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New and Practical Method for Synthesis of 1- and 1,3-Substituted Xanthines

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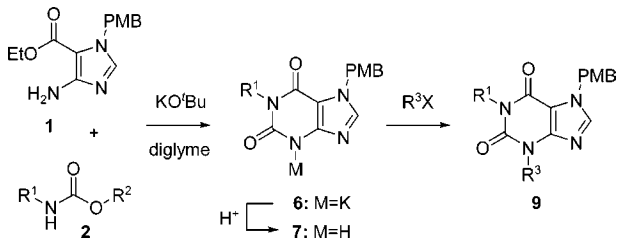
ABSTRACT



A new and practical method for the synthesis of 1- and 1,3-substituted xanthines is reported. Direct base-promoted condensation of the imidazole precursor 1 with carbamates 2 gives 1-substituted 7-PMB xanthines 7 in good yields. Alkylation of these derivatives or their potassium salts proceeds under mild conditions to give functionalized 1,3-substituted 7-PMB xanthines 9 in good to excellent yields. The obtained 7-PMB-protected derivatives can be readily deprotected to give the parent 1- and 1,3-substituted xanthines.

Functionalized xanthine derivatives comprise an important class of pharmacologically active compounds with well-known activity as adenosine receptor antagonists and phosphodiesterase inhibitors.[1] The range of therapeutic applications of xanthines continues to expand and currently includes their use in treatment of bronchial asthma and vascular diseases and as diuretics, psychoanaleptics, and pulmonary and cardiac stimulants.[2] Despite the continued interest in 1- and 1,3-substituted xanthines as promising pharmacophores, methods for their synthesis remain scarce. The classic Traube purine synthesis from 6-aminouracil derivatives[3] and its recent modifications[4] remain rather lengthy, utilize harsh reaction conditions, and are generally limited to the preparation of 1-primary alkyl-substituted xanthines. More recently, alternate approaches to substituted xanthines were reported utilizing a two-step cyclocondensation of 4-amino-5-alkoxycarbonylimidazoles with isocyanates[5] or 4-amino-5-carbamoylimidazoles with phosgene equivalents.[6] These methods allow for the introduction of unhindered primary, secondary, and aromatic substituents at N-1 and N-3; however, they generally suffer from long reaction times, extreme temperatures, and the use of highly toxic, volatile reagents.

As a part of our program on PDE 5 inhibitors, we needed a robust method to prepare multikilogram quantities of pure

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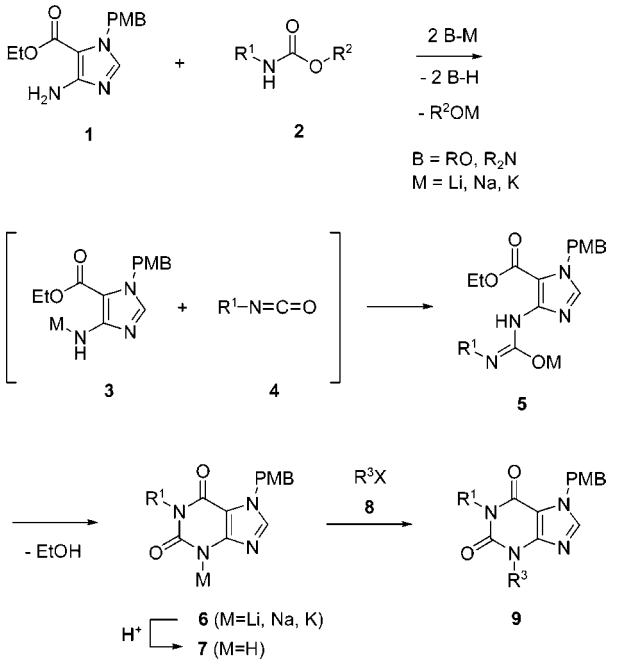
Scheme 1



1- and 1,3-substituted 7-PMB-protected xanthines. We reasoned that direct condensation of readily accessible[7] 1-PMB-4-amino-5-ethoxycarbonylimidazole precursor **1** with commercially available carbamates **2** could, in principle, provide an alternative and practical one-step approach to 1-substitituted 7-PMB xanthines **7** (Scheme 1). Due to the low nucleophilicity of the pendant 4-amino group, reactions of **1** with even the most reactive electrophiles such as isocyanates are known to be rather sluggish.[5] However, we envisioned that, in the presence of a suitable base, the reaction of **1** with **2** could be accelerated by simultaneous in situ formation of highly reactive metal amide **3** and isocyanate **4** intermediates (Scheme 1). This method has the advantage of replacing the toxic isocyanates or phosgene equivalents with readily available, stable carbamates. Moreover, the product of this reaction would be 1-substituted xanthine alkali metal salt **6**, which could offer practical advantages in product isolation and make further alkylation to produce 1,3-substituted 7-PMB xanthines **9** straightforward.

