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A Convenient Synthesis of 1-Ethoxymethyl-5-Nitro-6-Substituted Uracils

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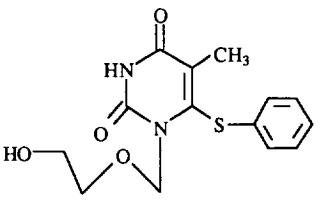
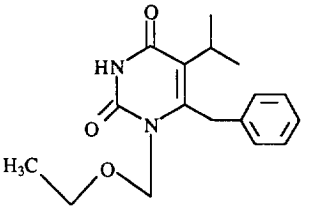
Abstract: Two new and versatile synthetic methods for preparing 5-nitro-analogues of HEPT and MKC-442 which are HIV-1 reverse transcriptase inhibitors, are reported. In both cases the key-step is based upon the displacement of a 6-methylthio or a 6-tosyl group by nucleophiles according an addition-elimination type mechanism.

Following the discovery of HIV as the causative agent for AIDS[1], enormous efforts have been made to understand the life cycle of this retrovirus, and from there to define biochemical targets for its selective inhibition by chimotherapeutic agent. Reverse transcriptase (RT), the polymerase specifically coded by HIV, was in this respect one of the first targets to be identified for the development of anti-AIDS drugs. Acting as inhibitors of this enzyme, the administration of AZT, ddI, and ddC to declared AIDS victims slows down the progression of the destruction of the immune system[2]. However, their *long term use* leads to problems of toxicity, and the appearance of drug resistant HIV mutant strains.[3]

Through interaction with RT at an "allosteric" binding pocket[4] which is proximal to the catalytic site for DNA synthesis, a number of structurally diverse heterocycles[5], including 1-[(2-hydroxyethoxy)methyl]-6-phenylthio)thymine or HEPT[6] display remarkably potent and selective inhibition profiles. Structure-activity studies in the HEPT series[7] have resulted in the identification of several new promising clinical candidates, including MKC-442[8].



HEPT

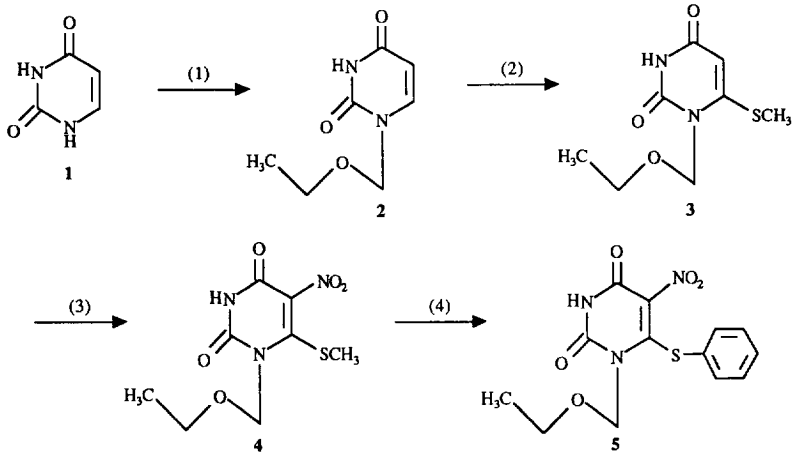


MKC-442

As part of our research program in this area[9], we have developed two different routes to 5-nitro-6-aryl thio substituted HEPT compounds as potential HIV-1 RT inhibitors. As will become apparent from the reactivity of **4**, these new molecules can also be employed for introduction of other functionality at the 5, and 6 positions of the pyrimidine (uracil) ring.

To obtain intermediate **3**, uracil was first selectively alkylated at N-1 through reaction with ethoxymethyl chloride following the Vorbruggen procedure[10] to give **2**. This product was then lithiated through treatment with lithium diisopropylamide and the derived C-6 anion was reacted with dimethyldisulfide. The isolation of only small amounts of the corresponding 6-chloro and 6-bromo compounds, issuing from the reaction of the anion of **2** with the appropriate succinimide reagent, and other halogenating reagents pointed to the interest in introducing the sulfur substituent at this stage. Unfortunately, problems arose in the following step as nitration of **3** using nitrous acid produced the 5,6-disubstituted compound **4** in only 17% yield.[11] However, as the C-6 position in this molecule is doubly activated with respect to Michael addition, the thiomethyl to thiophenyl exchange process was efficient, giving the desired 5-nitro nucleoside **5** in 64% yield.

