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# Straightforward and Highly Efficient Catalyst-Free One-Step Synthesis of 2-(Purin-6-yl)acetoacetic Acid Ethyl Esters, (Purin-6-yl)acetates, and 6-Methylpurines through $S_NAr$-Based Reactions of 6-Halopurines with Ethyl Acetoacetate

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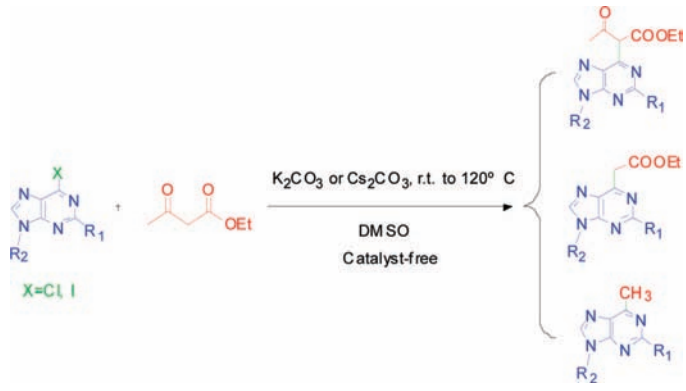
## ABSTRACT




**A novel approach to the synthesis of purines bearing functionalized carbon substituents or methyl in position 6 was developed. Under different reaction conditions, 6-halopurine derivatives could react with ethyl acetoacetate efficiently to yield 2-(purin-6-yl)acetoacetic acid ethyl esters, (purin-6-yl)acetates and 6-methylpurines respectively. No metal catalyst and ligand were required.**

Modifications on purines bearing carbon substituents in position 6 have been the focus for decades since the highly cytotoxicity[1] and antitumor activity[2] of 6-methylpurine and its ribonucleoside were found. Many of these derivatives were found to exhibit cytostatic effects. For example, 6-(arylalkynyl)-, 6-(arylalkenyl)-, and 6-(arylalkyl)purines show cytokinin[3] and antioxidant activity.[4] 9-Benzyl-6-

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arylpurines exhibit antimycobacterial, antibacterial, and cytotoxic effects.[5] 6-Hetaryl-purine ribonucleosides exhibit potent antiviral activity against HCV.[6] 6-Hydroxymethyl-9-($\beta$-D-ribofuranosyl)purine isolated from collybia maculata was reported to possess antifungal, cytotoxic, antiviral properties[7] and could be also used as an adenosine deaminase inhibitor.[8] Very recently, Michal Hocek et al. reported a series of purines bearing functionalized carbon substituents in position 6[9] and many of them display significant cytostatic activity.

The classical method for the synthesis of purines bearing carbon substituents in position 6 was heterocyclization.[10] Another method was radical addition.[11] Currently, the most frequently used methods were transition metal-catalyzed cross-coupling reactions of 6-halopurines. In this respect, the Suzuki-,[12a] Stille-,[12b] Negish-,[12c] and Sonogashira-,[12d,e] coupling reaction have all been exploited successfully, and various organometallic reagents[12f,g,9f] were involved. No matter what the carbon substituents in position 6 are, these methods seem to be versatile. For example, purin-6-yl acetates were prepared previously in moderate yields by heterocyclization of pyrimidines,[10a] arylation of malonates[13] or ethyl acetoacetate[14] with 6-halo or 6-tosyloxypurines followed by decarboxylation or cleavage of acetoacetate. However, these methods were laborious or hard to reduplicate.[9f] Michal Hocek et al. synthesize these compounds via Pd-catalyzed cross-couplings of 6-chloropurines with the Reformatsky reagent in the presence of ligands; 6-methylpurine bases were prepared by the conventional and tedious method of heterocyclization[10b−d] from 6-methyluracil with low yield.

