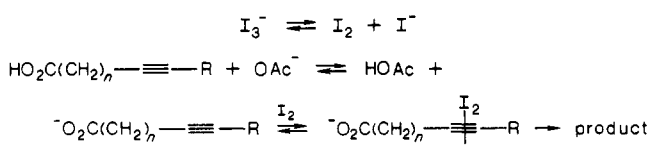
Scheme I



nor kinetic measures is self-consistent. Bromine reacts more rapidly with alkenes than with alkynes. For styrene:phenylacetylene the ratio is 400, whereas for 1-hexene:1-hexyne, the ratio is 1.7×10^6. The wide variation in the ratios has been interpreted in terms of the type of cationic intermediate that is formed, and the ratios are smaller when the intermediate is bridged rather than open, and when the solvent is more nucleophilic in nature. No ratios have been determined for iodine addition since iodine does not react readily with isolated double or triple bonds. In our iodolactonization reactions the alkenoic acids react only 50–100 times faster than the alkynoic acids, and the value depends on the concentration of KI (see Figure 1). The small and constant ratios are consistent with the postulated π-complex formation with both alkenes and alkynes[13] and the prominence of the neighboring carboxylate anion in these reactions.

Hydrolysis. For the corresponding 3-phenyl-substituted iodo enol lactones,[3b] it has been observed that 3-phenyl-6-(iodomethylene)tetrahydrofuran-2-one hydrolyzes 5.7 times more slowly than 3-phenyl-5-(iodomethylene)-tetrahydrofuran-2-one at pH 7.2. Compound **5** is formed 17 times more slowly than **4**, but if **5** also hydrolyzes more slowly than **4**, we should have observed hydrolysis of both compounds. For this reason we determined the rates of hydrolysis of **5** and **4** at pH 6.5 and found that they hydrolyze at approximately the same rate. There is precedent for the similar rates of hydrolysis of **5** and **4** since they are geometrically similar to anhydrides and it has been observed that succinic anhydride hydrolyzes at about the same rate as glutaric anhydride in neutral solution.[14] Thus, we can extrapolate the rates of iodo enol lactone formation to 0.2 M KI and compare the rates of iodo lactone formation (extrapolated from values at pH 5 in Figure 1–at pH 6.5 they would be slightly faster) and hydrolysis (see Results) under preparative conditions: for **5**, these rates are approximately 1:2.5, whereas for **4** the rates are approximately 10:1. Compound **5** is capable of hydrolyzing as soon as it is formed, while **4** is formed considerably more rapidly than it is hydrolyzed. For this reason 5-(iodomethylene)furan-2-ones such as **4** may be formed with aqueous iodine, but the 6-(iodomethylene)-pyran-2-ones such as **5** may be prepared only with concurrent extraction from the aqueous solution.

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Registry No. **1**, 6089-09-4; **2**, 53293-00-8; **3**, 3350-92-3; **4**, 120205-37-0; **5**, 120205-38-1; **6**, 120205-39-2; 4-benzoylbutyric acid, 1501-05-9; 3-(4-phenyl-1,2,3-selenadiazoyl-5-yl)propanoic acid, 49769-22-4; 5-hexyn-1-ol, 928-90-5; iodine, 7553-56-2.

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Synthesis of Pyrimidine 3′-Allyl-2′,3′-dideoxyribonucleosides by Free-Radical Coupling

Chung K. Chu,* B. Doboszewski, Walter Schmidt, and Giliyar V. Ullas

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The University of Georgia, Athens, Georgia 30602

