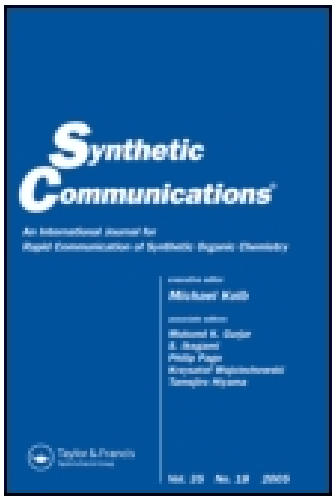


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Uridine Derivatives Containing Amino Acid Residues

Yu Gao [a] , Peng Zhang [a] , Ling Wu [a] , Teruo Matsuura [a] & Jiben Meng [a]
[a] Department of Chemistry , Nankai University , Tianjin, P.R. China
Published online: 17 Aug 2006.

To cite this article: Yu Gao , Peng Zhang , Ling Wu , Teruo Matsuura & Jiben Meng (2003) Synthesis of Uridine Derivatives Containing Amino Acid Residues, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:15, 2635-2641, DOI: 10.1081/SCC-120021984

To link to this article: http://dx.doi.org/10.1081/SCC-120021984

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 15, pp. 2635–2641, 2003

Synthesis of Uridine Derivatives Containing Amino Acid Residues

Yu Gao, Peng Zhang, Ling Wu, Teruo Matsuura,[#] and Jiben Meng[*]

Department of Chemistry, Nankai University, Tianjin, P.R. China

ABSTRACT

Convenient synthesis of uridine derivatives containing amino acid residues were carried out successfully by reacting triazolated uridine with the hydrochloride salts of some amino acid esters, which provides a general method for the direct introduction of amino acid group onto nucleoside residue.

Key Words: Nucleoside; Amino acid; Uridine; Modification.

[#]Current address: Teruo Matsuura, Emeritus Professor, Saikyoku, Kyoto, Japan.
*Correspondence: Jiben Meng, Department of Chemistry, Nankai University, Tianjin, 300071, P.R. China; E-mail: mengjiben@nankai.edu.cr.

DOI: 10.1081/SCC-120021984 0039-7911 (Print); 1532-2432 (Online)

INTRODUCTION

Nucleosides which contain substituents on the heterocyclic base other than the natural oxo and amino functionalities are proved to be important compounds for medicinal chemistry and biological studies.[1] Among modified nucleoside derivatives those containing amino acid residues are expected to exhibit promising antimicrobial activities.[2,3]

Divake and Reese[4] developed a method utilizing the transformation of a pyrimidine 4-oxo functionality into 1,2,4-triazolo group by treatment of uracil nucleoside derivative with phosphoryl chloride and 1,2,4-triazole, which enables us to prepare some uridine derivatives containing amino acid residue by nucleophilic substitution of the triazolo intermediates.

4-(1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)-pyrimidine-2(1H)-one (**3**) could be conveniently obtained by treatment of 2′,3′,5′-tri-*O*-acetyluridine (**1**) with the readily accessible tri(1-H-1,2,4-triazol-1-yl)phosphine oxide[5] (prepared in situ by treating phosphoryl chloride with at least 3 mol equiv. each of 1,2,4-triazole and triethylamine) in acetonitrile solution.

On treatment of **3** with different aliphatic amino acid esters in acetonitrile solution could we successfully prepare the desired products **5–14**.

