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Exploration of polystyrene-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ) as new coupling agent for the synthesis of 8-substituted xanthine derivatives

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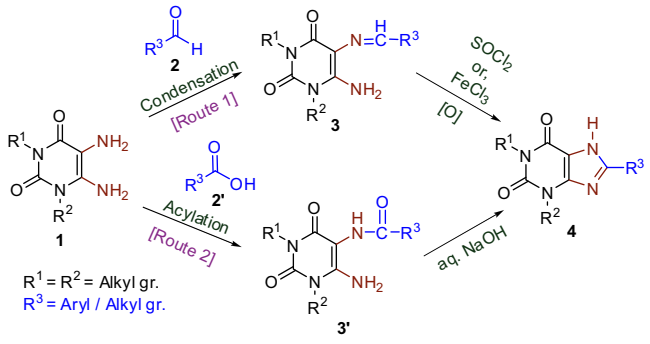
ABSTRACT

Polystyrene-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ), a polymer supported covalent coupling reagent, was successfully employed for the first time in the synthesis of 8-substituted xanthine derivatives. PS-IIDQ was observed to be more efficient than IIDQ and polymer-supported carbodiimide (PS-EDC).

Poly-substituted xanthine (purine-2,6-dione) derivatives are one of the most important chemical classes of adenosine receptor (AdoR) antagonists.[1a] Potent and selective AdoR antagonists display therapeutic potential as kidney protective (A_1), antifibrotic (A_{2A}), neuroprotective, antiasthmatic (A_{2B}), and antiglaucoma (A_3) agents.[1] To elicit high affinity toward AdoRs, adenosine receptor antagonists should be a flat, aromatic, π-electron rich, nitrogen-containing heterocycle.[2] Development of new approaches for their syntheses, employing efficient and economical routes, is thus a fascinating area of current research.

A number of synthetic routes have been reported for the synthesis of 8-substituted xanthine derivatives. The annulation strategies explored for the construction of xanthine nucleus **4**, involves the treatment of 5,6-diaminouracil **1** either with aldehyde **2** (route 1) or with carboxylic acid **2′** (route 2) via the intramolecular ring closure of the 6-amino-5-iminouracil intermediate **3**[3] under oxidative reaction conditions or by disconnection of the corresponding amino-acylaminouracil intermediate **3′** (Scheme 1), respectively.

Recently we have developed a rapid one-step protocol for the synthesis of a variety of 8-substituted xanthines considering aldehyde route.[3] Now we became interested in the prospect of developing a one-pot route to xanthines through a direct coupling between the readily available 5,6-diaminouracils **1** and a pertinent carboxylic acid **2′**, exploiting route 2. Conventionally, the first step involves the formation of 1,3-dialkyl-6-amino-5-carboxamidouracil (acylated) intermediate **3′** in the presence of l-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDAC·HCl)[4] or diisopropylcarbodiimide (DIC)[4a,5] as coupling agent at room temperature for several hours. However, none of the reagents reported so far can lead to the target compound with good conversion and most of them suffer from several bottlenecks, viz., use of unstable coupling agents, necessity of pre-activation step i.e. the carboxylic acid has to be added to the coupling reagent prior to



Scheme 1. Pathways for synthesis of 8-substituted xanthines through aldehyde (route 1) or carboxylic acid (route 2) routes.

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Table 1
Effect of PS-IIDQ concentration for the synthesis of 6-amino-5-benzoxamido-1,3-dimethyluracil (**3a**)[a]

Entry	PS-IIDQ concn (equiv)	Time[b] (h)	Yield[c] (%)
a	1	1	52
b	1.5	1	67
c	2	1	83
d	2.5	2	81
e	3	2	78

[a] Reaction condition: the mixture of 5,6-diamino-1,3-dimethyluracil (1 equiv, 1 mmol) and benzoic acid (1 equiv, 1 mmol) with different concentration (equiv) of PS-IIDQ was stirred in CH_3CN/H_2O (9:1, v/v) (10 mL) at room temperature.
[b] All the reactions monitored by TLC.
[c] Isolated yield.

