Pergamon

Tetrahedron Letters, Vol. 36, No. 35, pp. 6257-6260, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01238-9

A Convenient Approach to the Synthesis of 6-Substituted 1,5-Dialkyluracils and -2-thiouracils

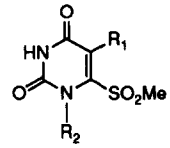
Dae-Kee Kim,* Young-Woo Kim, Jongsik Gam, Jinsoo Lim, and Key H. Kim

Life Science Research Center, Sunkyong Industries, 600, Jungja-Dong, Changan-Ku, Suwon-Si, Kyungki-Do 440-745, Korea

Key words *: 6-substituted 1,5-dialkyluracils, 6-substituted 1,5-dialkyl-2-thiouracils*

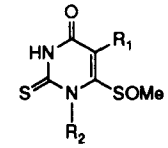
Abstract *: A general and convenient approach to the synthesis of 6-substituted 1,5-dialkyluracils and -2-thiouracils via 1,5-dialkyl-6-(methylsulfonyl)uracils 1 and 1,5-dialkyl-6-(methylsulfinyl)-2-thiouracils 2, respectively, has been described. The compounds 1 and 2 were synthesized from ethyl 2-alkyl-3,3-di(methylthio)acrylates 3 in five steps in good yields.*

Recently, Tanaka *et al.*[1] developed a general, regiospecific and simple route to various types of 6-substituted uridines, 2'-deoxyuridines, and acyclouridines based on the regiospecific LDA lithiation, which were difficult to synthesize by any other methods. The LDA lithiation was, however, found not to be applicable to the synthesis of 6-substituted 1-alkyluracil derivatives, presumably due to the lack of an oxygen atom on the N-1 alkyl group which stabilizes the C-6 lithiated species.[2] For instance, Miyasaka *et al.*[3] reported that treatment of 1-butyl-5-ethyluracil with LDA in THF followed by reaction with diphenyl disulfide afforded 1-butyl-5-ethyl-6-(phenylthio)uracil only in 7 % yield. Pontikis *et al.*[2] also reported that 1-(3-phenyl-2-propenyl)-6-(phenylthio)thymine was obtained from 1-(3-phenyl-2-propenyl)thymine in less than 10 % yield under similar condition.



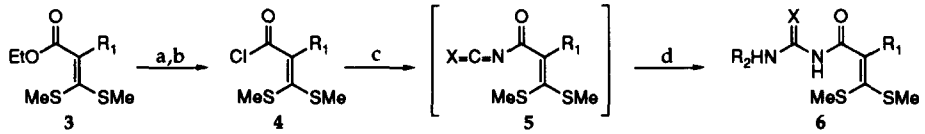
1

a : R_1=Me, R_2=*n*-Pr
b : R_1=Me, R_2=CH_2Ph
c : R_1=Et, R_2=*n*-Pr
d : R_1=Et, R_2=CH_2Ph



2

In this report, we wish to describe a general and convenient approach to the synthesis of 6-substituted 1,5-dialkyluracils and -2-thiouracils *via* 1,5-dialkyl-6-(methylsulfonyl)uracils 1 and



3
a : R_1=Me
b : R_1=Et

4
a : R_1=Me (80 %)
b : R_1=Et (78 %)