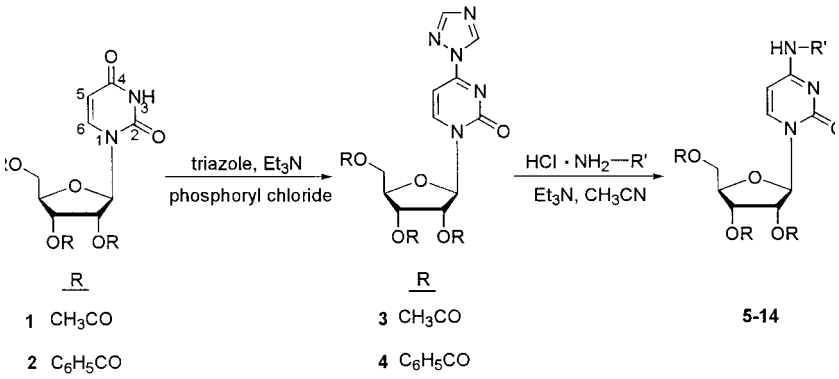
Our work may serve as the first step towards the understanding of the function of amino acid modifications of nucleosides and towards the synthesis of hypermodified nucleosides similar to those naturally present in t_{RNA}'s sequences.

EXPERIMENTAL

Melting points were determined with an X-4 apparatus and were uncorrected. The ^{1}H NMR spectra were measured with a BRUKER AC-200 spectrometer using tetramethylsilane as internal standard. The mass spectra were recorded on a VG ZAB-HS spectrometer. A YANACO CHN corder MT-3 apparatus was used for elemental analysis.

All chemicals were analytically pure. Acetonitrile, triethylamine, and pyridine were dried by heating, under reflux with calcium hydride for 3–5 h; the solvents were then distilled at atmospheric pressure. Acetonitrile and pyridine were stored over molecular sieves 4A. Phosphoryl chloride was freshly vacuum distilled before use.

4-(1,2,4-Triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl) pyrimidine-2(1H)-one (3). Phosphoryl chloride (0.485 mL, 5.2 mmol) was added to a



Scheme 1.

Table 1. Synthesis of uridine derivatives.

Product	-*R*	-*R*′	M.p. (°C)	Yield (%)
3	$OCCH_3$	n/a	184–187	74.8
4	OCC_6H_5	n/a	190–193	51.4
5	$OCCH_3$	CH_2COOEt	173–175	62.0
6	$OCCH_3$	$CH_2COOtBu$	161–163	68.6
7	$OCCH_3$	$CH_2CONHCH_2COOEt$	158–160	54.7
8	$OCCH_3$	CH_2CH_2COOEt	169–170	72.0
9	$OCCH_3$	$(CH_2)_4CH(NH_2)COOEt$	137–139	42.3
10	OCC_6H_5	CH_2COOEt	184–186	56.9
11	OCC_6H_5	$CH_2COOtBu$	172–174	68.2
12	OCC_6H_5	$CH_2CONHCH_2COOEt$	165–168	49.7
13	OCC_6H_5	CH_2CH_2COOEt	185–187	69.5
14	OCC_6H_5	$(CH_2)_4CH(NH_2)COOEt$	146–149	40.8

stirred, cold (ice-water bath) suspension of 1,2,4-triazole (1.678 g, 24.3 mmol) in acetonitrile (14 mL). After five minutes, triethylamine (3.24 mL, 23.2 mmol) was added dropwise during a period of 30 min. To the resulting mixture was added a solution of 2′,3′,5′-tri-*O*-acetyluridine[6,7] (**1**) (1.0 g, 2.7 mmol) in acetonitrile (8.5 mL) and the reaction mixture was stirred at ambient temperature for 90 min. The solvent was then evaporated under reduced pressure and the residue was partitioned between chloroform (13 mL) and saturated aqueous sodium hydrogen carbonate (10 mL). The aqueous layer was extracted with chloroform (2 × 7.5 mL)

and the combined organic layers were dried (Na_2SO_4) and evaporated and the residue was crystallized from ethanol to give **3** as colorless prisms. Yield 0.850 g (74.8%), m.p. 184–187°C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.05–2.12 (9H, m, –CO$\underline{CH_3}$), 4.15–4.25 (3H, m, H4′, H5′, H5′), 5.35 (1H, m, H3′), 5.46 (1H, m, H2′), 5.80 (1H, d, *J* 4.5 Hz, H1′), 5.93 (1H, d, *J* 7.5 Hz, H5), 7.66 (1H, d, *J* 7.5 Hz, H6), 9.42 (2H, s, H-triazolyl).