Patrick Van Roey

Medical Foundation of Buffalo, Buffalo, New York 14203

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Since 3′-azido-2′,3′-dideoxythymidine (AZT) has been reported[1] as a potent antiviral agent against human immunodeficiency virus (HIV), a number of 3′-azido- and 2′,3′-dideoxynucleosides have been synthesized and evaluated against the virus in order to determine the structure–activity relationships.[2-8] These studies suggest that any modification of the 5-position of AZT decreases the anti-HIV activity.[7] Therefore, modification of the ribose moiety seemed to be a logical extension of the above findings. From the X-ray crystallographic studies of AZT, Camerman et al.[9] proposed that the 3′-azido group plays a significant role in binding to the reverse transcriptase of HIV. As a part of our continuing efforts to study the structure–activity relationships of pyrimidine nucleosides as potential antiviral agents against HIV, it was of interest to synthesize 3′-allyl-substituted pyrimidine nucleosides **7** and **8** as nonpolar analogues of AZT and 3′-azido-2′,3′-dideoxyuridine (CS-87, AzddU),[10,11] which is expected to undergo clinical trials in the near future.

Results and Discussion

Our initial approach for the introduction of an allyl group at the 3′-position of pyrimidine nucleosides was to utilize 3′-ketonucleosides,[10-12] to which appropriate Grignard reagents could be added to obtain the corresponding 3′-alcohols (3′-up configuration).[12,14] In order to obtain the 3′-deoxygenated nucleosides **5** and **6** from the above-mentioned alcohols, various methods of deoxygenation were tried. Direct deoxygenation of the alcohols with arylalkylsilane–borontrifluoride[13] failed to give the desired products. Other deoxygenation methods such as reduction of 3′-oxalate[11] or 3′-xanthate[14] with tributyltin hydride were also unsuccessful, producing only complex mixtures.

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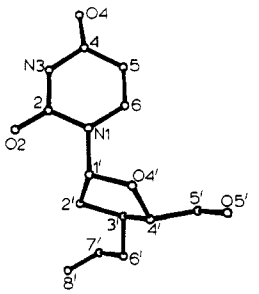


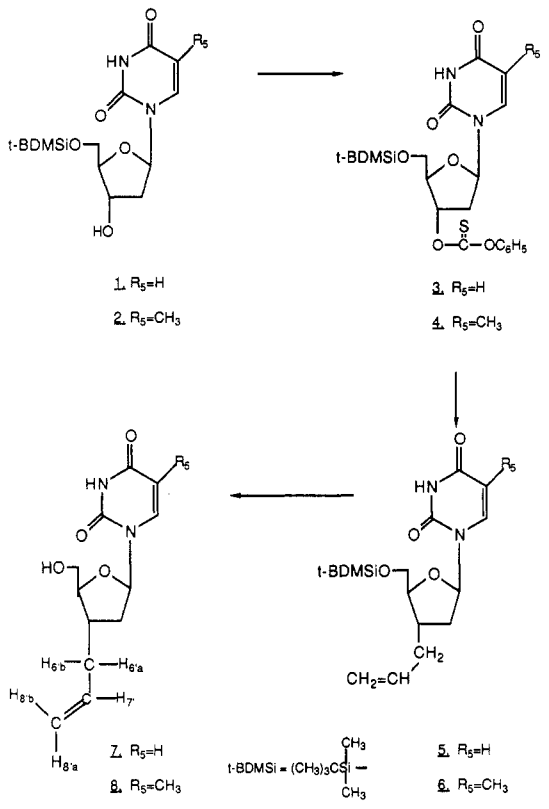
Figure 1. ORTEP drawing of the molecular structure of **7** as determined by X-ray crystallography, showing the numbering scheme used in the text.

Since alkyl-free radicals are known to undergo a free-radical reaction with an appropriate acceptor,[15,16] phenoxythiocarbonyl-substituted uridine **3** and thymidine **4**, which can readily form free radicals during the thermal reaction, were treated with allyltributyltin[16] in benzene or toluene in the presence of a radical generator to give 3′-allyl-2′,3′-dideoxynucleosides **5** and **6**. Although the allyl group has been introduced at the anomeric positions of carbohydrates under similar conditions,[16] this type of reaction has not been previously utilized in the modification of nucleosides.[17]