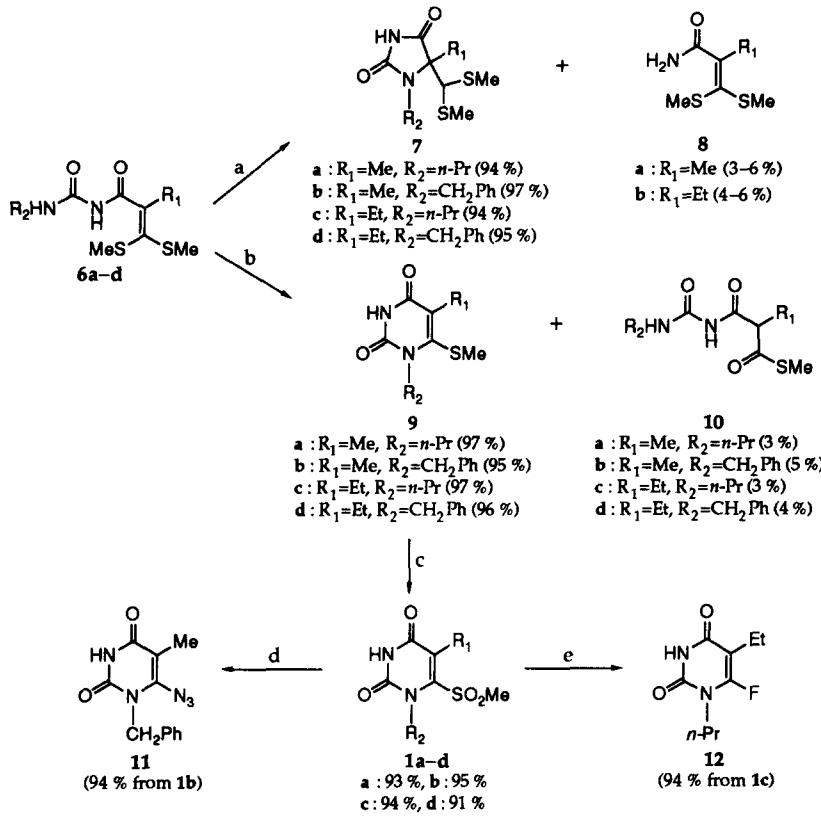
5
a : R_1=Me, X=O
b : R_1=Et, X=O
c : R_1=Me, X=S
d : R_1=Et, X=S

6
a : R_1=Me, R_2=*n*-Pr, X=O (90 %)
b : R_1=Me, R_2=CH_2Ph, X=O (91 %)
c : R_1=Et, R_2=*n*-Pr, X=O (87 %)
d : R_1=Et, R_2=CH_2Ph, X=O (88 %)
e : R_1=Me, R_2=*n*-Pr, X=S (81 %)
f : R_1=Me, R_2=CH_2Ph, X=S (75 %)
g : R_1=Et, R_2=*n*-Pr, X=S (82 %)
h : R_1=Et, R_2=CH_2Ph, X=S (98 %)

(a) 2*N* KOH (2 eq.), EtOH, reflux, 3 h; (b) $(COCl)_2$ (1.2 eq.), DMF (cat.), benzene, rt, 3 h; (c) AgOCN (1.05 eq.) (for **6a–d**) or NH_4SCN (1.05 eq.) (for **6e–h**), toluene, reflux, 0.5 h; (d) R_2NH_2 (1.1 eq.), toluene, –78 °C to rt over 2 h (for **6a–d**) or –20 °C to rt over 1 h (for **6e–h**)

1,5-dialkyl-6-(methylsulfinyl)-2-thiouracils **2**, respectively, which could overcome the limitation of LDA lithiation method.