4-(1,2,4-Triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-benzoylribofuranosyl)pyrimidine-2(1H)-one (4). Compound **4** was prepared from 2′,3′,5′-tri-*O*-benzoyluridine (**2**)[8] in the similar manner as colorless prisms. m.p. 190–193°C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 4.23–4.36 (3H, m, H4′, H5′, H5′), 5.41 (1H, m, H3′), 5.53 (1H, m, H2′), 5.92 (1H, d, *J* 4.5 Hz, H1′), 6.11 (1H, d, *J* 7.5 Hz, H5), 7.33–8.08 (16H, m, ArH, H6), 9.50 (2H, s, H-triazolyl).

4-Ethoxycarbonylmethylamino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)-pyrimidine-2(1H)-one (5). A mixture of 4-(1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl) pyrimidine-2(1H)-one (**3**) (200 mg, 0.48 mmol), glycine ethyl ester hydrochloride (120 mg, 0.84 mmol), triethylamine (0.132 mL, 0.96 mmol), and acetonitrile (3.0 mL) was stirred at ambient temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The resulting syrup was dissolved in chloroform and after preparative TLC on silica gel, the desired product 5 was obtained as colorless needles. Yield 134 mg (62.0%), m.p. 173–175°C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.16–1.23 (3H, t, *J* 7.4 Hz, –$CH_2\underline{CH_3}$), 2.03–2.06 (9H, m, –CO$\underline{CH_3}$), 4.05 (2H, s, –$\underline{CH_2}$CO–), 4.08–4.12 (2H, m, –$\underline{CH_2}CH_3$), 4.15–4.22 (3H, m, H4′, H5′, H5′), 5.30 (1H, m, H3′), 5.38 (1H, m, H2′), 5.84 (1H, d, *J* 4.6 Hz, H1′), 5.92 (1H, d, *J* 7.4 Hz, H5), 7.64 (1H, d, *J* 7.5 Hz, H6). MS (EI): *m*/*z* 455.1 (M^+). Anal. calcd. for $C_{19}H_{25}N_3O_{10}$ (455.1): C, 50.11; H, 5.53; N, 9.23. Found: C, 49.94; H, 5.59; N, 9.34.

4-*tert*-Butoxycarbonylmethylamino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)pyrimidine-2(1H)-one (6). Compound **6** was prepared from **3** and glycine *tert*-butyl ester hydrochloride in the similar manner as colorless needles. m.p. 161–163°C. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.40 (9H, s, –$C(CH_3)_3$), 2.07–2.12 (9H, m, –CO$\underline{CH_3}$), 3.94 (2H, s, –$\underline{CH_2}$CO–), 4.20–4.32 (3H, m, H4′, H5′, H5′), 5.32 (1H, m, H3′), 5.40 (1H, m, H2′), 5.85 (1H, d, *J* 4.4 Hz, H1′), 5.94 (1H, d, *J* 6.9 Hz, H5), 7.63 (1H, d, *J* 6.9 Hz, H6). Anal. calcd. for $C_{21}H_{29}N_3O_{10}$ (483.2): C, 52.17; H, 6.05; N, 8.69. Found: C, 52.40; H, 5.89; N, 8.78.