Scheme 1

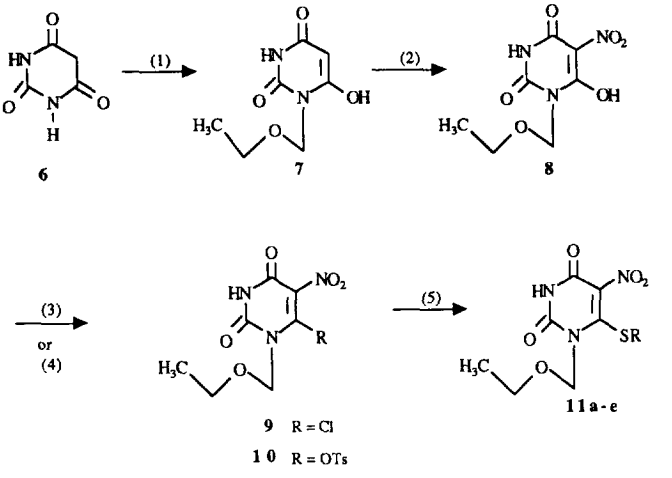


1) Bistrimethylsilylacetamide, CH_2Cl_2, $EtOCH_2Cl$, Bu_4NI 10%, 2h, 95%. 2) LDA (2.2 eq.), THF-78°C, 1h then MeSSMe (2.2 eq.), 89%. 3) HNO_2, AcOH, 17%. 4) PhSH (10 eq.), EtOH, Et_3N, 2h, 64%.

The poor yield observed during the nitration of sulfide **3** subsequently led us to consider a second strategy for construction of compound **5**, and other HEPT analogs, in which, the C-6 oxygen fonction as present in barbituric acid **6** is used as the leaving group in the addition-elimination sequence wherein the thiophenyl substituent is introduced. The N_1-alkylated intermediate **7** was again prepared under Vorbruggen conditions. In contrast to the conversion of **3** --> **4**, treatment of compound **7** with HNO_2 afforded **8** in greatly improved yield (87%). Cursory attempts were then made to prepare the corresponding 6-chloro derivative of **8**. However,

although compound **9** could be obtained, it proved to be highly unstable. For this reason we investigated the tosylation of the hydroxyl group in **8**.

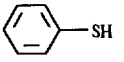
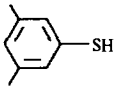
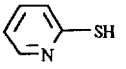
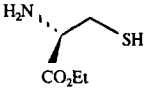
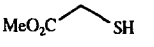
Scheme 2



1) Bistrimethylsilylacetamide, CH_2Cl_2, $EtOCH_2Cl$, Bu_4NI 10%, 2h, 97%. 2) HNO_2, AcOH, 87%. 3) $POCl_3$, NNDEA,HCl (4 eq.) 15-21%. 4) TsCl (excess), pyridine, 79%. 5) EtOH, catalytic Et_3N, t (min.), yield (%) see table 1.

Tosylate **10** was not only found to be sufficiently stable to permit handling, but also reactive toward a variety of sulfur nucleophiles (thiophenol, dimethylthiophenol, pyridinethiophenol, cysteine ethyl carboxylate and methylmercaptoacetate) (see Table 1) giving compounds **11a-11e**, respectively.[12]

Table 1. Nucleophilic substitutions of compound **10** with thio-derivatives.

Entry	Nucleophile	Time (min)	Product	Yield (%)	M.p. °C
1		15	**11a**	91	230-232
2		15	**11b**	87	208-210
3		20	**11c**	89	210-212
4		120	**11d**	63	syrup
5		30	**11e**	85	178-180

Antiviral activity: The five new nucleoside analogs **11a-11e** were evaluated for their protective effect against cytopathogenic effect produced by strain HIV-1 LAI replications in CEM/SS cells. However despite the fact that a series of related pyridinone derivatives containing adjacent nitro and thioaryl groups[13] in structure, show potent anti-HIV-1 activities, compounds **11a-11e** were inactive at concentrations up to 10^{-4} µM.

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References and notes.