Another straightforward method for the synthesis of 6-methylpurine involves the displacement of a suitable leaving group on the heterocycle by Wittig reagent[15] which usually requires rigorous reaction conditions (anhydrous, nitrogen atm at −30 to −35 °C). Similarly, cross-coupling reaction has been also widely applied[16] to the synthesis of 6-methylpurine derivatives. Regioselective methylation reactions[17] of 2,6-dihalopurines with methylzinc bromide or trimethylaluminum in the presence of Pd- or Fe- catalysts were also investigated by Michal Hocek et al. Despite the cross-coupling reaction provides a general and efficient methodology for the synthesis of purines bearing carbon substituents in position 6, the expensive catalyst and rigorous reaction conditions often make this method less desirable. In addition to the above-mentioned methods, a most promising route is the nucleophilic $S_NAr$ reaction of 6-alkanesulfonyl- or 6-halopurines with some salts of C-acids[14a,b,18] (such as malonates or acetoacetates), which have been less developed and usually were not reliably reproducible in accordance with previous literature.

Based on our preliminary study on various nucleoside analogues,[19] herein, we reported a novel and efficient method for the synthesis of purines bearing different carbon substituents in position 6 through nucleophilic aromatic substitution of 6-halopurines and ethyl acetoacetate without catalyst.

Initially, we investigated the $S_NAr$-based reactions between ethyl acetoacetate and 9-Bn-6-iodopurine.[20] As indicated in Table 1 (entries 1 and 2), our experiments were first conducted by coupling 9-Bn-6-iodopurine (1 eq) with ethyl acetoacetate (5 eq) in the absence of catalyst. This reaction proceeded at 80 °C in DMSO in the presence of 7.5 equiv of $K_2CO_3$ for 6 h to produce the desired (purin-6-yl)acetate **4a** in 81% yield along with other unidentified products (entry 1). Later, the unidentified products were confirmed to be arylation product **3a** and 9-Bn-6-methylpurine **5a** by HRMS, $^1$H NMR, and $^{13}$C NMR. The initial arylation product **3a** increased when the reaction time was shorten, indicating that different products could be formed with different reaction time (entry 2). The same results were obtained when 9-Bn-

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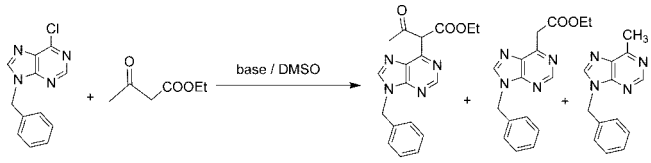
**Table 1.** Investigation on the Nucleophilic $S_NAr$ Reaction between Ethyl Acetoacetate and 9-Bn-6-Chloropurine in the Absence of Catalyst[a]