4-(Ethoxycarbonylmethylamino)carbonylmethylamino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl) pyrimidine-2(1H)-one (7). Compound **7** was prepared from **3** and glycyl glycine ethyl ester hydrochloride in the similar manner as colorless needles. m.p. 158–160°C. ^{1}H NMR (DMSO-d_6,

200 MHz) δ 1.18–1.25 (3H, t, J 7.1 Hz, –CH$\underline{CH_3}$), 2.03–2.10 (9H, m, –CO$\underline{CH_3}$), 3.83 (2H, s, –$\underline{CH_2}$CONH-), 3.96 (2H, s, –$\underline{CH_2}$COO–), 4.01–4.10 (2H, m, –$\underline{CH_2}CH_3$), 4.15–4.28 (3H, m, H4′, H5′, H5′), 5.31 (1H, m, H3′), 5.39 (1H, m, H2′), 5.84 (1H, d, J 4.3 Hz, H1′), 5.92 (1H, d, J 7.3 Hz, H5), 7.61 (1H, d, J 7.4 Hz, H6). Anal. calcd. for $C_{21}H_{28}N_4O_{11}$ (512.2): C, 49.22; H, 5.51; N, 10.93. Found: C, 49.50; H, 5.44; N, 10.79.

4-Ethoxycarbonylethylamino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)-pyrimidine-2(1H)-one (8). Compound **8** was prepared from **3** and β-alanine ethyl ester hydrochloride in the similar manner as colorless needles. m.p. 169–170°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18–1.25 (3H, t, J 7.2 Hz, –$CH_2\underline{CH_3}$), 2.05–2.10 (9H, m, –CO$\underline{CH_3}$), 2.57–2.65 (2H, m, –$CH_2\underline{CH_2}$CO–), 3.67–3.77 (2H, m, –$\underline{CH_2}CH_2$CO–), 4.08–4.17 (2H, m, –$\underline{CH_2}CH_3$), 4.21–4.35 (3H, m, H4′, H5′, H5′), 5.27–5.36 (2H, m, H2′ H3′), 5.70 (1H, d, J 7.1 Hz, H5), 6.12 (1H, d, J 4.4 Hz, H1′), 7.35 (1H, d, J 7.2Hz, H6). MS (EI): m/z 469.2 (M^+). Anal. calcd. for $C_{20}H_{27}N_3O_{10}$ (469.2): C, 51.17; H, 5.80; N, 8.95. Found: C, 51.37; H, 5.61; N, 8.74.

4-[((1*S*)-1-amino-1-ethoxycarbonyl)pentyl]amino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)pyrimidine-2(1H)-one (9). Compound **9** was prepared from **3** and L-lysine ethyl ester dihydrochloride in the similar manner as colorless needles. m.p. 137–139°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24–1.31 (3H, t, J 7.2 Hz, –$CH_2\underline{CH_3}$), 1.35–1.51 (2H, m, –NHCH$_2$CH$_2\underline{CH_2}$CH$_2$–), 1.57–1.72 (2H, m, –NHCH$_2\underline{CH_2}$CH$_2$CH$_2$–), 1.81–1.91 (2H, m, –NHCH$_2$CH$_2$CH$_2\underline{CH_2}$–), 2.03–2.09 (H, m, –CO$\underline{CH_3}$), 3.35–3.45 (2H, m, –NH$\underline{CH_2}$CH$_2$CH$_2$CH$_2$–), 4.00–4.08 (1H, m, –$\underline{CH}$CO–), 4.15–4.26 (2H, m, –$\underline{CH_2}CH_3$), 4.65–4.77 (2H, m, H5′, H5′), 4.84–4.92(1H, m, H4′), 5.65 (1H, d, J 7.2 Hz, H5), 5.73 (1H, m, H3′), 5.86 (1H, m, H2′), 6.47 (1H, m, J 4.6 Hz, H1′), 7.37 (1H, d, J 7.2 Hz, H6). Anal. calcd. for $C_{23}H_{34}N_4O_{10}$ (526.2): C, 52.46; H, 6.51; N, 10.64. Found: C, 52.75; H, 6.26; N, 10.38.

