Synthesis and Studies of Alkynyl Pyrimidinones as Metaphase Inhibitors

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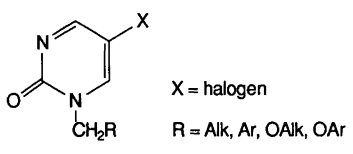
Methods are described for the syntheses of chloromethyl propargyl ethers and propargyl halides substituted with a hydroxyalkyl group, and their use in alkylation reactions of 2-pyrimidinoses. The *N*-alkynyl derivatives are reversible inhibitors of mitosis in the metaphase of the cell-cycle. The *in vivo* screening was on Chang liver cells.

We have reported that some N-1 substituted 5-halogeno-2(1*H*)-pyrimidinones (**I**; Scheme 1) will arrest mitosis in metaphase of cells grown in cultures.[1-3] The arrest is reversed when the active compound is removed, and the arrested cells suffer no damage provided that the time of arrest is no longer than the cell-cycling time.[1] In man cells of different origin will be arrested. If the recycling can be made to take place rapidly, cells in the cycle can be grouped according to their kinetics. This corresponds to a differential synchronization of cycling cells which may be used to prevent the destruction of vital and sensitive normal tissue cells, such as bone marrow cells, when phase-specific cytotoxic drugs are used in the treatment of diseases caused by rapidly proliferating cells.[1]

Metaphase-active 5-halogeno-2-pyrimidinones carry a hydrophobic aralkyl or α-aryloxyalkyl group in the 1-position.[1,2] Most of these compounds have relatively low water solubility and attempts to increase the water solubility by substitution with hydroxyalkyl groups have given derivatives which readily react with one another to form oligomeric structures. Presumably alcoholic hydroxy groups form intermolecular covalent adducts with π-electron deficient pyrimidinone. The hydrophobicity of the oligomers is higher than for the monomers, favouring precipitation, whereupon the activity is lost since the metaphase-arresting properties are dependent on the pyrimidine species being monomeric.[3] In the absence of an internal hydroxy group, adduct formation between the pyrimidinone and surrounding hydroxy-, amino- or mercapto-containing derivatives is reversible, as shown in separate studies.[4]

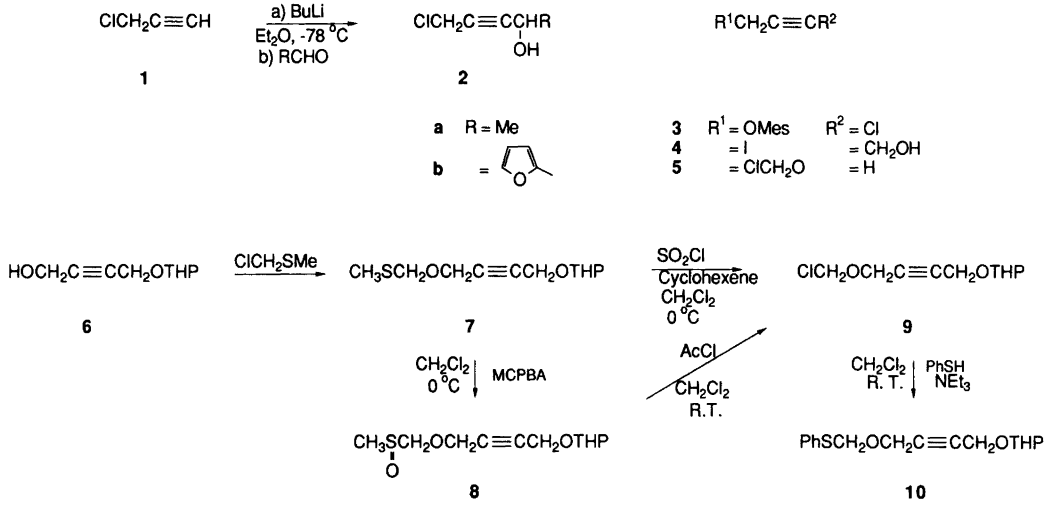


I

Scheme 1.