Despite the nature of free radical reactions, the above reaction only produced products with retention of configuration (vide infra). The observed stereoselectivity may be due to the presence of the bulky 5′-*tert*-butyldimethylsilyl as well as the pyrimidine moieties, which preferentially direct the incoming substituent to the less hindered face of the free-radical intermediate. This is consistent with the results reported by Keck et al.,[16] in which sterically hindered derivatives of mannose and xylose gave products with the retention of configuration. Desilylation of **5** and **6** gave the desired products **7** and **8**, respectively. The structural assignment of **7** and **8** was based mainly on the ^{1}H NMR studies: In the 2D homonuclear COSY spectra of **7** and **8**, strong couplings of H-4′ to H-6′ and H-6′ to H-2′ were observed (Scheme I). This together with the strong coupling of H-2′ and H-1′ suggests that H-4′, H-6′, H-2′, and H-1′ are on the same side of the ribose ring (i.e. α side). A 2D NOSY experiment confirms this conclusion, in which strong NOE cross peaks for H-4′ to H-6′, H-6′ to H-2′, and H-2′ to H-1′ were observed. The above structural assignment by ^{1}H NMR spectroscopy was subsequently confirmed by X-ray crystallography (Figure 1).

The crystal structure of **7** was determined to analyze the effect on the molecular conformation of the 3′-substituent. None of the bond lengths and angles are exceptional. The most important feature of the structure is the C3′-endo conformation of the sugar ring (pseudorotational phase angle P = 16.0°). This conformation is commonly observed for other uridine analogues, but not for AZT or 3′-azido-2′,3′-dideoxyuridine (CS-87),[18] active anti-HIV nucleosides which all have a C3′-exo conformation. The glycosyl link is in the anti conformation [torsion angle χ (C2–N1–C1′–O4′) = −161.6 (2)°] similar to that observed for CS-87, χ = −159.8 (3)°. The C6′–C7′ bond of the allyl group is in a conformation that is trans to the C4′–C3′ bond [torsion angle ϵ(C4′–C3′–C6′–C7′) = 178.1°].

Scheme I



The synthesized compounds **7** and **8** have been screened against HIV-1.[19] However, none of the compounds showed any significant anti-HIV activity. These results indicate that the 3′-allyl group does not contribute to anti-HIV activity. This is in contrast to what is observed for the 3′-azido group. It is interesting to note that Agyei-Aye and Baker[20] also found that 3′-alkyl-substituted pyrimidine nucleosides did not exhibit any significant anti-HIV activity.

In summary, this free-radical reaction leading to the C–C bond formation, applied in the synthesis of 3′-allyl-substituted pyrimidine nucleosides **7** and **8**, may be a potentially useful approach for the modification of other nucleosides of biological interest.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q or a Bruker AM 500 NMR spectrometer for the 90- and 500-MHz ^{1}H NMR spectra, respectively, with Me_4Si as internal standard; chemical shifts are reported in parts per million (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-3′-*O*-(phenoxythiocarbonyl)uridine (3). To an ice-cold solution of **1** (3.4 g, 10 mmol) in methylene chloride (25 mL) and pyridine (4 mL) was added phenyl chlorothionoformate (3.45 g, 20 mmol) and the mixture was stirred for 5 h at room temperature. The solvents were evaporated in vacuo, and the residue was suspended in water and then extracted with chloroform. The combined organic layer was washed with water, dried ($MgSO_4$), and evaporated to give