4-Ethoxycarbonylmethylamino-1-(β-D-2,3,5-tri-*O*-benzoylribofuranosyl)pyrimidine-2(1H)-one (10). Compound **10** was prepared from **4** and glycine ethyl ester hydrochloride in the similar manner as colorless needles. m.p. 184–186°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.27 (3H, t, J 7.2 Hz, –$CH_2\underline{CH_3}$), 4.12–4.24 (4H, m, –$\underline{CH_2}$CO–, –$\underline{CH_2}CH_3$), 4.73–4.81 (3H, m, H4′, H5′, H5′), 5.69–5.86 (3H, m, H3′ H2′ H5), 6.31 (1H, d, J 4.7 Hz, H1′), 7.30–8.07 (16H, m, ArH, H6). MS (EI): m/z 641.2 (M^+). Anal. calcd. for $C_{34}H_{31}N_3O_{10}$ (641.2): C, 63.65; H, 4.87; N, 6.55. Found: C, 63.27; H, 5.02; N, 6.68.

4-*tert*-Butoxycarbonylmethylamino-1-(β-D-2,3,5-tri-*O*-benzoylribofuranosyl)pyrimidine-2(1H)-one (11). Compound **11** was prepared from **4** and glycine *tert*-butyl ester hydrochloride in the similar manner as colorless needles. m.p. 172–174°C. ^{1}H NMR (CDCl, 200 MHz) δ 1.45

(9H, s, $-C(CH_3)_3$), 3.98 (2H, s, $-\underline{CH_2}CO-$), 4.62–4.83 (3H, m, H4′, H5′, H5′), 5.72–5.85 (3H, m, H3′ H2′ H5), 6.37 (1H, d, *J* 4.5 Hz), 7.35–8.08 (16H, m, ArH, H6). Anal. calcd. for $C_{36}H_{35}N_3O_{10}$ (669.2): C, 64.57; H, 5.27; N, 6.27. Found: C, 64.83; H, 5.09; N, 6.06.

4-(Ethoxycarbonylmethylamino)carbonylmethylamino-1-(β-D-2,3,5-tri-*O*-benzoylribofuranosyl)pyrimidine-2(1H)-one (12). Compound **12** was prepared from **4** and glycyl glycine ethyl ester hydrochloride in the similar manner as colorless needles. m.p. 165–168°C. ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 1.16–1.23 (3H, t, *J* 7.2 Hz, $-CH_2\underline{CH_3}$), 3.95 (2H, s, $-\underline{CH_2}CONH-$), 4.02–4.14 (2H, m, $-\underline{CH_2}CH_3$), 4.35 (2H, s, $-\underline{CH_2}COO-$), 4.66–4.78 (3H, m, H4′, H5′, H5′), 5.81–5.94 (2H, m, H2′ H3′), 6.22–6.37 (2H, m, H1′, H5), 7.30–8.04 (16H, m, ArH, H6). Anal. calcd. for $C_{36}H_{34}N_4O_{11}$ (698.2): C, 61.89; H, 4.90; N, 8.02. Found: C, 61.51; H, 5.07; N, 8.23.

4-Ethoxycarbonylethylamino-1-(β-D-2,3,5-tri-*O*-benzoylribofuranosyl)-pyrimidine-2(1H)-one (13). Compound **13** was prepared from **4** and β-alanine ethyl ester hydrochloride in the similar manner as colorless needles. m.p. 185–187°C. ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 1.18–1.25 (3H, t, *J* 7.0 Hz, $-CH\underline{CH_3}$), 2.56–2.63 (2H, m, $-CH_2\underline{CH_2}CO-$), 3.68–3.76 (2H, m, $-\underline{CH_2}CH_2CO-$), 4.06–4.15 (2H, m, $-\underline{CH_2}CH_3$), 4.60–4.77 (3H, m, H4′, H5′, H5′), 5.51 (1H, d, *J* 7.3 Hz, H5), 5.69 (1H, m, H3′), 5.87 (1H, m, H2′), 6.45 (1H, d, *J* 4.5 Hz, H1′), 7.29–8.08 (16H, m, ArH, H6). Anal. calcd. for $C_{35}H_{33}N_3O_{10}$ (655.2): C, 64.12; H, 5.07; N, 6.41. Found: C, 63.89; H, 5.30; N, 6.22.