The most active pyrimidinones carry an unsaturated substituent in the 1-position, and the biological data given (*vide infra*) show that simple alkynyl derivatives are significantly more active than corresponding alkenyl and alkyl derivatives. In this report, we describe studies of some alkynyl pyrimidinones. Small alkynyl groups are less hydrophobic than aralkyl groups. Therefore, improved water solubility of hydroxylated alkynyl derivatives in the oligomeric state may allow the oligomers to stay in solution and allow reversible dissociation to the monomeric, active species. In the aralkyl series, activity was improved when a heteroatom was substituted for the carbon in the β-position.[1,3] Accordingly, alkynyloxymethyl analogues (Scheme 3; **15**, **16**) have been prepared.

The N-1 substituted pyrimidinones were prepared by alkylation of the 5-halogenopyrimidinone **11** with an alkynyl halide, a mesylate or with an alkynyloxymethyl chloride in the presence of a tertiary amine (Scheme 3). The alkynyl reagents prepared are shown in Scheme 2. Deprotonation with butyllithium at the acetylenic carbon in propargyl chloride at low temperature and subsequent addition of furfural furnished the furyl-substituted alcohol **2b**. This compound was thermally unstable. An attempt to purify the product by distillation led to explosive decomposition. The methyl derivative **2a** was prepared in the same manner from acetaldehyde.[5] Substitution of the acetylenic hydrogen in propargyl alcohol on treatment with sodium hypochlorite gave the 3-chloro derivative,[6] which on mesylation furnished the intermediate **3**. In the preparation of the 3-hydroxymethyl analogue **4**, but-2-yne-1,4-diol was monochlorinated with thionyl chloride and the chlorine exchanged for iodine with sodium iodide in acetone.[7] Chloro-



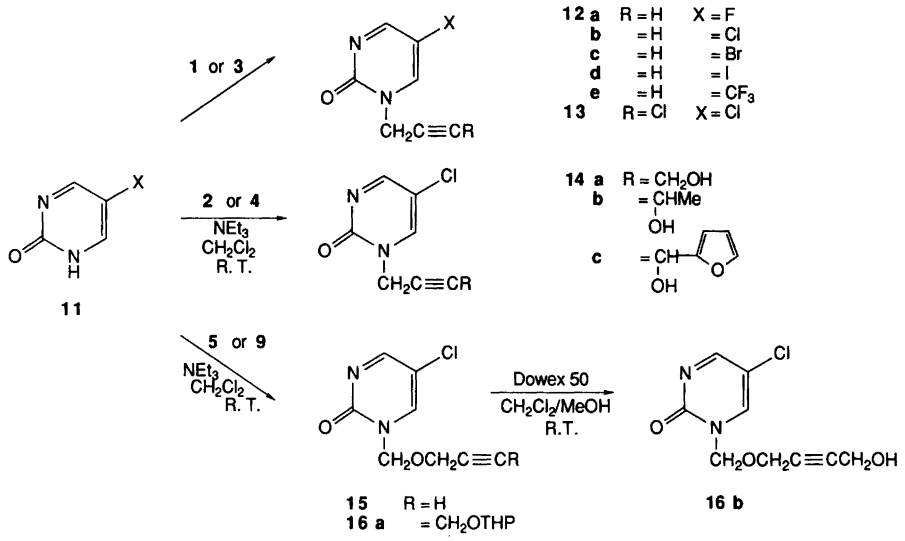
Scheme 2.

methylation of propargyl alcohol using paraformaldehyde and hydrogen chloride gave the chloromethyl ether **5**.[8] For the preparation of the *O*-protected chloromethyl ether reagent **9**, the tetrahydropyranyl (THP) derivative **6**,[9] was alkylated with chloromethyl methyl sulfide to furnish **7**. Cleavage of the thioacetal group to form the chloromethyl ether **9** was effected with sulfuryl chloride. The reaction was run in the presence of cyclohexene which acted as a scavenger for the methanesulfenyl chloride formed in the reaction.[10] The reactive chloromethyl ether **9** was used in the subsequent alkylation without separation from the scavenger adduct, *viz.* 1-chloro-2-methylsulfenylcyclohexane. In an alternative method, the chloromethyl ether **9** was prepared from the sulfoxide **8** which was cleaved with acetyl chloride and the product purified by distillation. The sulfoxide **8** was available by *m*-chloroperbenzoic acid (MCPBA) oxidation of the sulfide **7**.