Table 2
Comparison of coupling performance of PS-IIDQ with PS-EDC and IIDQ for the synthesis of 6-amino-5-benzoxamido-1,3-dimethyluracil (**3a**)[a]

Sl. No.	Coupling agent	Yield[b] (%)	Purity[c]
1.	PS-IIDQ	83	100
2.	IIDQ	81	84
3.	PS-EDC	49	81

[a] Reaction condition: the mixture of 5,6-diamino-1,3-dimethyluracil (1 equiv, 1 mmol) and benzoic acid (1 equiv, 1 mmol) with 2 equiv of coupling agent was stirred in CH_3CN/H_2O (9:1, v/v) (10 mL) at room temperature for 1 h.
[b] Isolated yield.
[c] All the reactions monitored by TLC and HPLC.

the addition of the diamine, poor stability of the coupling agent in the presence of a base, and most importantly, the formation of by-products, and low yields.

The second step of the reaction proceeds via intramolecular ring closure reaction of intermediate **3′** leading to the formation of xanthine nucleus using aqueous NaOH solution[4,5] under reflux condition. Most recently, this step, was also studied by making use of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) under conventional heating[6a] as well as microwave[6b] conditions. However, very low polarity of HMDS can cause solubility problems when polar compounds are to be reacted. Also, high temperatures (>120 °C) and long reaction times (from several hours to several days) are generally required, especially if uracil derivatives containing polar groups are used as precursors.[7,8] Therefore, as a consequence, search for new methods/reagents to overcome these limitations are still an important experimental challenge to organic chemists. Over the past decade, interest in the development of new polymer-supported reagents has increased,[9] predominantly because these reagents combine the traditional advantages of solution phase chemistry with the convenience of solid-phase handling. Thus using polymer-supported materials, unreacted reagents and by-products remain on the resin and in turn can be easily removed by filtration.

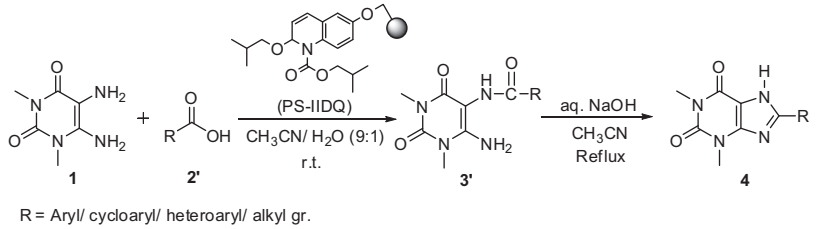
Recently, Bradley and Valeury reported[10] polystyrene-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ) as an efficient coupling reagent that couples carboxylic acids to amines to form amide bond in good yields and high purity. Therefore, encouraged by its features and associated advantages, including that it does not require any pre-activation, i.e. the order of addition of the amine, acid, and IIDQ makes no difference to the efficiency of coupling. Also the formation of volatile by-products and high stability of IIDQ under general laboratory conditions and its stability in the presence of base are the added advantages. With these issues in mind a polymer-supported equivalent of IIDQ was targeted. In continuation of our efforts in the field of new synthetic methodologies for the synthesis of nitrogen heterocycles,[11] and our recent report on the synthesis of 8-substituted xanthines,[3] the objective of the present study is to demonstrate the application of PS-IIDQ for the first time in the one-pot synthesis of 8-substituted xanthine derivatives by coupling 5,6-diamino-1,3-dimethyluracil with various carboxylic acid derivatives. A series of substrates have been coupled and cyclized to afford the target heterocycles at moderate temperature with quantitative yields and high purity.

In order to standardize the reaction conditions, the coupling conditions for PS-IIDQ were first optimized by coupling 5,6-diamino-1,3-dimethyluracil with benzoic acid in different solvents. It was found that 5,6-diamino-1,3-dimethyluracil, benzoic acid and PS-IIDQ in 1:1:2 equiv ratios in acetonitrile gave better results. To determine the optimal conditions for effective coupling, conjugates were prepared at five different equivalent ratios (1:1, 1:1.5, 1:2, 1:2.5, and 1:3) of starting materials and PS-IIDQ and it has been found that only 2 equiv (Table 1, entry c) of PS-IIDQ was necessary to ensure the high conversion for the formation of amide bond (acylation).

The reaction conditions were further optimized to give better result and it was found that the addition of a few drops of water with acetonitrile increased the initial homogenity of the reaction mixture which may cause better reactivity and yield. Further, replacement of acetonitrile with other water miscible solvents such as, methanol or ethanol did not succeed in giving good yields. The best result was obtained from a mixture of acetonitrile and water (9:1, v/v). The synthesis of 8-substituted xanthine[12] derivatives using PS-IIDQ is shown schematically in Scheme 2.

