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Mitsunobu reactions of nucleoside analogs using triisopropyl phosphite–DIAD

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Abstract—Herein, we report the use of triisopropyl phosphite (TIP) as an effective substitute for triphenylphosphine in the Mitsunobu reaction of nucleoside analogs. In addition, the use of triphenyl phosphite as an alternative reagent for the expensive hexamethylphosphorous triamide (HMPT) in the Véliz–Beal bromination protocol is reported.

The Mitsunobu reaction has found wide spread use in many fields because of its high reliability and extensive applicability.[1–3] However, the generation of phosphine oxide and hydrazinodicarboxylate as by-products often prevents the desired product from being isolated. Various ways of addressing this problem have been developed including triphenylphosphine (TPP) analogues that can be either removed by acid wash[4,5] or anchored to a resin.[6] The latter has also been applied to derivatives of dialkyl azodicarboxylates.[7] A new method that removes impurities via the novel ring opening metathesis (ROM) protocol has been developed by Barrett and Schröder.[8] Alkyl phosphines have also been introduced as a replacement for TPP. However, these compounds are highly expensive or pyrophoric. Palladium-catalyzed cross-coupling reactions are another example where significant amounts of expensive basic phosphine ligands are used. Because of this, organic chemists have demonstrated the ability of phosphites in combination with different types of palladium species as productive catalysts.[9–11] Here we describe the use of phosphites in Mitsunobu reactions yielding nucleoside analogs.

Maruyama et al. found that N^2-alkyl-6-chloropurine ribonucleoside derivatives can be synthesized via a Mitsunobu reaction from 6-chloro-2-acetamido-purine ribonucleoside.[12] However, the product was difficult to purify from the Mitsunobu by-products. These results and the significant outcome that phosphites can be used as a substitute of phosphines in palladium cross couplings prompted us to explore further the application of our substrate 6-bromo-2-acetamidopurine ribonucleoside and develop a new reagent system for the Mitsunobu reaction lacking the by-product problems. The use of phosphites would generate phosphates, which are more water soluble than their counterpart phosphine oxides. Morrison,[13] and later, Mitsunobu et al.[14] found that alkyl phosphites react with diethyl azodicarboxylate (DEAD). However, the intermediate suffered an intramolecular Arbuzov rearrangement. These results were used as the concept to develop our modified Mitsunobu reaction. If we blocked the intramolecular Arbuzov rearrangement by using a sterically hindered alkyl group, phosphites might be effective in the process. We found that triisopropyl phosphite (TIP) was an effective substitute for TPP in the Mitsunobu reaction. In addition, the use of triphenyl phosphite as an alternative reagent for the expensive hexamethylphosphorous triamide (HMPT) in our bromination protocol is also reported.

We have shown in our laboratories the unusually high reactivity of 6-bromo-2-acetamidopurine triacetyl ribonucleoside (**1**) toward nucleophiles.[15] To ensure the survival of this compound under the Mitsunobu conditions, we submitted the substrate to standard reaction conditions. Hence, we treated **1** with benzyl alcohol in the presence of TPP and DEAD in THF for 24 h. This reaction worked well to give the product in 89% yield after purification (Scheme 1).

We then used a phosphite in this reaction that would not suffer the Arbuzov rearrangement. For this purpose, we

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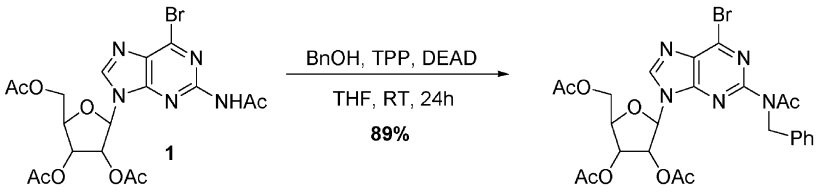


Scheme 1.

