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A MODEL STUDY FOR A NOVEL SYNTHETIC APPROACH TO 2-CARBOXYINOSINES

Vasanthakumar Rajappan and Ramachandra S. Hosmane*

Laboratory for Drug Design and Synthesis
Department of Chemistry and Biochemistry
University of Maryland, Baltimore County, 1000 Hilltop Circle
Baltimore, Maryland 21250
* Phone: 410-455-2520 Fax: 410-455-1148 E-Mail: hosmane@umbc.edu

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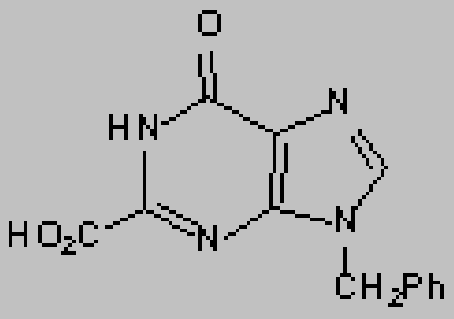
ABSTRACT

*A model study for a novel approach to the synthesis of 2-carboxyinosines has been described. The synthesis of 9-benzyl-2-carboxyhypoxanthine (**I**), a model for 2-carboxyinosine, was achieved in 4 steps starting from 1-benzyl-5-nitroimidazole-4-carboxylic acid. Also reported is the synthesis of 9-benzyl-2,2-bis(ethoxycarbonyl)hypoxanthine (**II**).*

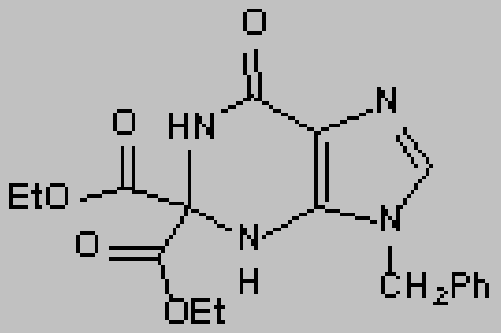
INTRODUCTION

There has been continued biomedical interest in the synthesis of analogues of

inosine substituted at the 2-position with a functional group that is a member of the carboxylic acid family, including the parent carboxylic acid moiety,[1] a carboxamide group,[2] a nitrile,[1,3] an imidate,[1] or an ester functionality.[4] Also reported are inosines or 2'- or 3'-deoxyinosines or hypoxanthines substituted with a carboxaldehyde or a ketone group at the 2-position.[3,5] Most of these reported methods involve direct functional group transformations of nucleosides. While the use of nucleosides has an advantage in that it forgoes the glycosylation step, it nevertheless suffers from extensive protection and deprotection steps of not only the heterocyclic moiety, but also of the sugar hydroxyls. This is especially true in case of 2-substituted purines since the formation of a C-C bond by direct nucleophilic displacement reaction, for example, of a 2-halo substituent by cyanide anion, has largely been unsuccessful.[1,2] This often necessitates organometallic reactions that call for stringent requirements of protection/deprotection steps, such as the Stille coupling[6] between an organic iodide and tri-*n*-butyl cyanide in the presence of tetrakis(triphenylphosphine) palladium. Thus the reported conversion of guanosine into 2-cyano-3'-deoxyinosine, an analogue of the naturally occurring antibiotic cordycepin,[7] involved ten synthetic steps.[3] Although sulfonylmethyl[1] and sulfonylphenyl[2] groups at the purine 2-position have been reported to be far better leaving groups than the corresponding halogen substituents, the attempted direct displacement reactions by a cyanide or other carbanions on the sulfonyl substituents failed on both guanosine[1] and inosine.[2] The explanation given for these failures is that the dissociable N-1 proton in either guanosine or inosine, especially at a reasonably high temperature that is normally employed for such displacement reactions (~100 C in DMF), renders the C-2 position less susceptible for nucleophilic attack.[1,2] The support for such a notion came from the successful nucleophilic displacement reactions with 2-sulfonylalkyl or 2-sulfonylaryl derivatives of either adenosine[1] or 6-methoxypurine.[2]