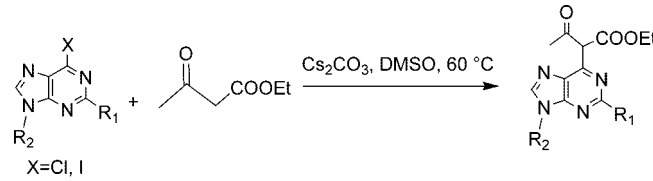



1a 2 3a 4a 5a

| entry | base (equiv) | temp. (°C) | time (h) | yield of **3a** (%)[b] | yield of **4a** (%)[b] | yield of **5a** (%)[b] |
|---|---|---|---|---|---|---|
| 1[c] | $K_2CO_3$ (7.5) | 80 | 6 | 8 | 81 | trace |
| 2[c] | $K_2CO_3$ (7.5) | 80 | 2 | 45 | 47 | 0 |
| 3 | $K_2CO_3$ (7.5) | 80 | 6 | 19 | 75 | 0 |
| 4 | $K_2CO_3$ (7.5) | 80 | 1 | 63 | 31 | 0 |
| 5 | $K_2CO_3$ (7.5) | 80 | 7 | 11 | 76 | trace |
| 6 | $K_2CO_3$ (2) | 80 | 7 | 32 | 57 | 0 |
| 7 | $K_2CO_3$ (7.5) | 80 | 1 | 56 | 33 | 0 |
| 8 | $K_3PO_4 3H_2O$ (7.5) | 80 | 1 | 74 | 16 | 0 |
| 9 | NaH (7.5) | 80 | 0.5 | 32 | 37 | trace |
| 10 | $Cs_2CO_3$ (7.5) | 80 | 0.5 | 83 | trace | 0 |
| 11 | $Cs_2CO_3$ (2) | 80 | 2 | 66 | 0 | 0 |
| 12 | $Cs_2CO_3$ (7.5) | 60 | 0.5 | 91 | 0 | 0 |
| 13[d] | $Cs_2CO_3$ (7.5) | 80 | 0.5 | 81 | 0 | 0 |
| 14 | $Cs_2CO_3$ (7.5) | rt | 5 | 83 | 0 | 0 |
| 15 | $K_2CO_3$ (7.5) | 80 | 24 | trace | 41 | 45 |
| 16 | $K_2CO_3$ (7.5) | 120 | 5 | trace | trace | 76 |

[a] Reagents and conditions: 0.5 mmol **1a**, 2.5 mmol ethyl acetoacetate **2** in 2 mL solvent for the indicated time. [b] Isolated yield based on **1a**. [c] 9-Bn-6-iodopurine was used. [d] DMF was used.

**Table 2.** Reaction of Ethyl Acetoacetate with Various 6-Halopurine Derivatives to Yield 2-(6-Purinyl)acetoacetic Acid Ethyl Esters **3**[a]




1a-o 2 3a-o

| entry | X | $R_1$ | $R_2$ | time (h) | products | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | Cl | H |  | 1 | **3a** | 90 |
| 2 | Cl | H |  | 1 | **3b** | 92 |
| 3 | Cl | H |  | 1 | **3c** | 90 |
| 4 | Cl | H |  | 1 | **3d** | 94 |
| 5 | Cl | H |  | 2 | **3e** | 89 |
| 6[c] | Cl | Cl |  | 0.5 | **3f** | 95 |
| 7 | Cl |  |  | 6 | **3g** | 0 |
| 8[d] | Cl | H |  | 5 | **3h** | 68 |
| 9[c] | Cl | Cl |  | 0.5 | **3i** | 93 |
| 10[c] | Cl | Cl |  | 1 | **3j** | 93 |
| 11 | Cl | H | H | 6 | **3k** | 0 |
| 12 | I | H | H | 6 | **3l** | 0 |
| 13 | I | H |  | 0.5 | **3a** | 91 |
| 14 | I | H |  | 0.5 | **3b** | 92 |
| 15 | I | H |  | 1 | **3c** | 89 |

[a] Reagents and conditions: 0.5 mmol 6-halopurine derivatives **1**, 3.75 mmol (7.5 eq) $Cs_2CO_3$, 2.5 mmol (5 eq) ethyl acetoacetate **2** in 2 mL DMSO at 60 °C for the indicated time. [b] Isolated yield based on 6-chloropurine derivatives **1**. [c] Reaction was carried out at rt. [d] Reaction was carried out at rt and $K_2CO_3$ was used as the base.

6-chloropurine[21] was used (entries 3−4), demonstrating that 6-chloropurine derivatives could also act as efficient substrates in this reaction. Next, we investigated the effect of temperature, solvent, reaction time and the type and amount of base on the relative yields of **3a**, **4a** and **5a**. The deacylation product **4a** need much longer time (entry 5), while generation of **3a** could be performed in a relatively short time (entries 7 and 10−14). Compared with other investigated bases ($Na_2CO_3$, KOAc, $K_3PO_4{\cdot}3H_2O$, KOH, $K_2HPO_4{\cdot}3H_2O$, NaH), $Cs_2CO_3$ was inclined to favor the arylated acetoacetate **3a** and was much less effective in the deacylation reaction, whereas $K_2CO_3$ was considered as the preferred base for the deacylation product **4a** (entries 5−7, 10, and 12). $K_3PO_4{\cdot}3H_2O$ could also serve as an effective base to yield the arylated acetoacetate **3a** (entry 8). When NaH was used, the reaction proceeded acutely in a very short time but gave some complex unidentified products (entry 9), which was in agreement with previous literature.[9f]