Reformation of a hemithioacetal (**10**) from the chloromethyl ether **9** proceeded readily on treatment with thiophenol.

In the alkylation of the pyrimidinone **11**, the chloromethyl ethers, which are relatively hard electrophiles,[11] give some *O*-alkylation besides the main *N*-alkylated product. The *O*-alkyl isomer was removed either by chromatography or by means of its higher solubility in diethyl ether.

The hydroxy derivative **16b** is sensitive to polymerisation reactions, but can be kept in neutral, aqueous solution. Compound **16b** was generated from the tetrahydropyranyl protected precursor **16a** by reaction with an acidic cation exchanger[12] in methanol. In solution the product was partly present as a methanol adduct which released the methanol and polymerised on attempted removal of the solvent by distillation. The desired product **16b** was isolated from the mixture together with its methanol adduct by chromatog-



Scheme 3.

Table 1. Minimum inhibitory concentration (MIC) for complete arrest of metaphase in Chang liver cells.

Compd.	MIC/mM[a]	Compd.	MIC/mM[a]	Compd.	MIC/mM[a]
12a[13]	0.75	**14a**	0.5	**15**	0.125
12b[13]	0.18	**14b**	0.25	**16a**	0.125
12c[13]	0.36	**14c**	0.032	**16b**	0.016
12d[13]	0.36				
12e[14]	0.75				
13	0.125				

[a]The concentration in the medium is halved in each dilution step.

raphy. The propargyl alcohols (**14a–c**) were chemically sensitive compounds, especially the furyl derivative **14c** which slowly decomposed on contact with air.

The Chang line of human liver cells was used for testing of metaphase inhibition.[3,15] The test compound was dissolved in the culture medium. The testing was started at 1.5 mM concentration for the propargyl derivatives **12** and at 0.5 mM concentration for the other compounds. In each dilution step of the medium, the concentration of the test compound was halved which explains the order of the activity figures in Table 1. Metaphase arrest was assessed 6 h after addition of the pyrimidinone to monolayer cultures of the cells. The minimum inhibitory concentration refers to complete accumulation of the cells in metaphase with no ana- or telo-phases.

Saturated aliphatic derivatives of the pyrimidinone **I** (Scheme 1; R = propyl, X = Cl; R = $HOCH_2$, X = Cl) cause complete accumulation of the cells at 3.0 mM concentration.[1] An allyl and a butenyl derivative (**I**; R = $CH{=}CH_2$, X = Cl and R = $CH_2CH{=}CH_2$, X = Cl) were active at the same concentration.[1,15] The activity was increased by four dilution steps (0.18 mM) in the propargyl derivative **12b**. The 5-chloro derivative was the most active of the 5-halogeno propargyl pyrimidinones **12** (Table 1) which is often the case in a homologous halogeno series.[15] The activity of **12** is retained when there is a chloro substituent on the terminal acetylenic carbon (**13**) (0.125 mM) but its toxicity to the cells is increased.

The activity fell to 0.5 mM in the water-soluble hydroxymethyl derivative **14a**. A methyl group on the hydroxy-bearing carbon (**14b**) gave full inhibition at 0.25 mM concentration, and the activity was increased by three dilution steps to 0.032 mM in the furyl derivative **14c**. The alkynyloxymethyl derivatives (**15**, **16b**) are more active than their alkynyl analogues **12b** and **14a**, respectively, the figures being 0.18 and 0.125 mM for the pair **12b** and **15**, and 0.5 and 0.018 mM for the pair **14a** and **16b**. The latter was a good compound by our activity scale, and comparable in activity to the best aryloxymethyl derivatives.[1,15]

Experimental

Mass spectra were recorded at 70 eV ionising current under electron impact conditions, and isobutane or ammonia was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.). The ^1H NMR spectra were recorded in $CDCl_3$ at 60 MHz and the ^{13}C NMR spectra at 75 MHz unless otherwise specified.