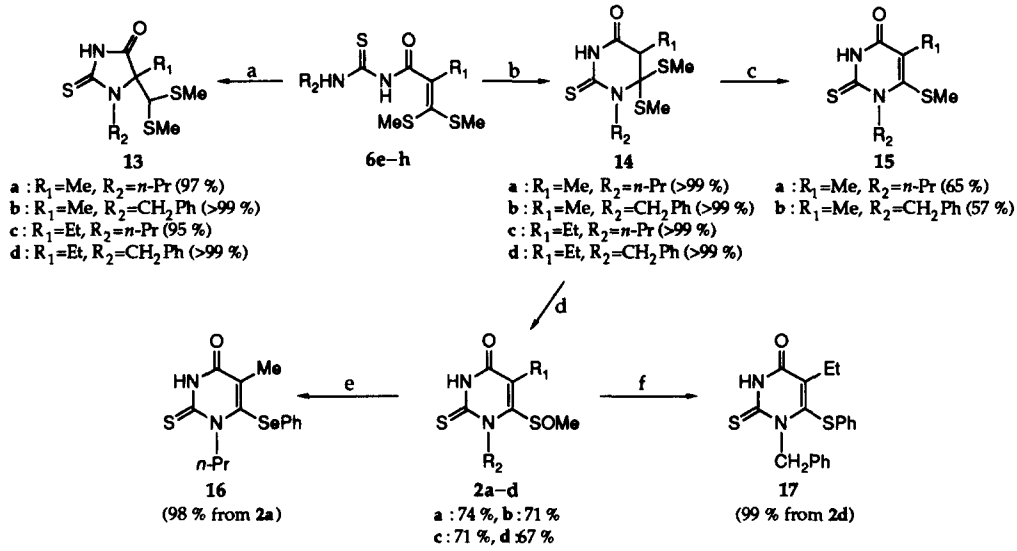
We envisioned that readily accessible ethyl 2-alkyl-3,3-di(methylthio)acrylates **3a–b** from ethyl propionate or ethyl butyrate according to a published procedure[4] would be a good starting point for the synthesis of compounds **1** and **2**. Thus, hydrolysis of esters **3a–b** with 2*N* KOH in EtOH and subsequent reaction of the corresponding carboxylic acids with oxalyl chloride in benzene in the presence of a catalytic amount of DMF afforded 2-alkyl-3,3-di(methylthio)acryloyl chlorides **4a–b** in good yields. Treatment of **4a–b** with either silver cyanate or ammonium thiocyanate in toluene followed by reaction of the resulting isocyanates **5a–b** or isothiocyanates **5c–d** with an appropriate amine gave *N*-alkyl-*N'*-[2-alkyl-3,3-di(methylthio)acryloyl]ureas **6a–d** or -thioureas **6e–h** in good to excellent yields.



(a) K_2CO_3 (2 eq.), EtOH, reflux, 0.5 h; (b) methanesulfonic acid (0.2 eq.), anhydrous AcOH, 80 °C, 3 h; (c) 3-chloroperoxybenzoic acid (5 eq.), benzene, reflux, 1 h; (d) NaN_3 (1 eq.), DMF, rt, 0.5 h; (e) $(n\text{-Bu})_4NF$ (3 eq.), THF, reflux, 0.5 h

Base-induced cyclization of **6a–d** with K_2CO_3 in EtOH led to the exclusive formation of five-membered ring, thus, affording hydantoin derivatives **7a–d** in excellent yields along with a small amount of hydrolyzed by-products **8a–b**. On the other hand, when **6a–d** were treated with a catalytic amount of methanesulfonic acid in anhydrous acetic acid, only six-membered ring compound, 1,5-dialkyl-6-(methylthio)uracils **9**, were obtained in 95–97 % yields along with 3–5 % of hydrolyzed by-products **10a–d**. Oxidation of **9a–d** with 3-chloroperoxybenzoic acid in

benzene resulted in high yields of 1,5-dialkyl-6-(methylsulfonyl)uracils **1a–d**[5]. It has been known that 6-phenylthio uridine derivatives or 6-phenylsulfinyl acyclouridine derivatives were highly susceptible to nucleophillic addition-elimination reactions with a variety of nucleophiles under mild conditions.[1d,6] Likewise, when 6-methylsulfonyl compounds **1b** and **1c** were allowed to react with NaN_3 and $(n\text{-Bu})_4NF$, respectively, 6-azido-1-benzylthymine (**11**) and 5-ethyl-6-fluoro-1-propyluracil (**12**) were obtained in excellent yields.