4-[((1*S*)-1-amino-1-ethoxycarbonyl)pentyl]amino-1-(β-D-2,3,5-tri-*O*-benzoylribofuranosyl)pyrimidine-2(1H)-one (14). Compound **14** was prepared from 4 and L-lysine ethyl ester dihydrochloride in the similar manner as colorless needles. m.p. 146–149°C. ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 1.22–1.29 (3H, t, *J* 7.1 Hz, $-CH_2\underline{CH_3}$), 1.39–1.56 (2H, m, $-NHCH_2CH_2\underline{CH_2}CH_2-$), 1.60–1.73 (2H, m, $-NH\underline{CH_2}\underline{CH_2}CH_2CH_2-$), 1.86–1.97 (2H, m, $-NHCH_2CH_2CH_2\underline{CH_2}-$), 3.38–3.45 (2H, m, $-NH\underline{CH_2}CH_2CH_2CH_2-$), 4.02–4.08 (1H, m, $-\underline{CH}CO-$), 4.20–4.29 (2H, m, $-\underline{CH_2}-$), 4.67–4.73 (2H, m, H5′, H5′), 4.83–4.88 (1H, m, H4′), 5.67 (1H, d, *J* 7.2 Hz, H5), 5.78 (1H, m, H3′), 5.87 (1H, m, H2′), 6.44 (1H, m, *J* 4.6 Hz, H1′), 7.33–8.17 (16H, m, ArH, H6). Anal. calcd. for $C_{38}H_{40}N_4O_{10}$ (712.2): C, 64.04; H, 5.66; N, 7.86. Found: C, 64.36; H, 5.80; N, 7.62.

ACKNOWLEDGMENT

We want to thank the National Natural Science Foundation of China for the financial assistance (Grant No. 20072018 and 29832030).

REFERENCES

1. Su, T.-L. Synthesis of nucleosides and their application for the development of anticancer agents. Chemistry (The Chinese Chem. Soc. Taipei) **2000**, *58* (4), 611–619.
2. Malkiewicz, A.; Sochacka, E.; Sayed Ahmed, A.E.; Yassin, S. The modified nucleosides from the ''wobble position'' of tRNAs. The synthesis of 5-carboxymethylaminomethyluridine and 5-carboxymethylaminomethyl-2-thiouridine. Tetrehedron Lett. **1983**, *24*, 5395.
3. Reese, C.B.; Sanghvi, Y.S. The synthesis of 5-carboxymethylaminomethyluridine and 5-carboxymethylaminomethyl-2-thiouridine. J. Chem. Soc. Chem. Commun. **1984**, *1*, 62.
4. Divakar, K.J.; Reese, C.B. 4-(1,2,4-triazol-1-yl)-and 4-(3-nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)pyrimidine-2(1H)-one. Valuable intermediates in the synthesis of derivatives of 1-(β-D-arabinofuranosyl)cytosine (Ara-C). J. Chem. Soc. Perkin Trans. 1 **1982**, 1171–1176.
5. Kraszewski, A.; Stawinski, J. Phosphoryl tris-triazole—a new phosphorylating reagent. Tetrahedron Lett. **1980**, *21*, 2935.
6. Rajabalee, F.J.M. A convenient synthesis of 2′,3′,5′-tri-*O*-acetyl-adenosine and -uridine. Angew. Chem. Int. Ed. Engl. **1971**, *10*, 75.
7. Brown, D.M.; Todd, A.; Varadarajan, S. J. Chem. Soc. **1956**, 2388.
8. Fox, J.J.; Van Praag, D.; Wempen, I.; Doerr, I.L.; Cheong, L.; Knoll, J. E. Thiation of nucleosides. II. Synthesis of 5-methyl-2'-deoxycytidine and related pyrimidine nucleosides. J. Am. Chem. Soc. **1959**, *81*, 178–187.

Received in Japan October 15, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016