Screening for metaphase arrest. Chang human liver cells were grown in an E2a culture medium containing human serum (20 %) and horse serum (10 %). Experimental details are described elsewhere.[3,15] Monolayers of the cells on slides kept in tubes were incubated in a medium containing the test substances in the desired concentration, and the slides examined after incubation for 6 h. 1 000 cells were counted on each slide, and the cells assigned to one of the following categories: prophase, metaphase, anaphase, telophase and interphase. The results given in Table 1 are the average results from five slides in each experiment.

Substances available by literature methods. 5-Chloro-3-pentyn-2-ol (**2a**).[5] 4-(2-Tetrahydropyranyloxy)-2-butyn-1-ol (**6**).[9]

4-Chloro-1-(2-furfuryl)-2-butyn-1-ol (**2b**). Butyllithium in hexane (1.5 M; 100 ml, 0.15 mol) was added dropwise with stirring to a solution of propargyl chloride (11.18 g, 0.15 mol) in dry diethyl ether at −78 °C. After 30 min of stirring furfural (14.4 g, 0.15 mol) was added, the mixture allowed to reach ambient temperature and the stirring continued overnight. Aqueous saturated ammonium chloride was then added, the mixture extracted with diethyl ether and, the ether solution dried ($MgSO_4$) and evaporated. **WARNING: an attempt was made to purify the liquid product by distillation, but this resulted in explosive decomposition!** The crude product, yield: 23 g (90 %), was used in the subsequent reactions without further purification. ^1H NMR: δ 4.1 (1 H, m, CH), 4.25 (2 H, d, *J* 2 Hz, CH_2), 5.5 (1 H, br s, OH), 6.4 (2 H, m, Fur), 7.5 (1 H, m, Fur).

1-(Methylthiomethoxy)-4-(2-tetrahydropyranyloxy)-2-butyne (**7**). The title compound was prepared according to the literature;[16] yield 72 %, b.p. 98–102 °C/0.05 mmHg. Anal. $C_{11}H_{18}O_3S$: H. Calc. C, 57.36. Found C, 57.88. ^1H NMR: δ 1.4–1.9 (6 H, m, THP), 2.18 (3 H, s, MeS), 3.4–3.7 (2 H, m, THP), 4.35 (4 H, s, $2\times CH_2$), 4.75 (2 H, s, SCH_2O), 4.7–4.9 (1 H, m, THP). MS(CI; NH_3): 248 (19, *M*+18), 231 (28, *M*+1), 215 (1), 184 (5), 183 (5), 169 (2), 145 (85), 85 (100).

1-(Methylthiomethoxy)-4-(2-tetrahydropyranyloxy)-2-butyne (**8**). MCPBA (85 %; 0.77 g, 3.8 mmol) was added in small portions at 0 °C to a solution of 1-(methylthiomethoxy)-4-(2-tetrahydropyranyloxy)-2-butyne (0.89 g, 3.8 mmol) in dichloromethane (15 ml). The mixture was stirred at 0 °C for 2.5 h, whereupon the solution was washed consec-

utively with sodium thiosulfate (×2), sodium hydrogen carbonate, sodium hydroxide and brine. The dried solution ($MgSO_4$) was evaporated and the residue washed with pentane (×2); yield 0.77 g (86 %) of an oily substance. Anal. $C_{11}H_{18}O_4S$: H. Calc. C, 53.63. Found C, 53.13. ^1H NMR (300 MHz): δ 1.5–1.9 (6 H, m), 2.61 (3 H, s), 3.5–3.6 (1 H, m), 3.8–3.9 (1 H, m), 4.2–4.4 (2 H, m), 4.5–4.6 (4 H, m), 4.82 (1 H, t, *J* 3 Hz). ^{13}C NMR: δ 19.1, 25.4, 30.3, 35.3, 54.2, 60.1, 60.7, 62.1, 80.1, 84.8, 85.7, 97.1. MS(Cl; NH_3): 264 (4, *M*+18), 247 (10, *M*+1), 231 (1), 196 (1), 180 (22), 164 (14), 162 (100), 102 (8), 85 (56).