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a foam, which was chromatographed on a silica gel column with chloroform–methanol (100:1, then 60:1) to give **3** as a foam (4.84 g, 97%): ^{1}H NMR ($CDCl_3$) δ 0.13 [s, 6 H, $Si(CH_3)_2$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 2.54 (m, 2 H, H-2′), 4.00 (s, 2 H, H-5′), 4.42 (s, 1 H, H-4′), 5.74 (apparent d, 2 H, H-5 and H-3′), 6.50 (dd, 1 H, J = 5.5 and 8.5 Hz, H-1′), 6.97–7.57 (m, 5 H, C_6H_5), 7.93 (d, 1 H, J = 8.2 Hz, H-6), 9.35 (br s, 1 H, NH). Anal. Calcd for $C_{22}H_{30}N_2O_6SSi$: C, 55.21; H, 6.32; N, 5.85. Found: C, 55.46; H, 6.45; N, 5.83.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-(phenoxythiocarbonyl)thymidine (4). 5′-*O*-(*tert*-Butyldimethylsilyl)thymidine **2** (3.56 g, 10 mmol) in methylene chloride (25 mL) and pyridine (6 mL) was stirred with phenyl chlorothionoformate (5.0 g, 29 mmol) at 0 °C for 1 h and then left overnight in the refrigerator. The solvents were evaporated in vacuo, and the residue was suspended in water and extracted with chloroform. After evaporation of the chloroform, the residue was chromatographed on a silica gel column with chloroform–methanol (60:1) as the eluent to give **4** (4.29 g, 87%); mp 167–169 °C (ether); ^{1}H NMR (Me_2SO-d_6) δ ~0.0 [s, 6 H, Si $(CH_3)_2$], 0.78 [s, 9 H, $SiC(CH_3)_3$], 1.69 (s, 3 H, C_5-CH_3), 1.88–2.64 (m, 2 H, H-2′), 3.80 (d, 2 H, J = 2.0 Hz, H-5′), 4.24 (br s, 1 H, H-4′), 5.60 (d, 1 H, J = 3.7 Hz, H-3′), 6.22 (dd, 1 H, J = 4.8 and 6.5 Hz, H-1′), 6.99–7.50 (m, 6 H, C_6H_5 and H-6), 11.29 (br s, 1 H, NH). Anal. Calcd for $C_{23}H_{32}N_2O_6SSi$: C, 56.07; H, 6.55; N, 5.69. Found: C, 56.16; H, 6.60; N, 5.68.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-allyl-2′,3′-dideoxyuridine (5). A mixture of **3** (0.65 g, 1.36 mmol), allytributyltin (0.84 mL, 2.72 mmol), and azobisisobutyronitrile (AIBN) (0.037 g, 0.272 mmol) in toluene (10 mL) was heated at 78–83 °C for 24 h. Additional AIBN (0.03 g) was added, and the heating was continued for 4 more days. Evaporation of the solvent and chromatography on a silica gel column with hexanes–ethyl acetate (3:2) yielded **5** as a syrup (0.249 g, 50%): UV (MeOH) λ_{max} (pH 6) 264 (ϵ 9240), (pH 1) 264 (ϵ 9930), (pH 11) 263 (ϵ 7340); ^{1}H NMR ($CDCl_3$) δ 0.11 [s, 6 H, $Si(CH_3)_2$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 1.90–2.45 (m, 5 H, H-2′, H-3′, and CH_2), 3.62–4.18 (m, 3 H, H-4′ and H-5′), 5.64 (d, 1 H, H-5), 4.90–5.21 and 5.49–5.92 (2 m, 3 H, $CH{=}CH_2$), 6.07 (dd, 1 H, J = 4.1 and 4.8 Hz, H-1′), 8.13 (d, 1 H, J = 7.9 Hz, H-6), 9.48 (br s, 1 H, NH). Anal. Calcd for $C_{18}H_{30}N_2O_4Si$: C, 58.98; H, 8.25; N, 7.64. Found: C, 59.10; H, 8.29; N, 7.57.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-allyl-2′,3′-dideoxythymidine (6). A mixture of **4** (0.69 g, 1.4 mmol), allyltributyltin (2.5 mL, 8.07 mmol), and AIBN (0.037 g, 0.272 mmol) in toluene (5 mL) was heated at 80 °C for 15 h. Another portion of AIBN (0.040 g) was added gradually over a period of 8 h, and the heating was continued for 2 days. The solvent was evaporated in vacuo, and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (7:3) as the eluent to obtain the major fraction **6** (0.395 g, 74%): mp 114–115 °C (hexanes–ether); UV (MeOH) λmax (pH 7) 268 (ϵ 10550), (pH 1) 268.5 (ϵ 10415), (pH 11) 268.5 (ϵ 8440); ^{1}H NMR (Me_2SO-d_6) δ 0.12 [s, 6 H, $Si(CH_3)_2$], 0.94 [s, 9 H, $SiC(CH_3)_3$], 1.92 (s, 3 H, 5-CH_3), 1.70–2.53 (m, 5 H, H-2′, H-3′, and CH_2), 3.57–4.14 (m, 3 H, H-4′, H-5′), 4.86–5.22 and 5.50–6.02 (2 m, 3 H, $CH{=}CH_2$), 6.11 (t, 1 H, J = 3.4 Hz, H-1′), 7.59 (s, 1 H, H-6), 9.87 (s, 1 H, NH). Anal. Calcd for $C_{19}H_{32}N_2O_4Si$: C, 59.97; H, 8.47; N, 7.36. Found: C, 59.98; H, 8.51; N, 7.35.