The number of stoichiometric equivalents of base used in the reaction could also make a difference. When 2 equiv of $K_2CO_3$ or 2 equiv of $Cs_2CO_3$ was used, the desired products **3a** or **4a** declined, even in the prolonged reaction time (entries 6 and 11). Temperature also played an important role in this reaction. The arylation of ethyl acetoacetate to yield **3a** could proceed smoothly at room temperature, but required longer reaction time (entry 14). And 60 °C turned out to be the best choice to yield **3a** (entry 12). Higher temperature was favorable to the deacylation and decarboxylation of **3a** (entries 15−16). When the temperature was elevated to 120 °C, 9-Bn-6-methylpurine **5a** was obtained in 76% within 5 h (entry 16). In all of the investigated solvents (DMSO, DMAc, DMF, Dioxane), DMSO was proved to be the most effective solvent, and DMF also gave a satisfactory result (entry 13). Different from the previous literature,[22] single decarboxylation product of **3a** was not observed in all the cases.

Next, 2-(purin-6-yl)acetoacetic acid ethyl esters **3** were prepared under the optimized reaction condition (shown in Table 1, entry 12). The effects of substituents of 6-halopurine derivatives were investigated. Various 6-halopurine derivatives could react with ethyl acetoacetate smoothly in high yields within short time (Table 2). 6-Iodopurine and 6-chloropurine derivatives gave similar results (entries 1−3 and 13−15), indicating that the leaving group at 6 position had little effects in this reaction. Compared with other 6-cholopurine derivatives substituted at N9, **1b** and **1d** gave the

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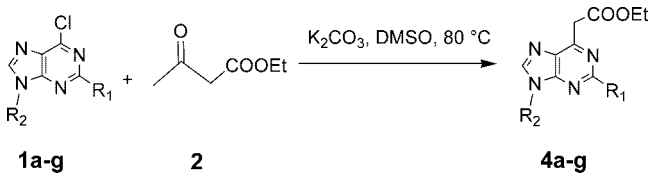
**Table 3.** Reaction of Ethyl Acetoacetate with Various 6-Chloropurine Derivatives to Yield (Purin-6-yl)acetates **4**[a]

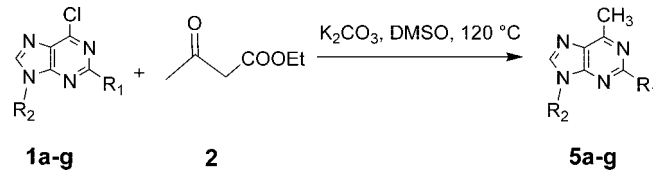



**1a-g** **2** **4a-g**

| entry | $R_1$ | $R_2$ | time (h) | products | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H |  | 7 | **4a** | 76 |
| 2 | H |  | 7 | **4b** | 85 |
| 3 | H |  | 7 | **4c** | 81 |
| 4 | H |  | 7 | **4d** | 74 |
| 5 | H |  | 7 | **4e** | 71 |
| 6 | Cl |  | 9 | **4f** | 0 |
| 7 |  |  | 12 | **4g** | 23 |

[a] Reagents and conditions: 0.5 mmol 6-chloropurine derivatives **1**, 3.75 mmol (7.5 eq) $K_2CO_3$, 2.5 mmol (5 eq) ethyl acetoacetate **2** in 2 mL DMSO at 80 °C for the indicated time. [b] Isolated yield based on 6-chloropurine derivatives **1**.