An initial screening for the optimal reaction conditions was performed using a reaction of **1** with carbamate **2c** ($R^1 = R^2 =$ Et, Scheme 1) to give product **6b** ($R^1 =$ Et, M = K). Since 1 equiv of base was irreversibly consumed in the formation of the product xanthine metal salt, at least 1.5 equiv of base was used in all experiments. Our results are summarized in Table 1. Among the solvents examined, most promising results were obtained in ethereal solvents such as THF, DME, or diglyme, with little or no reaction observed in alcohols or toluene. Sodium bases such as NaOMe (entries 6, 8, 12), NaOEt (entries 1, 13), and NaO^{t}Bu (entry 15) and unhindered potassium bases such as KOEt (entry 14) generally gave low to moderate yields of product **6b**. With lithium bases such as LDA (entry 5) or LHMDS (entry 11), product yields were also modest and reaction times rather long due to slow ring closure of intermediate lithiated ureido species **5b** ($R^1 =$ Et, M = Li). In some of the above examples (e.g., entries 6, 13), low overall product yields could simply be attributed to low reaction conversions. Yet in other instances (e.g., entries 11, 14, 15), low to moderate product yields were obtained despite the virtually complete consumption of starting imidazole **1**. Careful analysis of the reaction impurity profile and mass balance in the latter cases indicated significant background base-promoted degradation of **1**. Fortunately, this unproductive degradation of **1** could be appreciably minimized when strong hindered potassium bases such as KO^{t}Bu, KHMDS, or KO^{t}Am were employed in diglyme (entries 16−18). To suppress the background degradation even further, reagent addition order was modified to slowly add a solution of base in diglyme to the preheated (70−80 °C) agitated diglyme solution of **1** and **2c**. Under these conditions, the product potassium salt **6b** precipitated directly from reaction medium and was isolated by filtration. A simple aqueous acid workup of isolated salt **6b** delivered the desired xanthine **7b** in 80−85% isolated yields and >99% purity.

Table 1. Effect of Base and Solvent on Product Yield in Reaction of **1** with **2c**[a]

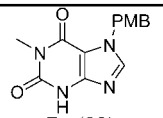
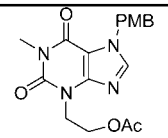
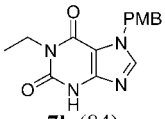
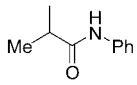
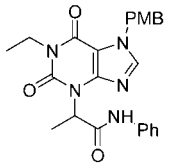
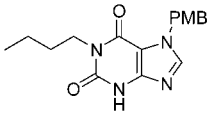
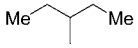
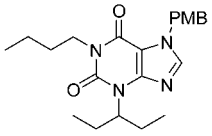
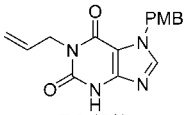
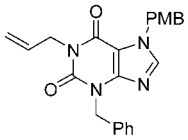
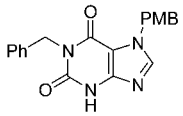
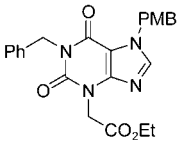
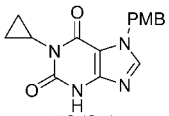
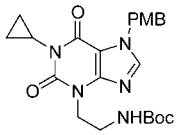
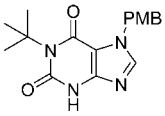
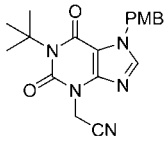
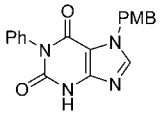
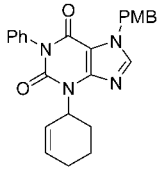
entry	solvent	base	reaction time, h	conversion of **1**, %	solution yield of **6b**, %[b]
1	EtOH	NaOEt	24	0	0
2	^{i}PrOH	KO^{t}Bu	24	0	0
3	toluene	KO^{t}Am	24	31	12
4	toluene	KO^{t}Bu	24	29	15
5	THF	LDA	24	95	45
6	THF	NaOMe	24	5	4
7	THF	KO^{t}Bu	2	>99	72
8	DME	NaOMe	24	2	2
9	DME	KO^{t}Bu	2	>99	80
10	DEM	KO^{t}Bu	2	56	37
11	diglyme	LHMDS	24	97	61
12	diglyme	NaOMe	24	5	3
13	diglyme	NaOEt	24	8	5
14	diglyme	KOEt	3	>99	50
15	diglyme	NaO^{t}Bu	3	98	45
16	diglyme	KO^{t}Bu	2	>99	89
17	diglyme	KO^{t}Am	2	>99	80
18	diglyme	KHMDS	2	>99	85