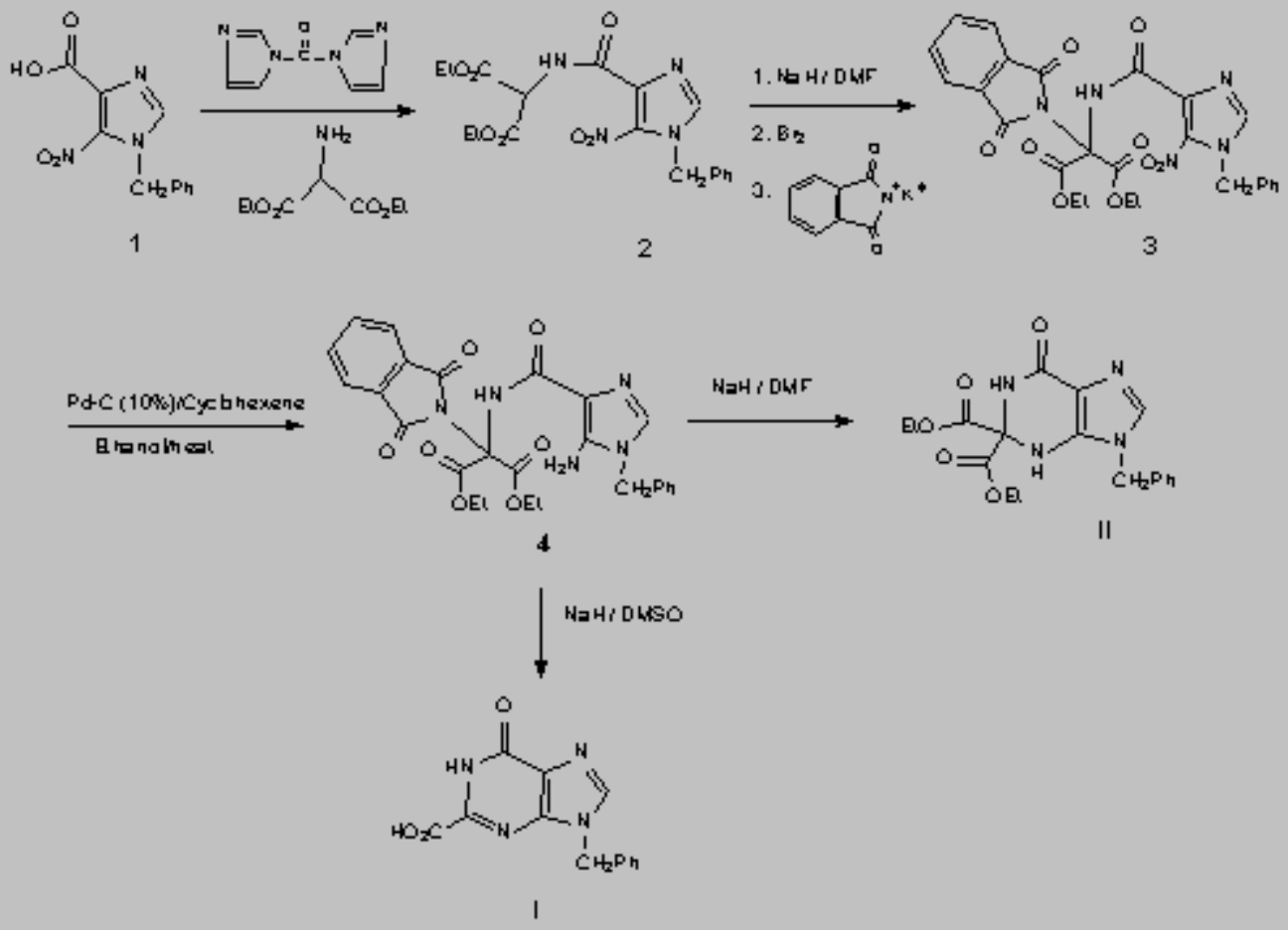
I



II

We report here an alternative short approach to the synthesis of 2-substituted hypoxanthines. The synthesis of 9-benzyl-2-carboxyhypoxanthine (**I**), described herein, is a heterocyclic model for 2-carboxyinosine. Since the parent carboxylic acid group can be conveniently converted to other members of the carboxylic acid family as well as to aldehydes and ketones employing conventional chemical methods, the synthesis is potentially versatile. Also reported here is the synthesis of 2,2-diester-substituted analogue **II** that was obtained by mere change of solvent in the final ring-closure step. Although the initial purpose of its synthesis was to confirm the anticipated mechanism of formation of **I**, compound **II** is apparently a good precursor to a wide variety of 2,2-disubstituted analogues of hypoxanthine and inosine, which may otherwise be difficult to prepare by usual synthetic methods.