**Table 4.** Reaction of Ethyl Acetoacetate with Various 6-Chloropurine Derivatives to Yield 6-Methylpurines **5**[a]




**1a-g** **2** **5a-g**

| entry | $R_1$ | $R_2$ | Time (h) | products | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H |  | 5 | **5a** | 76 |
| 2 | H |  | 5 | **5b** | 85 |
| 3 | H |  | 5 | **5c** | 69 |
| 4 | H |  | 7 | **5d** | 72 |
| 5 | H |  | 8 | **5e** | 65 |
| 6 | Cl |  | 5 | **5f** | 82 |
| 7 |  |  | 10 | **5g** | 0 |

[a] Reagents and conditions: 0.5 mmol 6-chloropurine derivatives **1**, 3.75 mmol (7.5 eq) $K_2CO_3$, 2.5 mmol (5 eq) ethyl acetoacetate **2** in 2 mL DMSO at 120 °C for the indicated time. [b] Isolated yield based on 6-chloropurine derivatives **1**.

desired products **3b** and **3d** in higher yields respectively (entries 1−5 and 8). While 9-H-6-halopurines did not give the desired products regardless of the leaving group at 6 position (entries 11−12), which was in agreement with the previous literature.[9f,23] The effect of substituents at C2 were also studied. Replacement of H by Cl led to a so intense reaction that it could be performed at rt in 0.5 h (entries 6 and 9−10). When H at C2 was replaced by the nitrogen-containing substituent, the desired arylation product **3g** could not be obtained even after 6 h (entry 7).

As shown in Table 3, (purin-6-yl)acetates **4** were also prepared under the optimized reaction condition shown in Table 1 (entry 5). When there was no substituent at 2 position, all the 6-chloropurine derivatives gave the desired products **4a**−**4e** in moderate to good yields (entries 1−5). However, When H at C2 was replaced by Cl, except for compounds **3f** and **5f**, no desired product **4f** was observed (entry 6), presumably owing to the electron-donating effect. By contrast, replacement of H by the nitrogen-containing substituent which is unfavorable to the nucleophilic $S_NAr$ reaction led to the desired product **4g** with only 23% yield (entry 7).

Finally, several 6-methylpurines **5** were prepared under relatively strenuous conditions shown in Table 1 (entry 16), the results are summarized in Table 4. All the 6-chloropurine derivatives gave the desired products **5a**−**5f** in moderate to good yields (entries 1−5). The 2,6-dichloropurine **1f** gave the regioselective monomethylation product **5f** under the same condition (entry 6). However, when H at C2 was replaced by the nitrogen-containing substituent, the desired **5g** could not be obtained even after 10 h (entry 7).

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In conclusion, we have developed a novel and efficient method[24] for the preparation of 2-(6-purinyl)acetoacetic acid ethyl esters, (purin-6-yl)acetates and 6-methylpurines from 6-chloropurine derivatives and ethyl acetoacetate. Compared with previously known approaches, the simplicity of this procedure, the absence of expensive catalyst and ligand, and generally satisfactory yields make this method particularly attractive. The presence of a diverse range of substituents and functional groups in the purines also suggests an opportunity to acquire many other derivatives from these initial purines. Extension of this methodology to other active methylene compounds is undergoing.

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**Supporting Information Available:** NMR data of all synthesized compounds and full characterization of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Typical procedure for the $S_NAr$-based reaction between the 9-Bn-6-chloropurine (**1a**) and ethyl acetoacetate (**2**). 9-Bn-6-chloropurine **1a** (0.5 mmol), anhydrous cesium carbonate or anhydrous potassium carbonate (3.75 mmol), and ethyl acetoacetate **2** (2.5 mmol) were sequentially added to 2 mL of DMSO. The mixture was then stirred at the indicated temperature for the indicated time as shown in Tables 2, 3, and 4 (TLC monitoring). After cooling to room temperature, the resulting mixture was mixed with an ample amount of water (ca. 10 mL). The mixture was then extracted with methylene chloride (3 × 10 mL). The collected organic layers were dried with $Na_2SO_4$ and the solvent was evaporated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate) to give the desired products **3a**, **4a**, and **5a**, respectively.