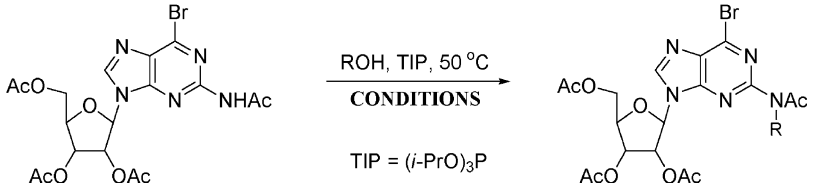
initially chose triphenyl phosphite. However, no product was obtained. We reasoned that a more nucleophilic, but sterically hindered, phosphite might be needed, and repeated the reaction using triisopropyl phosphite (TIP). As a model system, substrate **1** was allowed to react with a series of alcohols under Mitsunobu conditions (Table 1).[20] Data presented in Table 1 indicate that activated alcohols gave good to excellent yields using DEAD or DIAD in THF or dioxane as solvents at 50 °C (entries 1–4, and 7). Increasing the steric hindrance at the *ortho* position did not affect the reactivity of the alcohol (entries 2 and 3). However, unactivated alcohols and more hindered activated alcohols (entries 5, 9, and 10) did not form the desired product.

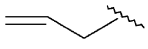
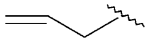
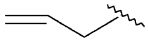
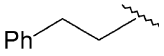
Next, we studied different combinations of azodicarboxylate reagent/solvent for the optimization of the reaction conditions. Consequently, 4-trifluoromethylbenzyl alcohol was allowed to react under different conditions according to Table 2. We found that DEAD or DIAD in THF were the best combinations for this reaction. The new reagent *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD), which was developed to be used with weak acids, gave traces of the desired product.[16–18]

In addition to the use of phosphites in the Mitsunobu reaction, we explored the utility of this type of reagent in the Véliz–Beal bromination procedure.[15,19] Our protocol calls for the use of hexamethylphosphorous triamide (HMPT), which is an expensive reagent and has precluded the use of this procedure on large scales. We found that substituting HMPT for triphenyl phosphite gave the desired bromo derivative in 76–82% yield (Scheme 2). However, the reaction took longer to go to completion (5 h instead of 1.5 h) and 5 equiv of triphenyl phosphite were needed instead of 2 equiv of HMPT. To our surprise, no product was observed when the 2-acetamido derivative was used.

In conclusion, we have demonstrated the use of triisopropyl phosphite in the Mitsunobu reaction as an alternative to phosphine reagents. Activated alcohols reacted well and DIAD/THF or DEAD/THF gave the best results as reagent systems. The formation of phosphate as by-product simplifies its purification due to its higher solubility in water. More experiments are being conducted in our laboratories to further study the scope of this reagent system and will be published in due time.

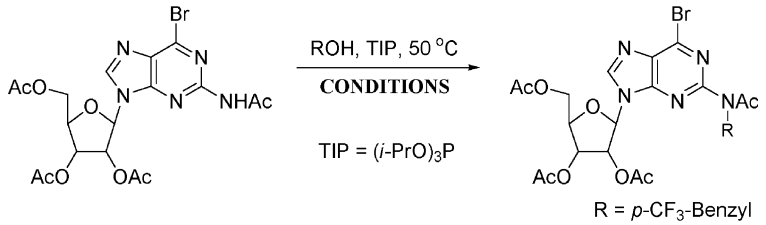
Table 1.



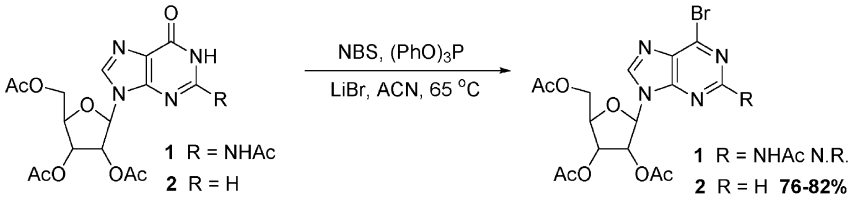
R	Azo derivative	Solvent	Time (h)	Yield (%)
Benzyl	DIAD	Dioxane	5	95
2-BrBn	DIAD	Dioxane	18	97
2-BrBn	DEAD	THF	24	97
p-CF_3-Bn	DIAD	THF	24	95
1-Ph–ethanol	DIAD	Dioxane	24	NR
	DIAD	Dioxane	24	NR
	DIAD	THF	24	85
	DTAD	Dioxane	24	Incomplete
	DIAD	THF	24	NR
2-Butanol	DIAD	Dioxane	5	NR

Ref. 20.

Table 2.



Azo derivative	Solvent	Yield (%)
DIAD	Dioxane	Separation problems
DEAD	Dioxane	Traces
TMAD	Dioxane	Traces
DEAD	THF	90
DIAD	THF	95
TMAD	THF	Traces



Scheme 2.