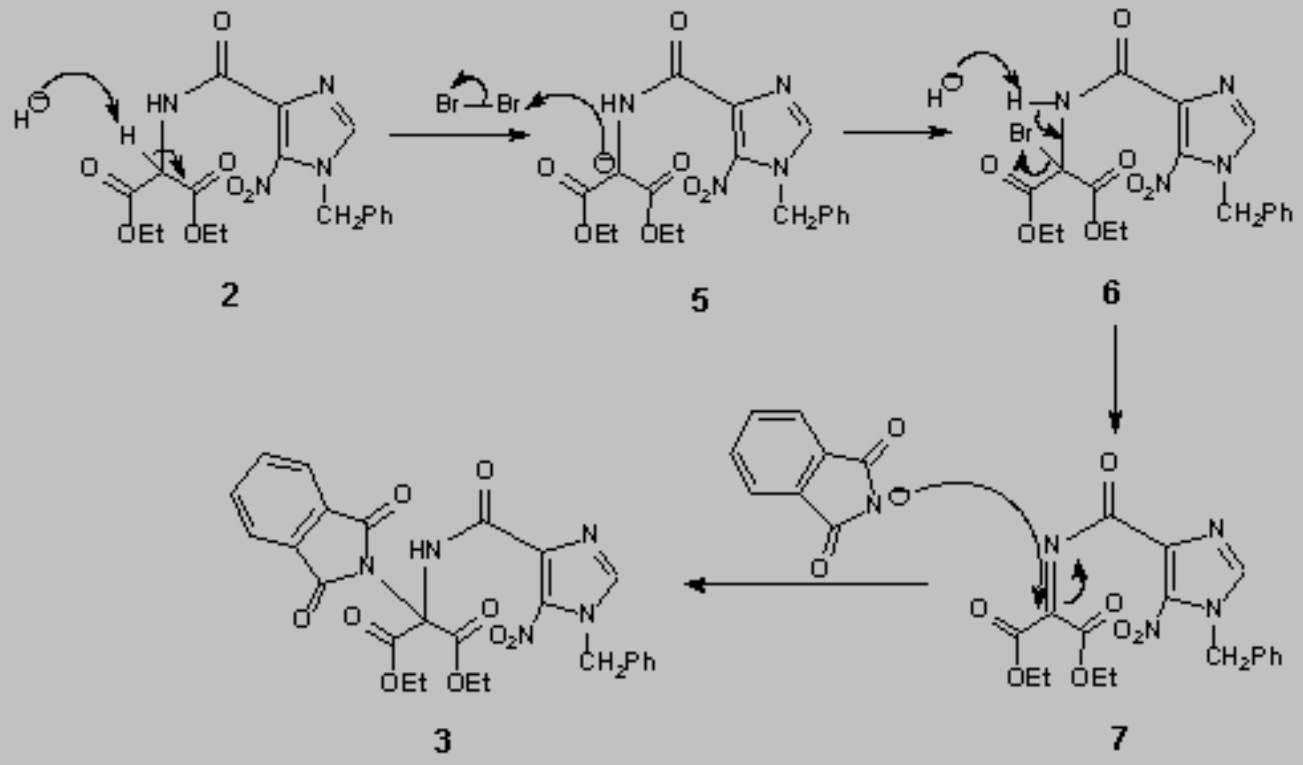
SCHEME I



The synthesis of target **I** was achieved in four steps commencing from 1-benzyl-5-nitroimidazole-4-carboxylic acid (**1**)[8] (**Scheme I**). Condensation of **1** with diethylaminomalonate, mediated by 1,1'-carbonyldiimidazole (CDI), yielded diethyl 2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**2**) in 93% yield, mp 88 C; ^{1}H NMR (300 MHz, DMSO-d_6) 9.27-9.29 (d, J = 7.2 Hz, 1H, NH, ex./ w. D_2O), 8.28 (s, 1H, CH), 7.10-7.83 (m, 5H, Ar-H), 5.54 (s, 2H, NCH_2), 5.22-5.24 (d, J_{NH-CH} = 7.2 Hz, 1H, CH), 4.18 (q, 4H, 2xCH_2), 1.20 (t, 6H, 3xCH_3); Anal. C, H, N.[9] The reaction of **2** with bromine in the presence of sodium hydride in dimethylformamide, followed by treatment with potassium phthalimide afforded diethyl 2-phthalimido-2-[*N*- (1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**3**) in 92% yield, mp 83-85 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) d 9.06 (s, 1H, NH), 8.26 (s, 1H, CH), 7.92 (m, 4H, Ar-H), 7.35 (m, 5H, Ar-H), 5.48 (d, 2H, NCH_2), 4.30 (q, 4H, 2XCH_2),

1.10 (t, 6H, 2XCH_3); Anal. C, H, N. This reaction is presumed to proceed (**Scheme II**) via base-catalyzed bromination of the side-chain malonate moiety to produce **6**, followed by dehydrohalogenation to form the