Synthesis of 8-substituted xanthine was carried out with both PS-IIDQ and IIDQ under the optimized reaction conditions followed by a quick aqueous work-up. The different amides were in most cases obtained in acceptable yield and very high purity. It was noticed that the results were better in terms of purity when PS-IIDQ was used. This illustrates the advantage of PS-IIDQ over the classic solution-phase reagent IIDQ, where an intensive work-up is necessary to remove all the quinoline generated during the coupling. In order to assess the coupling performance of PS-IIDQ compared to existing supported carbodiimide approaches, specifically PS-EDC, they were used separately as coupling reagents in the optimized reaction conditions and PS-IIDQ was observed to be more efficient than polymer-supported carbodiimides (PS-EDC) and gave better yields and higher purity for amide bond formation (Table 2).

With the optimized reaction conditions in hand, the scope of the protocol was further explored for the reaction of a variety of substituted aryl carboxylic acids (Table 3). An excessive coupling



Scheme 2. PS-IIDQ mediated one-pot synthesis of 8-subtituted xanthines.

Table 3
PS-IIDQ mediated synthesis of 8-substituted xanthines[a]

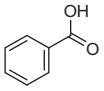
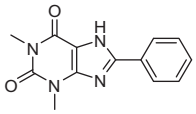
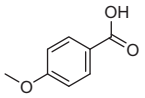
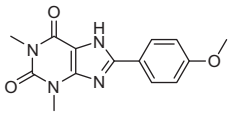
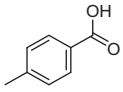
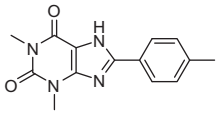
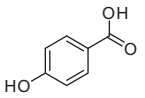
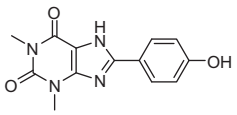
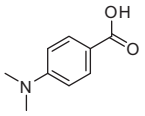
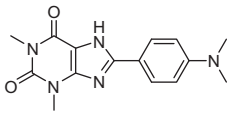
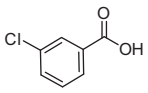
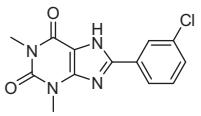
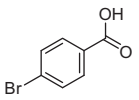
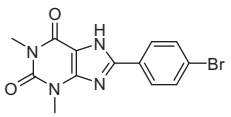
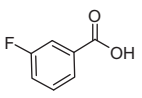
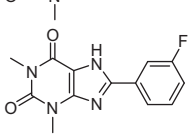
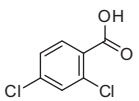
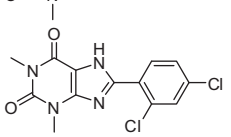
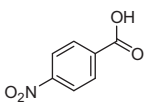
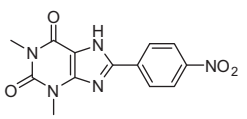
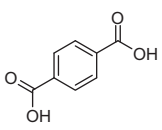
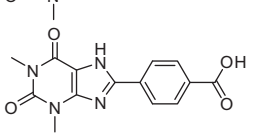
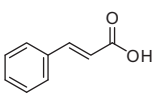
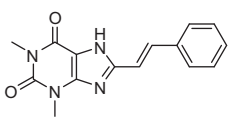
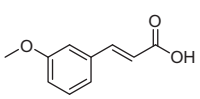
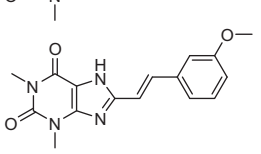
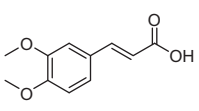
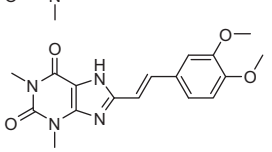
Entry	Acid (**2′**)	Product (**4**)	Time[b] (h)	Yield[c] (%)
a			3	78
b			3.5	71
c			3	74
d			3	76
e			4	64
f			3	68
g			3.5	70
h			3	67
i			3.5	65
j			3	71
k			4	73
l			3	72
m			3	79
n			4	74