3′-*C*-Allyl-2′,3′-dideoxyuridine or 3′-(2-Propen-1-yl)-2′,3′-dideoxyuridine (7). A mixture of **5** (0.249 g, 0.69 mmol) and tetrabutylammonium fluoride (1.5 mL, 1 M solution in THF) in THF (5 mL) was stirred for 3 h. After the removal of the solvent in vacuo, the residue was chromatographed on a silica gel column with chloroform–methanol (22:1) as the eluent to obtain **7** (0.13 g, 76%): mp 137–138 °C (chloroform–ether); UV (MeOH) λmax (pH 6) 263.5 (ϵ 10780), (pH 1) 263.5 (ϵ 11215), (pH 11) 263 (ϵ 7900); ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 2.06 (m, 2 H, $J_{2',3'}$ = 3.3 Hz, $J_{2',1'}$ = 6.9 Hz, H-2′), 2.07 (m, 1 H, H-3′), 2.24 (m, 1 H, $J_{6'b,8'a}$ = 4.2 Hz, H-6′b), 2.32 (m, 1 H, $J_{6'a,7'}$ = 2.8 Hz, H-6′a), 3.33 (s, 1 H, OH exchangeable), 3.51 (dt, 1 H, $J_{8'a,7'}$ = 11.9 Hz, H-8′a), 3.64 (dt, 1 H, $J_{8'b,7}$ = 8.3 Hz, $J_{8'b,6'a}$ = 2.8 Hz, H-8′b), 3.75 (dq, 1 H, $J_{7',8'a}$ = 11.9 Hz, H-7′), 5.06 (m, 2 H, H-5′), 5.58 (d, 1 H, $J_{5,6}$ = 7.1 Hz, H-5), 5.80 (m, 1 H, H-4′), 5.97 (q, 1 H, $J_{1',2'}$ = 6.9 Hz, H-1′), 8.02 (d, 1 H, $J_{6,5}$ = 7.1 Hz, H-6), 11.23 (s, 1 H, NH exchangeable). Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 56.96; H, 6.41; N, 11.02.