Acknowledgements

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19. Véliz, E. A.; Beal, P. A. *Tetrahedron Lett.* **2000**, *41*, 1695–1697.
20. *Typical procedure*: To a solution of the 6-bromo tetraacetyl purine derivative (50 mg, 0.097 mmol) in dry solvent (7 mL) (see Table 1) was added sequentially the alcohol (3.0 equiv, 0.292 mmol), triisopropyl phosphite (60.6 mg, 0.292 mmol), and the azodicarboxylate derivative (3.0 equiv, 0.292 mmol). The reaction mixture was stirred at 50 °C and followed by thin layer chromatography. After completion, the mixture was concentrated and redissolved in EtOAc (15 mL). The organic solution was successively washed with water (1 × 15 mL) and brine (1 × 15 mL), and then concentrated under reduced pressure. The syrup obtained was purified by flash column chromatography (2% MeOH/$CHCl_3$) to afford the N^2-alkylated derivative. Yields are reported for compounds that appeared homogenous by thin layer chromatography and ^1H NMR. All products gave satisfactory spectral data (^1H and ^{13}C NMR, MS, and HRESMS). *6-Bromo-2-(N-2-bromobenzyl)acetamido-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine*. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.22 (s, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.19–7.17 (m, 2H), 7.06–7.03 (m, 1H), 6.11 (d, $J = 5.0$ Hz, 1H), 5.73 (app. t, $J = 5.5$ Hz, 1H), 5.41 (d, $J = 7.0$ Hz, 2H), 5.37 (app. t, $J = 5.0$ Hz, 1H), 4.42 (app. q, $J = 5.0$ Hz, 1H), 4.31 (dd, $J = 12.0$, 3.0 Hz, 1H), 4.22 (dd, $J = 12.5$, 4.5 Hz, 1H), 2.59 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 172.0, 170.1, 169.4, 169.1, 155.0, 150.6, 143.1, 142.8, 136.5, 132.6, 131.5, 128.4, 127.8, 127.5, 122.6, 86.4, 80.1, 73.1, 70.2, 62.8, 50.2, 25.5, 20.7, 20.5, 20.3. HRCIMS: calcd for $C_{25}H_{25}Br_2N_5O_8$ (M^+)

681.0070, obsd 681.0062. *6-Bromo-2-(N-allyl)acetamido-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine*. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 8.23 (s, 1H), 6.11 (d, J = 4.5 Hz, 1H), 5.86 (app. t, J = 5.0 Hz, 1H), 5.50 (app. t, J = 5.0 Hz, 1H), 5.17 (dq, J = 17, 1.5 Hz, 1H), 5.08 (dq, J = 10, 1.5 Hz, 1H), 4.75 (app. d, J = 5.5 Hz, 2H), 4.48–4.45 (m, 1H), 4.40 (dd, J = 12.5, 3.5 Hz, 1H), 4.34 (dd, J = 12.5, 4.5 Hz, 1H), 2.48 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 171.6, 170.1, 169.5, 169.2, 155.2, 150.5, 143.1, 142.8, 133.2, 131.5, 116.8, 86.9, 80.1, 73.1, 70.0, 62.7, 48.8, 25.5, 20.7, 20.4, 20.3. HRCIMS: calcd for $C_{21}H_{25}BrN_5O_8$ $(M+H)^+$ 554.0887, obsd 554.0885. *6-Bromo-2-(N-p-trifluoromethylbenzyl)acetamido-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine*. ^{1}H NMR ($CDCl_3$, 500 MHz): δ ppm) 8.22 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H), 6.06 (d, J = 4.0 Hz, 1H), 5.82 (app. t, J = 5.0 Hz, 1H), 5.41–5.39 (m, 2H), 4.45–4.42 (m, 1H), 4.30 (dd, J = 12.5, 3.0 Hz, 1H), 4.24 (dd, J = 12.5, 4.5 Hz, 1H), 2.56 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 172.0, 170.1, 169.4, 169.1, 155.0, 150.5, 143.3, 143.0, 141.9, 131.7, 129.3 (q, ^{2}J = 31.75 Hz), 127.9, 124.1 (q, J = 270.1 Hz), 125.3 (q, ^{3}J = 3.75 Hz), 86.9, 79.9, 73.0, 69.9, 62.6, 49.4, 25.6, 20.6, 20.4, 20.2. HRCIMS: calcd for $C_{26}H_{26}BrF_3N_5O_8$ $(M+H)^+$ 672.0918, obsd 672.0955.