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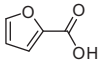
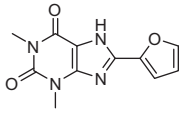
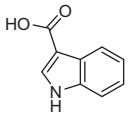
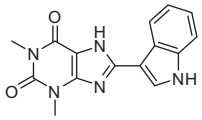
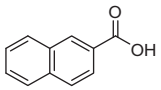
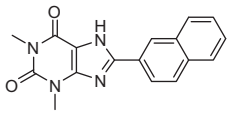
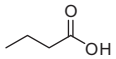
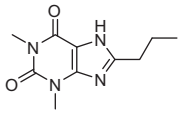
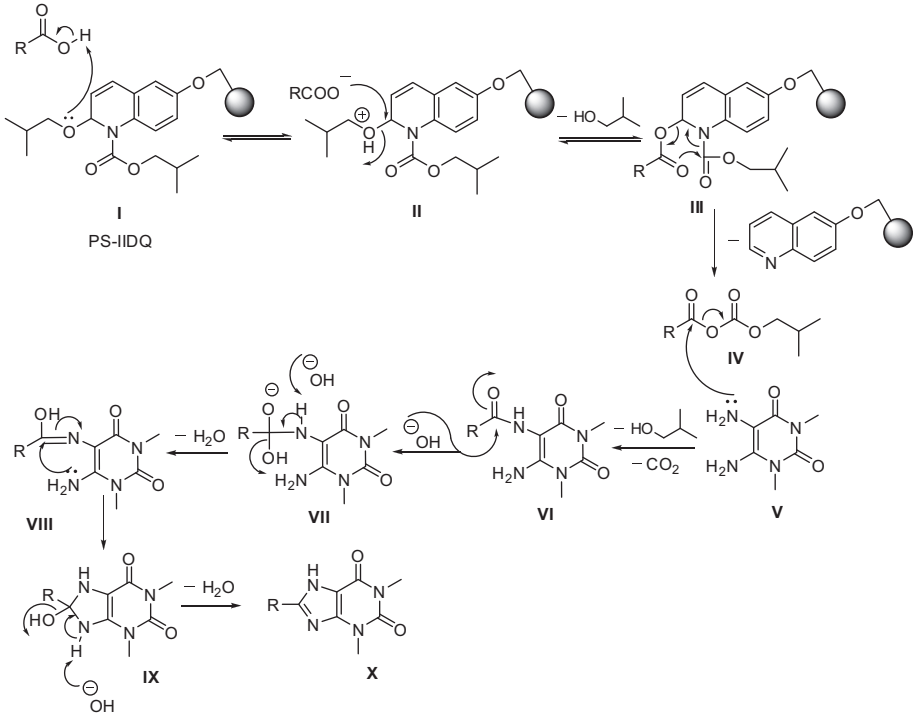
Table 3 (*continued*)

Entry	Acid (**2′**)	Product (**4**)	Time[b] (h)	Yield[c] (%)
o			4	62
p			4.5	73
q			4.5	65
r			3	71

[a] Reaction conditions: (a) 5,6-diamino-1,3-dimethyluracil (1 equiv), carboxylic acid derivative (1 equiv), and PS-IIDQ (2 equiv) in CH_3CN/H_2O at rt, (b) 2.5 N aqueous NaOH solution, CH_3CN, reflux.
[b] Total reaction time (step I + step II).
[c] Isolated yield.



Scheme 3. Proposed mechanism for the PS-IIDQ mediated one-pot synthesis of 8-substituted xanthines.

time of 2 h was used in order to enable difficult substrates to react. This contrasts with many coupling reagents, which although often having a very high intrinsic reactivity are unstable in solution, with most of the reagent (or active HOBt ester) having degraded after an hour, a characteristic which is unsuitable for hindered substrates or if the coupling is slow. Considering this problem, PS-IIDQ offers a good balance between reactivity and stability. The desired coupling followed by intramolecular cyclization was obtained with mono and di substituted aryl carboxylic acids (Table 3, entries a–k) with 64–78% yield. Likewise, using this protocol, substituted cinnamic acid derivatives and 5,6-diamino-1,3-dimethyluracil underwent coupling followed by intramolecular ring closure to give the corresponding 8-styryl-7*H*-xanthine derivatives (Table 3, entries l, m, and n) with 72–79% yield. Furthermore, heteroaryl carboxylic acid such as furan-2-carboxylic acid (Table 3, entry o) also afforded the desired products with 62% yield. Additionally, the reaction was also successful with cycloaryl carboxylic acid, such as indole-3-carboxylic acid, naphthalene-2-carboxylic acid (Table 3, entries p and q), under the same reaction condition with 65–73% yield. Our effort to produce 1,3,8-trialkyl xanthine derivative, that is, 8-propyl-1,3-dimethyl-7*H*-xanthine (Table 3, entry r) was also successful with 71% yield. In all these cases, the reactions were clean and the products were obtained with simple work-up in quantitative yields and high purity.