(a) K_2CO_3 (2 eq.), EtOH, reflux, 0.5 h; (b) methanesulfonic acid (0.2 eq.), anhydrous AcOH, rt, 15 min; (c) methanesulfonic acid (0.2 eq.), anhydrous AcOH, 120 °C (bath temp.), 22 h; (d) $NaIO_4$ (6 eq.), H_2O, MeOH, reflux, 0.5 h; (e) PhSeH (3 eq.), NaOH, EtOH, rt, 16 h; (f) PhSH (1 eq.), NaOH, EtOH, rt, 16 h

Cyclization of the acryloyl thioureas **6e–h** under the same basic condition as for the acryloyl ureas **6a–d** produced the corresponding 2-thiohydantoin derivatives **13a–d** as the sole products in >95 % yields. In contrast to the acryloyl ureas, **6e–h** were readily cyclized in anhydrous acetic acid containing methanesulfonic acid at room temperature within 15 min to give the 1,5-dialkyl-5,6-dihydro-6,6-di(methylthio)-2-thiouracils **14a–d** in quantitative yields, but further conversion of **14** to the 1,5-dialkyl-6-(methylthio)-2-thiouracils **15** in the same acidic medium appeared to be less facile. Thus, a rather drastic reaction condition such as higher temperature and longer reaction time (120 °C, 22 h) was required to obtain the elimination products **15a** and **15b** in 65 % and 57 % yields from **14a** and **14b**, respectively. It was speculated that oxidation of methylthio groups in **14** could facilitate their subsequent elimination. When **14a–d** were exposed to excess $NaIO_4$, 1,5-dialkyl-6-(methylsulfinyl)-2-thiouracils **2a–d**[7] were obtained in fair yields. Reactions of **2a** and **2d** with PhSeH and PhSH in ethanolic NaOH solution, respectively, afforded 6-(phenylselenenyl)-1-propyl-2-thiothymine (**16**) and 1-benzyl-5-ethyl-6-(phenylthio)-2-thiouracil (**17**) in excellent yields.

Some of the present compounds, such as 6-phenylthio and 6-phenylselenenyl derivatives, may have anti-HIV-1 activity in view of the reported activity of HEPT analogues.[1d,1e,8]

In summary, the present study shows that various types of 6-substituted uracils and 2-thiouracils having two different alkyl groups at N-1 and C-5, which have so far been difficult to synthesize, can be prepared in good yields from readily accessible ethyl 2-alkyl-3,3-di(methylthio)-acrylates using this six-step procedure .