1-Chloromethoxy-4-(2-tetrahydropyranyloxy)-2-butyne (**9**). *Method A.* Acetyl chloride (0.19 ml, 22.7 mmol) was added to a solution of 1-(methylthiomethoxy)-4-(2-tetrahydropyranyloxy)-2-butyne (0.32 g, 1.4 mmol) in dichloromethane (5 ml) at 0 °C. The mixture was stirred at ambient temperature for 20 min whereupon the solvent was evaporated and the residue distilled in a Kugelrohr apparatus; b.p. 120 °C/0.05 mmHg, yield 0.17 g (56 %). ^1H NMR: δ 1.5–1.9 (6 h, m), 3.6–4.1 (2 H, m), 4.33 (21 H, s), 4.4–4.5 (2 H, m), 4.82 (1 H, t, *J* 3 Hz).

Method B. Sulfuryl chloride (0.09 ml, 1.12 mmol) in dichloromethane (2 ml) was added to a mixture of 1-(methylthiomethoxy)-4-(2-tetrahydropyranyloxy)-2-butyne (258 mg, 1.12 mmol) and cyclohexene (180 mg, 2.20 mmol) in dichloromethane (2 ml). The mixture was stirred at 0 °C for 20 min, and the solvent evaporated. The residue, which was a 1:1 mixture of the title compound and 1-chloro-2-methylsulfenylcyclohexane, was used without further purification in the alkylation of 5-chloro-2-pyrimidinone.

1-(Phenylthiomethoxy)-4-(2-tetrahydropyranyloxy)-2-butyne (**10**). A 1:1 mixture of 1-chloromethoxy-4-(2-tetrahydropyranyloxy)-2-butyne (1.12 mmol) and 1-chloro-2-methylthiocyclohexane (coproduct in the preparation of **9**) in dichloromethane (2 ml) was added at 0 °C to a solution of thiophenol (0.12 ml, 1.2 mmol) and triethylamine (0.17 ml, 1.2 mmol) in dichloromethane (2 ml). The mixture was stirred at ambient temperature for 2 h, diethyl ether was added and the solution was washed with aqueous sodium hydroxide (×3). The ether layer was separated, dried ($MgSO_4$) and evaporated. The product was isolated by chromatography on silica gel using EtOAc–Hexane (1:10); yield 251 mg (77 %). Anal. $C_{16}H_{20}O_8S$: H. Calc. C, 65.71. Found C, 64.98. HRMS: Calc. $C_{11}H_{12}O_2S$: 208.0557. Found: 208.0557. ^1H NMR: δ 1.4–1.9 (6 H, m, THP), 3.4–3.6 (2 H, m, THP), 3.7–3.9 (2 H, m), 4.24 and 4.34 (2 H, AB, CH_2, *J* 12 Hz), 4.10 (2 H, s, CH_2), 4.80 (1 H, t, *J* 2 Hz), 5.10 (2 H, s, SCH_2O), 7.2–7.3 (3 H, m, Ph), 7.4–7.5 (2 H, m, Ph) ^{13}C NMR: δ 19.0, 25.3, 30.2, 54.2, 54.9, 61.9, 74.0, 80.9, 83.0, 96.8, 146.8, 128.9, 130.0, 135.5. MS(Cl, isobutane): 293 (3, *M*+1), 209 (1), 207 (2), 191 (5), 162 (14), 161 (23), 123 (51), 85 (100).

5-Chloro-1-(3-chloro-2-propynyl)-2(1H)-pyrimidinone (**13**). Methanesulfonyl chloride (5.6 ml, 72.7 mmol) was added slowly with stirring to a solution of 3-chloro-2-propyn-1-ol[6] (5.98 g, 66.1 mmol) and triethylamine (13.8 ml, 99.1 mmol) in dichloromethane (300 ml) at 0 °C. The mixture was stirred at ambient temperature for 30 min, cooled to 0 °C and 5-chloro-2(1*H*)-pyrimidinone (7.86 g, 66.1 mmol) and triethylamine (13.8 ml, 99.1 mmol) added. The mixture was stirred at ambient temperature for 17 h, shaken with water (4×100 ml), the organic solution dried ($MgSO_4$), the solvent evaporated and the product isolated by chromatography on silica gel using $CHCl_3$–EtOH (97:3); yield 5.3 g (40 %), m.p. 135 °C (EtOAc). Anal. $C_7H_4Cl_2N_2O$: C, H. ^1H NMR: δ 4.73 (CH_2), 8.01 (H-6, d, *J* 3 Hz), 8.53 (H-4, d, *J* 3 Hz). MS: 206/204/202 (3/15/25, *M*), 176 (3), 174 (6), 169 (6), 167 (22), 149 (9), 147 (13), 141 (13), 139 (38), 73 (100).