[a] Experimental conditions: base (15 mmol) was added to the stirred solution of **1** (10 mmol) and **2c** (12 mmol) in 50 mL of solvent at 70−80 °C, and the reaction was agitated for the specified period of time. [b] Determined by HPLC assay vs analytically pure standard.

With optimized reaction conditions in hand, we next examined the scope and generality of this method. A variety of 1-substituted 7-PMB-protected xanthine derivatives **7** with primary alkyl (entries 1−5), secondary alkyl (entry 6), tertiary alkyl (entry 7), and aromatic (entry 8) N-1 substituents were prepared in good to excellent yields (Table 2).[7] In the majority of cases, precipitated pure product xanthine

(7) See Supporting Information for detailed experimental procedures.

Table 2. Preparation of 1- and 1,3-Substituted 7-PMB Xanthines

entry	R^1, R^2	1-substituted xanthine **7** (% yield)[a]	R^3	1,3-substituted xanthine **9** (% yield)
1	**2a**: R^1=Me, R^2=Et **2b**:R^1=Me, R^2=2,3-di-Cl-Ph	 **7a** (82) **7a** (89)	CH_2CH_2OAc **8a**	 **9a** (85)
2	**2c**: R^1=Et, R^2=Et **2d**:R^1=Et, R^2=Ph	 **7b** (84) **7b** (90)	 **8b**	 **9b** (82)
3	**2e**: R^1=Bu, R^2=Et	 **7c** (87)	 **8c**	 **9c** (79)
4	**2f**: R^1=allyl, R^2=^{t}Bu	 **7d** (79)	Bn **8d**	 **9d** (87)
5	**2g**: R^1=Bn, R^2=^{t}Bu	 **7e** (81)	CH_2CO_2Et **8e**	 **9e** (91)
6	**2h**: R^1=cyclopropyl, R^2=Et	 **7f** (85)	CH_2CH_2NHBoc **8f**	 **9f** (90)
7	**2i**: R^1=^{t}Bu, R^2=Me **2j**: R^1=^{t}Bu, R^2=Ph	 **7g** (15) **7g** (79)	CH_2CN **8g**	 **9g** (86)
8	**2k**: R^1=Ph, R^2=Et **2l**: R^1=Ph, R^2=Ph	 **7h** (5) **7h** (69)	 **8h**	 **9h** (77)

[a] Yields of 1-substituted xanthines are given for the respective carbamates shown on the left in column 2.

potassium salts **6** were isolated by filtration and converted to parent xanthines **7** on acidification. Where the product salts did not directly precipitate (entries 5, 7, 8), isolation and purification of **7** was achieved following a standard acid−base workup. Reactions with *O*-alkyl carbamates typically required 1.5−2.0 equiv of KO^{t}Bu for optimum performance, while at least 3.0 equiv of KO^{t}Bu was needed to drive the reactions with *O*-aryl carbamates to completion