3′-*C*-Allyl-2′,3′-dideoxythymidine or 3′-(2-Propen-1-yl)-2′,3′-dideoxythymidine (8). A mixture of **6** (0.27 g, 0.7 mmol) and tetrabutylammonium fluoride (2 mL, 1 M solution in THF) in THF (10 mL) was stirred at 0 °C for 3 h. The product having R_f 0.35 (chloroform–methanol, 25:1) was isolated by a silica gel column with the above solvent mixture as the eluent to give **8** (0.145 g, 77%) as a syrup: UV (MeOH) λmax (pH 7) 268 (ϵ 7760), (pH 1) 269 (ϵ 7610), (pH 11) 268 (ϵ 6410); ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 1.76 (s, 3 H, $J_{5,6}$ = 1.0 Hz, CH_3), 2.02 (m, 1 H, $J_{2'a,2'b}$ = 2.1 Hz, $J_{2'a,1'}$ = 6.9 Hz, H-2′a), 2.04 (m, 1 H, $J_{2'b,2'a}$ = 2.1 Hz, $J_{2'b,1'}$ = 3.5 Hz, H-2′b), 2.08 (m, 1 H, $J_{3',4'}$ = 7.8 Hz, $J_{3',6'}$ = 9.3 Hz, H-3′), 2.24 (m, 1 H, $J_{6'b,6'a}$ = 7.1 Hz, $J_{6'b,8'b}$ = 1.1 Hz, H-6′b), 2.31 (m, 1 H, $J_{6'a,7'}$ = 6.1 Hz, H-6′a), 3.56 (dq, 1 H, $J_{8'b,7'}$ = 12.1 Hz, $J_{8'b,8'a}$ = 3.7 Hz, H-8′b), 3.63 (dt, 1 H, $J_{8'a,7'}$ = 2.7 Hz, H-8′a), 3.75 (dq, 1 H, $J_{7',8'a}$ = 2.7 Hz, $J_{7',6'a}$ = 6.1 Hz, H-7′), 5.01 (m, 1 H, $J_{5'a,5'b}$ = 1.8 Hz, $J_{5'a,4'}$ = 10.2 Hz, H-5′a), 5.07 (s, 1 H, OH exchangeable), 5.09 (m, 1 H, $J_{5'b,4'}$ = 10.2 Hz, H-5′b), 5.78 (m, 1 H, $J_{4',5'a}$ = 10.2 Hz, $J_{4',3'}$ = 7.9 Hz, H-4′) 5.96 (dd, 1 H, $J_{1',2'a}$ = 6.9 Hz, $J_{1',2'b}$ = 3.5 Hz, H-1′), 7.87 (d, 1 H, $J_{6,5}$ = 1.0 Hz, H-6), 11.20 (s, 1 H, NH, exchangeable). Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.66; H, 6.77; N, 10.52. Found: C, 58.38; H, 6.79; N, 10.47.

Diffraction Analysis of 7. The sample was recrystallized by slow evaporation of an aqueous ethyl acetate solution. The crystal used had approximate dimensions of 0.12 × 0.60 × 0.65 mm. The crystal belongs to the monoclinic space group $P2_1$ with cell dimensions a = 14.490 (1) Å, b = 8.338 (1) Å, c = 5.199 (1) Å, β = 99.375 (7)°, V = 619.70 (9) Å^3, Z = 2. The intensity data were measured on a Nicolet P3 diffractometer using Nb-filtered Mo Kα radiation (λ = 0.71069 Å). A total of 1362 of the 1474 unique data measured had $F > 3\sigma(F)$ and were considered observed. The structure was refined by full-matrix least-squares methods. Hydrogen atom positions were determined from difference maps and included in the refinement after the refinement of the nonhydrogen atoms had convered.

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Registry No. **1**, 76223-04-6; **2**, 40733-28-6; **3**, 120232-05-5; **4**, 120232-06-6; **5**, 120232-07-7; **6**, 120232-08-8; **7**, 120232-09-9; **8**, 120232-10-2; phenyl chlorothionoformate, 1005-56-7; allyltributyltin, 24850-33-7.

Supplementary Material Available: Atomic coordinates and anisotropic thermal parameters (2 pages); observed and calculated structure factor amplitudes (10 pages). Ordering information is given on any current masthead page.

Ambident Nucleophilicity of Silver Hyponitrite toward Organic Halides

E. M. Y. Quinga, T. Bieker, M. P. Dziobak, and G. D. Mendenhall*

Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931

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Organic esters of *trans*-hyponitrous acid are useful sources of alkoxyl radicals for a wide range of theoretical and practical applications.[1] The reaction of silver hyponitrite with alkyl halides is the oldest and most universal synthesis of these esters:[1,2]

$$2RX + \underset{\mathbf{I}}{Ag_2N_2O_2}(s) \rightarrow 2AgX(s) + RON{=}NOR \quad (1)$$

R = organic group; X = Cl, Br, I

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