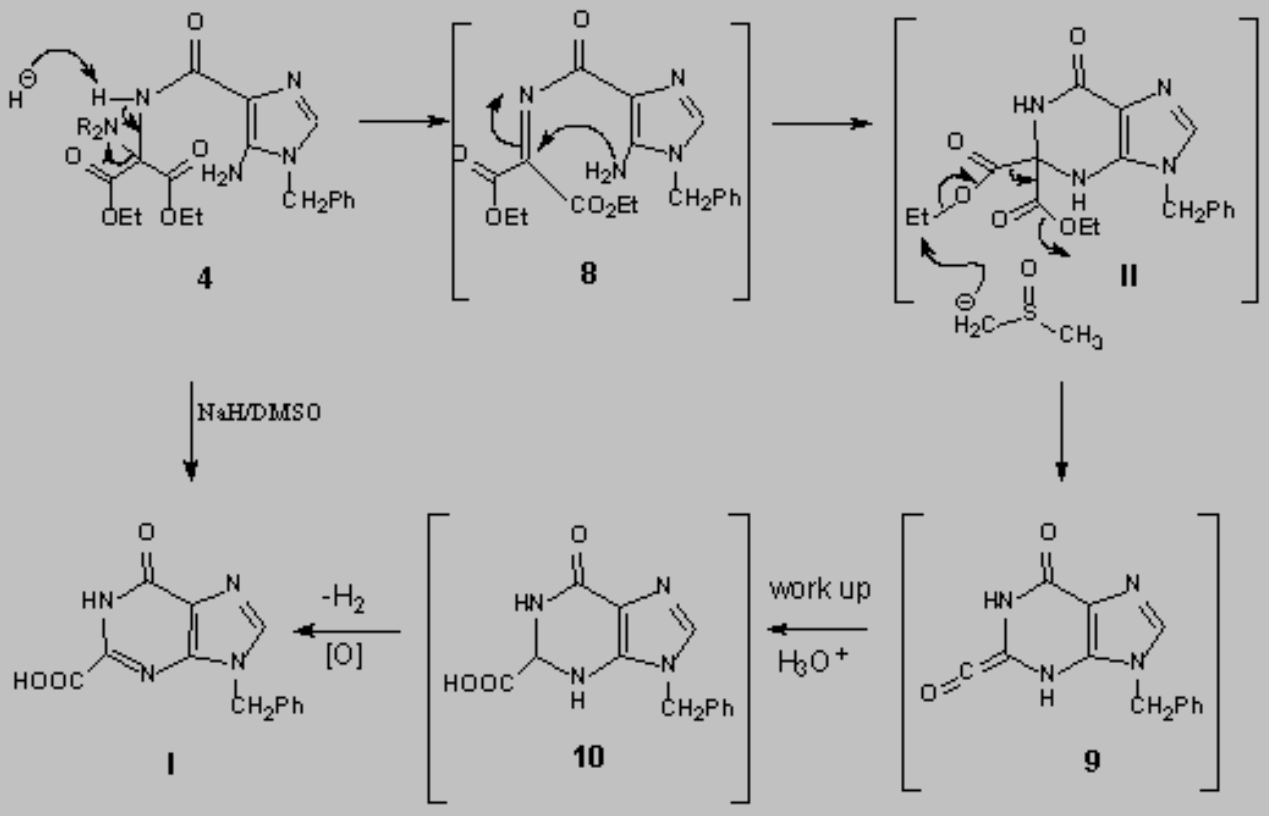
SCHEME II



imine intermediate **7**. The latter would readily react with the phthalimide anion to produce **3**. The nitro group of **3** was reduced by catalytic transfer hydrogenation[10] using cyclohexene and palladium on charcoal, which gave diethyl 2-phthalimido-2-[*N*-(5-amino-1-benzylimidazolyl-4-carbonyl)amino] malonate (**4**) in 45% yield, mp 162 - 164 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) d 9.22 (s, 1H, NH), 8.19 (s, 1H, CH), 7.59-7.18 (m, 9H, phenyl H), 5.94 (s, 2H, NH_2), 5.10 (s, 2H, NCH_2), 4.22 (q, 4H, 2XCH_2), 1.15 (t, 6H, 2XCH_3); Anal. C, H, N.[9] Finally, the target 9-benzyl-2-carboxyhypoxanthine (**I**) was prepared in 78% yield by heating **4** at 70 C for ten minutes in anhydrous dimethyl sulfoxide containing slightly over two equivalents of sodium hydride, mp >200 C; ^{1}H NMR (300 MHz, DMSO-d_6) d 13.56 (br, s, 1H, CO_2H), 8.43 (s, 1H, NH), 8.12 (s, 1H, CH), 7.38-7.21 (m, 5H, Ar-H), 5.05 (s, 2H, CH_2); Anal. C, H, N.[9]

The conversion of **4** into **I** is believed to go through an imine intermediate **8** (**Scheme III**), formed by base-catalyzedelimination of phthalimide, followed by ring-closure to produce **II** in situ. The latter undergoes facile nucleophilic

SCHEME III