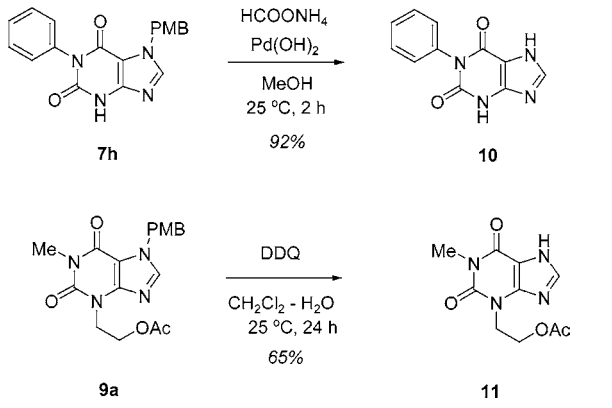
due to the low basicity of in situ-generated aryloxide R^2OM (R^2 = Ar, Scheme 1), limiting its ability to further catalyze the desired reaction. Due to their faster rate of isocyanate generation, *O*-aryl carbamates offered shorter reaction times, lower reaction temperatures, and higher product yields than the corresponding *O*-alkyl carbamates with the same N-substituent (e.g., entries 1, 2, 7, 8). In fact, the use of *O*-phenyl carbamates **2j** and **2l** was essential to obtain good yields of 1-^{t}Bu- and 1-Ph-substituted xanthines **7g** and **7h**, respectively, as all attempts to prepare these xanthines via condensations of **1** with the corresponding *O*-alkyl carbamates **2i** and **2k** resulted in poor yields and extensive starting material decomposition.

Even with the activated *O*-phenyl carbamate **2j**, conversion of **1** to **7g** was observed to be rather slow (~95% after 12 h at 70−80 °C) due to the difficult ring closure of the sterically hindered ureido intermediate **5g** (R^1 = ^{t}Bu, M = K). Nevertheless, the successful preparation of 1-tertiary alkyl xanthine **7g** in good yield under these mild conditions is quite remarkable and, to the best of our knowledge, unprecedented in the literature.

Alkylation of 1,7-substituted xanthines at N-3 is traditionally performed in DMF in the presence of an excess of alkylating reagent and scavenger base, with reaction times often exceeding 24 h.[3a] We have found that alkylation of both xanthine potassium salts **6** and their parent xanthines **7** to form 1,3-substituted 7-PMB derivatives can be conveniently performed in THF or MeCN in the presence of a phase-transfer catalyst Bu_4NBr (Table 2).[7] Alkylation of isolated potassium salts **6a**−**d**,**f** was particularly facile and straightforward, producing functionalized xanthines **9a**−**d**,**f** in good to excellent yields (entries 1−4, 6). The preparation of compounds **9e**, **9g**, and **9h** from xanthines **7** was best achieved in MeCN in the presence of K_2CO_3 and catalytic Bu_4NBr (entries 5, 7, 8). As shown by the examples in Table 2, the mild reaction conditions of this method are compatible with a wide variety of functional groups, including acetate, ester, nitrile, and amide. Both primary and secondary alkyl groups can be introduced in good yield, and the reaction selectivity toward N-alkylation versus O-alkylation was typically better than 98:2.

Finally, prepared 7-PMB-protected derivatives can be conveniently deprotected to their parent 1- and 1,3-substituted xanthines either by catalytic hydrogenation (**7h** to **10**, Scheme 2) or under oxidative conditions (**9a** to **11**) using standard procedures detailed elsewhere.[2a,5b,8] The ability to choose

Scheme 2



from the two complementary deprotection protocols highlights the utility of the present method and makes it potentially applicable to the preparation of a wide range of functionalized xanthine derivatives. Alternatively, 1,3-substituted 7-PMB xanthines can serve as convenient precursors to 9-substituted purines, whereby the PMB protecting group is removed after the N9-alkylation.[9]

In summary, we have developed a new and practical approach to the preparation of both 1- and 1,3-substituted xanthines. Direct condensation of the imidazole precursor **1** with carbamates in the presence of certain potassium bases gives 1-substituted 7-PMB xanthines in good yields. In many cases, product isolation is greatly simplified by formation of its insoluble potassium salt. Further alkylation of 1-substituted 7-PMB xanthines or their potassium salts proceeds under mild conditions in the presence of a phase-transfer catalyst and gives a variety of functionalized 1,3-substituted 7-PMB xanthines in good to excellent yields. Among the advantages of the new method are its experimental simplicity, generally good yields for a variety of functionalized substrates, and the use of nontoxic, readily available starting materials. Prepared using this method, 7-PMB-protected derivatives can be readily deprotected to give the parent 1- and 1,3-substituted xanthines.

Acknowledgment. We thank Dr. Larry Heimark for help with HRMS analysis.

Supporting Information Available: Experimental procedures and spectral data for compounds **1**, **7a**−**h**, **9a**−**h**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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