5-Chloro-1-(4-hydroxy-2-butynyl)-2(1H)-pyrimidinone (**14a**). A solution of 4-iodo-2-butyn-1-ol[7] (36.04 g, 183.9 mmol) in dichloromethane (50 ml) was added slowly with stirring to a solution from 5-chloro-2-(1*H*)-pyrimidinone (20.00 g, 153.2 mmol) and triethylamine (25.6 ml, 183.9 mmol) in dichloromethane (200 ml) at 0 °C. The mixture was stirred at ambient temperature for 17 h, filtered and the filtrate extracted with water (5×100 ml). The pH of the water solution was adjusted to 8 by addition of sodium hydrogen carbonate and the volume concentrated to ca. 200 ml and extracted with ethyl acetate (15×100 ml). The combined ethyl acetate extracts were dried ($MgSO_4$), the solution evaporated and the product purified by chromatography on silica gel using acetonitrile and subsequent recrystallization from acetonitrile; yield 6.60 g (22 %), m.p. 132 °C. Anal.: $C_8H_7ClN_2O_2$: C, H. ^1H NMR (CD_3CN): δ 3.43 (OH, t, *J* 6 Hz), 4.23 (CH_2O, dt, *J* 6, 2 Hz), 4.68 (CH_2N, d, *J* 2 Hz), 8.23 (H-6, d, *J* 3 Hz), 8.55 (H-4, d, *J* 3 Hz). MS: 200/198 (12/39, *M*), 199 (7), 197 (8), 184 (3), 183 (29), 182 (22), 181 (100), 180 (41).

5-Chloro-1-(4-hydroxy-2-pentynyl)-2(1H)-pyridinone (**14b**). 5-Chloro-3-pentyn-2-ol[5] (1.60 g, 15.3 mmol) and sodium iodide (0.2 g) were added to a solution of 5-chloro-2(1*H*)-pyrimidinone (2.0 g, 15.3 mmol) and triethylamine (2.1 ml, 15.3 mmol) in dry dichloromethane (50 ml). The reaction mixture left at ambient temperature overnight, after which the solvent was evaporated, the residue extracted with acetonitrile and the product isolated from the solution by flash cromatography (acetonitrile); yield 1.36 g (42 %), m.p. 120 °C. Anal. $C_9H_9ClN_2O_2$: C, H. ^1H NMR (300 MHz): δ 1.50 (Me, d, *J* 3 Hz), 3.3 (OH), 4.6 (CH, m,), 4.73 (CH_2, br s), 8.18 (H-6, d, *J* 3 Hz), 8.55 (H-4, d, *J* 3 Hz). ^{13}C NMR: δ 23.83 (C-5′), 40.54 (C-1′), 57.83 (C-4′), 74.17 and 92.37 (C-2′ and C-3′), 111.50 (C-5), 143.56 (C-6), 154.02 (C-2), 165.12 (C-4). MS: 214/212 (3/9, *M*), 197 (20), 195 (27), 179 (17), 133 (7), 131 (25), 86 (5), 53 (10), 43 (100).

5-Chloro-1-[4-(2-furfuryl)-4-hydroxy-2-butynyl]-2(1H)-pyrimidinone (**14c**). 4-Chloro-1-(2-furfuryl)-2-butyn-1-ol (5.2 g; 30 mmol) and sodium iodide (0.2 g) were added to a solution of 5-chloro-2(1*H*)-pyrimidinone (2.0 g, 15.3 mmol) and triethylamine (2.1 ml, 15.3 mol) in dry dichloromethane (50 ml) at 0 °C and the mixture stirred at ambient temperature for 72 h then evaporated. The residue was extracted with acetonitrile and the solution subjected to flash chromatography on silica gel using acetonitrile. The product was hygroscopic and was stored under N_2; yield 2.0 g (50 %). ^{1}H NMR: δ 4.6 (CH, m), 4.81 (CH_2, d, *J* 2 Hz), 5.6 (OH, br s), 6.4 (2 H, m, Fur), 7.4 (1 H, m, Fur), 8.25 (H-6, d, *J* 3 Hz), 8.45 (H-4, d, *J* 3 Hz).