The structures of all the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ESI-MS data, and their purity by HPLC analysis. PS-IIDQ was easily regenerated; intensive washing followed by reaction with isobutyl chloroformate yielded a recycled polymer-supported IIDQ with an efficiency similar to the original material.

On the basis of the above observations and literature reports,[13] a plausible mechanism for the synthesis of 8-substituted xanthine derivatives using PS-IIDQ is depicted in Scheme 3. The treatment of a carboxylic acid with PS-IIDQ **I** in MeCN/H_2O rapidly generates in situ the corresponding isobutoxycarbonyl mixed anhydride[14] **IV**. Attack by nucleophile (amine) **V** preferentially takes place at the less hindered and more electrophilic carbonyl of the carboxylic acid moiety, giving **VI** by forming amide bond concurrently with the release of volatile carbon dioxide and isobutanol as by-products. The electronic environment on nitrogen of two free amino groups of 5,6-diamino-1,3-dimethyluracil **V** are not identical. The electrons present on nitrogen of –NH_2 group (adjacent to N–CH_3 group) take part in resonance with the pyrimidine ring, due to which the electron availability on that nitrogen is reduced, while the electron density on nitrogen of the other –NH_2 group (adjacent to C=O group) is much greater due to their non-participation in resonance. This electron rich nitrogen attacks the electron deficient carbonyl carbon of carboxylic acid moiety of **IV** to form selectively 6-amino-5-carboxamido-1,3-dimethyluracil intermediate **VI**. The cleavage of the amide bond of **VI** occurs by the attack of hydroxide anions to form **VII**, which on dehydration, gives **VIII**. In the subsequent steps, the intermediate **VIII** cyclizes to afford xanthine nucleus **X**. It is noteworthy to mention that, starting from the formation of **VI**, the intramolecular ring closure occurs selectively from one side of the carbon skeleton to afford exclusively a single product.

In conclusion, we successfully demonstrated the application of PS-IIDQ for the first time in the synthesis of 8-substituted xanthine derivatives starting from 5,6-diamino-1,3-dimethyluracil. PS-IIDQ was observed to be an efficient polymer-supported coupling reagent as compared to IIDQ and polymer-supported carbodiimide (PS-EDC) for amide bond formation with better yields and higher purity. Additionally, it does not require any pre-activation, stable in the presence of base and high stability under general laboratory conditions. A clean and efficient reaction, simple isolation of the product and wide applicability to a variety of substrate (including hindered substrates) renders this method to be of high practical utility.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.135. These data include MOL files and InChiKeys of the most important compounds described in this article.

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12. Typical synthetic procedure for the preparation of the 8-substituted xanthines. In a round bottom flask, 5,6-diamino-1,3-dimethyluracil (0.170 g, 1 mmol, 1 equiv) and carboxylic acid derivative (1 mmol, 1 equiv) were stirred in CH_3CN/H_2O (9:1, v/v) (10 mL) for 10 min. To this, PS-IIDQ (2 equiv) (loading of the resin 1.6 mmol g^{-1}) was added. The reaction mixture was then stirred at room temperature for 1–2 h. The unreacted reagents and by-products (polymer-supported quinolines) remain adsorbed on the resin surface and thereby removed through filtration at the end of the reaction work-up. The mother liquor was then concentrated under reduced pressure and mixed with CH_3CN (10 mL) and 2.5 N aqueous NaOH solution (15 mL). The mixture was heated under reflux for the appropriate time in each case and allowed to cool down to room temperature. After cooling to 0 °C, the corresponding 1*H*-purine-2,6-dione precipitated by adjusting the pH to 5.0 with concentrated HC1. After filtration and washing with cold 1 N HCl, and H_2O, further washed with ethyl acetate (2 × 5 mL) and methanol (3 × 5 mL) to obtain the pure product. The progress of the reaction was monitored by TLC (dichloromethane: methanol = 19:1, v/v) as well as by HPLC (HPLC grade methanol (100%) was used as an isocratic eluent at a flow rate of 1 mL min^{-1}).
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