electrophiles like alkyl bromides and iodides react preferentially with sulfur nucleophiles (5,6), MBI could be used as a starting material for synthesis of N-alkyl derivatives only after masking the sulfur. Reaction of MBI with trityl chloride proceeded under mild conditions to give S-trityl MBI in reasonable yield (see Scheme). Reaction of S-trityl MBI with a variety of alkyl, aryl, alkenyl and alkynyl iodides and bromides was observed and following facile deprotection with acetic acid/methanol, the desired N-substituted derivatives were isolated in good overall yields (see Table 1). The products were characterized by UV ($CHCl_3$), ^{1}H-NMR (CD_3OD) and mass spectrometry (direct insertion probe) (Table 2).

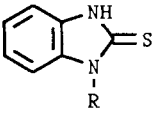


SCHEME

The preparation of N-acyl MBI derivatives does not require the protection of sulfur since the nitrogen center of MBI preferentially reacts with hard electrophiles (e.g. acetic anhydride and acetyl chloride) (7). The synthesis of N-acetyl MBI from reaction of MBI with acetic anhydride in pyridine was previously reported (7) and in this study N,N-diacetyl MBI was synthesized by the reaction of MBI with acetic anhydride. Under these conditions, the reaction proceeds directly to diacetyl MBI with no detectable formation of the monoacetyl derivative. The reaction of S-trityl MBI with acetyl chloride in methylene chloride (-78°C) was found to be an alternate method to prepare N-acetyl MBI.

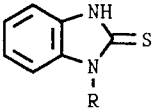
In conclusion, convenient syntheses were developed which allow the introduction of a variety of N-substituents into MBI. These methods could prove

Table 1

Physical Properties of 

Compound	Yield (%)	Melting Point (°C)
R = Methyl	79%	190-191
Allyl	78	97-98
Ethyl	89	158-161
n-Propyl	41	122-124
Pentafluorobenzyl	83	186-188
Propargyl	60	152-153
Acetyl	42	198-199
Diacetyl	71	97-99

Table 2

Spectroscopic Properties of 

Compound	UV λmax	Mass Spec.	^{1}H-NMR (CD_3OD)
R = Methyl	312 nm	m/z164, 30%	7.28 ppm (4H, m)
		150, 100%	3.71 (3H, s)
Allyl	312	190, 86%	7.30 (4H, m)
		175, 100%	5.94 (1H, dt)
Ethyl	314	178, 28%	7.25 (4H, m)
		163, 53%	4.61 (2H, q)
		150, 100%	1.62 (3H, t)
n-Propyl	310	192, 56%	7.21 (4H, m)
		150, 100%	4.26 (2H, t)
			1.89 (2H, m)
			1.03 (3H, t)
Pentafluorobenzyl	330	330, 100%	7.39 (4H, m)
		167, 67%	5.59 (2H, s)
Propargyl	310	188, 100%	7.29 (4H, m)
		187, 100%	5.15 (2H, s)
			2.20 (1H, s)
Acetyl	332	192, 9%	7.97 (2H, m)
		150, 100%	7.30 (2H, m)
			3.05 (3H, s)
Diacetyl	316	234, 2%	7.96 (2H, dd)
		192, 13%	7.29 (2H, dd)
		150, 100%	3.05 (6H, s)

valuable in the synthesis of new and effective anti-hyperthyroid drugs.

Experimental Section

General Methods. Melting points (Table 1) were taken on a Buchi apparatus and are uncorrected. Nuclear magnetic resonance spectroscopy (Nicolet NT300 spectrometer), mass spectrometry (VG Trio 2) and UV-VIS spectrophotometry (Hewlett Packard 8452A) were performed on all compounds (Table 2). All reagents were obtained from Aldrich Chemical Co. and used as received.

Synthesis of S-Trityl MBI. To a solution of 1.5 g MBI (10 mmole) in 30 ml dry THF was added simultaneously 2.79 g triphenylmethyl chloride (10 mmole) and 1.3 g triethylamine (1.3 equivalents). The reaction was stirred at room temperature for 8 hr and the crystalline triethylamine HCl removed by filtration. The solvent was removed in vacuo and the solids recrystallized from benzene to yield 2.88 g S-trityl MBI (73%, off-white crystals, mp 250-253; UV 296 nm).

General Procedure for Synthesis of N-Substituted MBI. Preparation of N-Methyl Benzimidazoline-2-thione.

To a solution of 1 g (2.55 mmole) of trityl MBI in 18 ml dry acetone was added 714 mg (12.75 mmole) powdered KOH. The mixture was stirred vigorously

for 3 min and then 542 mg (3.82 mmole) methyl iodide was added and the reaction was stirred for 10 min. The mixture was poured into 200 ml benzene and washed with 25 ml distilled water and 25 ml saturated NaCl solution. The organic layer was separated, dried over sodium sulfate and the solvent removed in vacuo to leave a white solid. The solids were dissolved in 25 ml of 5% acetic acid in methanol and refluxed for 30 min. The solution was concentrated in vacuo and the crude 1-methyl MBI was dissolved in 10 ml dichloromethane and washed twice with 10% sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, concentrated and the solids recrystallized from aqueous ethanol to yield 328 mg 1-methyl MBI (colorless needles).

Synthesis of 1,3-diacetyl MBI. To a solution of 150 mg (1 mmole) MBI in 10 ml methylene chloride at -78°C was added simultaneously 1 mmole of triethylamine and 0.5 mmole acetic anhydride while maintaining continuous stirring. A crystal of N,N-dimethylaminopyridine was added and the reaction stirred at -78°C for 10 min. The solvent was removed in vacuo and the product recrystallized from chloroform/methanol (96/4) to yield 173 mg Ac_2MBI (colorless needles).

Acknowledgment. This work was supported in part by grant number ES04622 from the National Institutes of Health.

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(Received in US 9 May, 1991)