1. (a) Barré-Sinoussi, F.; Cherman, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vézinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868-871; (b) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. *Science* **1984**, *224*, 500-503.
2. (a) Fischl, M. A.; *et al. . N. Engl. J. Med.* **1987**, 317, 185-191; (b) Lambert, J.S.; Seidlin, M.; Reichman, R. C.; Planck, C. S.; Laverty, M.; Morse, G. D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F. T.; Dolin, R. *N. Engl. J. Med.* **1990**, *322*, 1333-1345.
3. Richman, D. D.; Fischl, M. A.; Grieco, M. H.; Gattlieb, M. S.; Volberding, P. A.; Laskin, O.L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Hirsch, M. S.; Jackson, G. G.; Durack, D. T.; Nussinoff-Lehrman, S.; and the AZT collaborative Working Group. *N. Engl. J. Med.* **1987**, *317*, 192-197.
4. a) Verheyden, J. P. H. *Current Opinion in Therapeutic Patents*, **1991**, 1, 1294-1304; (b) De Clercq, E.; *AIDS Res. Hum. Retroviruses* **1992**, *8*, 119; (c) Saunders, J.; Storer R. *Drug News Perspect.* **1992**, *5*, 153; (d) Romero, D. L. *Ann. Rep. in Med. Chem.* **1994**, *29*, 123-132.
5. Goldman, M. E.; Nunberg, J. H.; O'Brien J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. S.; Hupe, D. J.; Emini, A. E.; Stern, A. M. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 6863-6867.
6 Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R.T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 2507-2509.
7. Balzarini, J., Karlsson, A.; De Clercq E., *Molecular Pharmacol.* **1993**, *44*, 694-701 and references cited therein.
8. MKC-442 demonstrating higher synergistic anti-HIV activity with AZT than nevirapine will soon enter clinical studies: Yuasa, S. *et al.*, 9th Int. Conf. AIDS/4th STD World Congr.[June 6-11] Berlin, 1993. Abstract PO-B26-2064; Mitsubishi Kasei Corporation. Annual Report 1993.
9. Pontikis, R.; Monneret, C. *Tetrahedron Lett.*, **1994**, *35*, 4351-4354.
10. Niedballa, U.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 461-462.
11. It must be noticed that in the case where the phenylthio group was introduced prior to the nitration-step, side-products having nitro substituent on the aromatic ring were obtained as main products.
12. Data for new compounds (NMR in CD_3OD): **11a**: ^1H NMR : δ 1.18 (t, 3H, J = 7 Hz, CH_3), 3.64 (q, 2H, J = 7 Hz, CH_2), 5.35 (s, 2H, CH_2), 7.45 (m, 5H, Ph); ^{13}C : δ 15.47, 66.41, 69.71, 128.84, 128.90, 131.59, 136.00, 158.63; 172.53; MS (DCI/NH_3) *m/z* 324 (MH^+); **11b**: ^1H NMR : δ 1.19 (t, 3H, J = 7Hz, CH_3), 2.43 (s, 6H, 2 x CH_3), 3.73 (q, 2H, J = 7 Hz, CH_2), 5.63 (s, 2H, CH_2), 7.20 (d, 1H, J = 1.5 Hz, H-Ar), 7.26 (bs, 2H, H-Ar); ^{13}C: δ 15.49, 21.23, 66.39, 71.67, 124.12, 130.08; 132.47, 134.26, 140.23, 160.40, 172.25; MS (DCI/NH_3): *m/z* 352 (MH^+); **11c**: ^1H NMR : 1.68 (t, 3H, J = 7 Hz, CH_3), 3.65 (q, 2H, J = 7 Hz, CH_2), 5.42 (s, 2H, CH_2), 7.39 (dd, 1H, J = 5 Hz, J' = 1.6 Hz, H-Ar), 7.82 (dd, 1H, J = 7.5 Hz, J' = 1.6 Hz, H-Ar), 8.61 (d, 1H, J=5 Hz, H-Ar); ^{13}C NMR: δ 15.45, 66.48, 71.85, 125.24, 133.14, 150.76, 154.46, 155.61, 161.15, 174.05; MS (DCI/NH_3): *m/z* 325 (MH^+); **11d**: ^1H NMR: δ 1.66 (t, 3H, J = 7 Hz, CH_3), 1.80 (t, 3H, J = 7.5 Hz, CH_3), 3.61-3.85 (m, 2H, CH_2), 4.04 (q, 2H, J = 7 Hz, CH_2), 4.52-4.68 (m, 3H), 5.40 (s, 2H, CH_2), 5.88 (bs, 2H, CH_2); ^{13}C NMR : δ 14.49, 15.60, 54.78, 62.84, 63.03, 66.15, 71.56, 157.64, 159.43, 162.78, 171.72; MS (DCI/NH_3): *m/z* 363 (MH^+); **11e**: ^1H NMR : δ 1.18 (t, 3H, J = 7 Hz, CH_3), 3.68 (q, 2H, J = 7 Hz, CH_2), 3.76 (s, 3H, CH_3), 3.86 (s, 2H, CH_2); ^{13}C NMR : δ 15.48, 34.55, 50.26, 66.48, 71.87, 155.75, 161.54, 172.06, 174.70; MS (DCI/NH_3): *m/z* 320 (MH^+).
13 Dollé, V.; Nguyen, C. H.; Aubertin, A. M.; Kirn, A.; Andreola, M. L.; Jamieson, G.; Tarrago-Litvak, L.; Bisagni, E. *J. Med. Chem.* **1995**, *38*, 4679-4686.

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