5-Chloro-1-(2-propynyloxy)methyl-2(1H)-pyrimidinone (**15**). Triethylamine (7.0 ml, 50 mmol) was added to a suspension of 5-chloro-2(1*H*)-pyrimidinone (6.53 g, 50 mmol) in dichloromethane (100 ml). The mixture was stirred for 10 min at ambient temperature before chloromethyl propynyl ether[8] (5.23 g, 50 mmol) in dichloromethane (20 ml) was added dropwise. The mixture was stirred at ambient temperature for 24 h after which aqueous sodium chloride was added. The organic layer was separated, dried ($MgSO_4$) and evaporated to give a mixture of the *N*- and *O*-alkylated isomers (5:1; 7.4 g, 75 %). The isomers could be separated by means of the lower solubility of the *N*-alkyl isomer in diethyl ether. We were only interested in the isolation and purification of the *N*-alkyl isomer; yield 5.0 g (51 %), m.p. 94 °C (diisopropyl ether). Anal. $C_8H_7ClN_2O_2$: C, H. ^{1}H NMR: δ 2.55 (CH≡, t, *J* 3 Hz), 4.41 (CH_2C=, d, *J* 3 Hz), 5.50 (NCH_2O, s), 7.95 (H-6, d, *J* 3 Hz), 8.5–8.7 (H-4). MS: 198 (2, *M*), 168 (3), 147 (20), 144 (67), 133 (14), 114 (11), 69 (33), 39 (100).

5-Chloro-1-(4-tetrahydropyran-2-yloxy-2-butynyloxy)methyl-2(1H)-pyrimidinone (**16a**). A 1:1 mixture of 1-chloromethoxy-4-(2-tetrahydropyranyloxy)-2-butyne (4.0 mmol) and 1-chloro-2-phenylthiocyclohexane (coproduct in the preparation of **9**) in dichloromethane (4 ml) was added to a solution of 5-chloro-2(1*H*)-pyrimidinone (522 mg, 4.0 mmol) and triethylamine (0.56 ml, 4.0 mmol) in dichloromethane (10 ml). The mixture was stirred for 24 h at ambient temperature whereupon water was added and the organic layer was separated, dried ($MgSO_4$) and evaporated; yield 600 mg (48 %). Anal. $C_{14}H_{17}ClN_2O_4$: H. Calc. C, 53.75. Found C, 52.97. ^{1}H NMR: δ 1.4–1.9 (6 H, m), 3.4–3.6 (1 H, m), 3.7–3.9 (1 H, m), 4.2–4.3 (2 H, m), 5.40 (NCH_2O, s), 7.89 (H-6, d, *J* 3.8 Hz), 8.5–8.7 (H-4, br). MS(Cl, NH_3): 313 (100, *M*+1), 248 (13), 246 (40), 231 (17), 229 (47), 183 (3), 148 (4), 144 (2).

5-Chloro-1-(4-hydroxy-2-butynyloxy)methyl-2-pyrimidinone (**16b**). 5-Chloro-1-(4-tetrahydropyran-2-yloxy)-2-butynyloxy-2(1*H*)-pyrimidinone (0.61 g, 2.0 mmol) and a cationic exchange resin[12] (Dowex 50 W-X8, 0.70 g) were stirred together in dichloromethane (3 ml) and methanol (3 ml) for 20 min at ambient temperature. The resin was filtered off, the filtrate evaporated and the residue purified by chromatography on silica plates (7 % MeOH in CH_2Cl_2); yield 60 mg (13). ^{1}H NMR ($CDCl_3$–acetone-d_6): δ 4.29 (4 H, s), 5.45 (2 H, s), 8.10 (1 H, d, *J* Hz), 8.58 (1 H, d, *J* 3 Hz). MS: 228 (1, *M*), 210 (1), 199 (1), 197 (2), 183 (8), 181 (26), 146 (18), 144 (60), 133 (11), 131 (35), 41 (100).

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