displacement by the dimsyl anion present in the medium with concomitant elimination of carbon dioxide to form a ketene-type intermediate **9**. The aqueous work-up of **9** to produce **10**, accompanied by spontaneous aromatization of the latter by loss of molecular hydrogen, yields the target 2-carboxyinosine analogue **I**. The support for the speculated mechanism came from the ring-closure reaction of **4** carried out in in a solvent that is non-nucleophilic or is incapable of forming a nucleophilic species by reaction with with sodium hydride, such as the dimsyl anion mentioned above. Accordingly, when the final ring-closure of **4** was carried out in dimethylformamide instead of dimethyl sulfoxide as the solvent, it gave 9-Benzyl-2,2-bis(ethoxycarbonyl)hypoxanthine (**II**), mp 166-171 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) 10.06 (s, 1H, NH), 9.57 (s, 1H, NH), 8.23 (s, 1H, CH), 7.42 (m, 5H,

Ar-H), 5.18 (s, 2H, CH_2), 4.18 (q, 4H, 2xCH_2), 1.62 (t, 6H, 2xCH_3); Anal. C, H, N.[9] The speculated intermediacy of **II** in the conversion of **4** to **I** was further corroborated by a separate treatment of the isolated **II** with sodium hydride in dimethyl sulfoxide under identical reaction conditions as used for **4 I** conversion, which indeed afforded **I**.

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