References and Notes

1. (a) Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron* **1982**, *38*, 2635–2642. (b) Tanaka, H.; Matsuda, A.; Iijima, S.; Hayakawa, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1983**, *31*, 2164–2167. (c) Tanaka, H.; Hayakawa, H.; Iijima, S.; Haraguchi, K.; Miyasaka, T. *Tetrahedron* **1985**, *41*, 861–866. (d) Tanaka, H.; Baba, M.; Hayakawa, H.; Sakamaki, T.; Miyasaka, T.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R. T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 349–357. (e) Tanaka, H.; Baba, M.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1991**, *34*, 1394–1399.
2. Pontikis, R.; Monneret, C. *Tetrahedron Lett.* **1994**, *35*, 4351–4354.
3. Miyasaka, T.; Tanaka, H.; De Clercq, E.; Baba, M.; Walker, R. T.; Ubasawa, M. *European Patent* 420,763 A_2.
4. (a) Ali, S. M.; Tanimoto, S. *J. Chem. Soc., Chem. Commun.* **1989**, 684–685. (b) Ali, S. M.; Tanimoto, S. *Bull. Inst. Chem. Res., Kyoto Univ.* **1990**, *68*, 199–207.
5. **1a** : mp 206.0–208.9 °C (dec) (EtOH); IR (KBr) 1148, 1335 (SO_2), 1692 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.94 (t, *J* = 7.4 Hz, 3 H, $NCH_2CH_2CH_3$), 1.76 (tq, *J* = 8.0 Hz, *J* = 7.4 Hz, 2 H, NCH_2CH_2), 2.38 (s, 3 H, CH_3), 3.22 (s, 3 H, SO_2CH_3), 4.17 (t, *J* = 8.0 Hz, 2 H, NCH_2), 9.98 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 10.42, 12.16, 22.45, 44.33, 48.01, 117.60, 147.29, 150.07, 162.60; EI-MS *m/z* 246 (M^+). **1b** : mp 226.8–227.4 °C (dec) (EtOH); IR (KBr) 1156, 1341 (SO_2), 1674, 1698 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 2.23 (s, 3 H, CH_3), 3.25 (s, 3 H, SO_2CH_3), 5.40 (s, 2 H, NCH_2), 7.10–7.37 (m, 5 H, Ph), 12.04 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 12.46, 43.99, 48.53, 117.50, 125.92, 126.70, 128.23, 137.73, 147.43, 150.44, 162.91; EI-MS *m/z* 294 (M^+). **1c** : mp 204.7–205.3 °C (dec) (EtOH); IR (KBr) 1148, 1337 (SO_2), 1682 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 0.84 (t, *J* = 7.5 Hz, 3 H, $NCH_2CH_2CH_3$), 1.03 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.64 (tq, *J* = 7.8 Hz, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.72 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 3.47 (s, 3 H, SO_2CH_3), 3.95 (t, *J* = 7.8 Hz, 2 H, NCH_2), 11.89 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 10.74, 14.16, 19.59, 22.16, 44.79, 48.32, 122.32, 147.81, 150.28, 162.54; EI-MS *m/z* 260 (M^+). **1d** : mp 211.1–211.8 °C (dec) (EtOAc); IR (KBr) 1157, 1331 (SO_2), 1678, 1716 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 1.06 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.74 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 3.26 (s, 3 H, SO_2CH_3), 5.39 (s, 2 H, NCH_2), 7.10–7.38 (m, 5 H, Ph), 12.04 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 14.30, 20.05, 44.72, 48.95, 123.31, 126.11, 126.91, 128.44, 137.90, 147.77, 150.64, 162.68; EI-MS *m/z* 308 (M^+).
6. (a) Tanaka, H.; Iijima, S.; Matsuda, A.; Hayakawa, H.; Miyasaka, T.; Ueda, T. *Chem. Pharm. Bull.* **1983**, *31*, 1222–1227. (b) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Nitta, I.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1992**, *35*, 337–345.
7. **2a** : mp 132.9–134.4 °C (EtOAc); IR (KBr) 1068 (SO), 1616 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.98 (t, *J* = 7.4 Hz, 3 H, $NCH_2CH_2CH_3$), 1.70 (m, 2 H, NCH_2CH_2), 2.17 (s, 3 H, CH_3), 2.83 (s, 3 H, $SOCH_3$), 3.50 (br s, 2 H, NCH_2); EI-MS *m/z* 246 (M^+). **2b** : mp 169.1–169.8 °C (EtOAc); IR (KBr) 1057 (SO), 1627 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 2.12 (s, 3 H, CH_3), 2.68 (s, 3 H, $SOCH_3$), 4.71 (s, 2 H, NCH_2), 7.20–7.40 (m, 5 H, Ph); EI-MS *m/z* 294 (M^+). **2c** : mp 123.3–125.2 °C (EtOAc); IR (KBr) 1068 (SO), 1622 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.98 (t, *J* = 7.4 Hz, 3 H, $NCH_2CH_2CH_3$), 1.15 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.70 (m, 2 H, NCH_2CH_2), 2.62 (m, 2 H, CH_2CH_3), 2.86 (s, 3 H, $SOCH_3$), 3.50 (br s, 2 H, NCH_2); EI-MS *m/z* 261 $(MH)^+$. **2d** : mp 178.0–178.8 °C (EtOAc); IR (KBr) 1061 (SO), 1610 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.11 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 2.59 (m, 2 H, CH_2CH_3), 2.71 (s, 3 H, $SOCH_3$), 4.72 (s, 2 H, NCH_2), 7.20–7.40 (m, 5 H, Ph); EI-MS *m/z* 308 (M^+).
8. Goudgaon, N. M.; Schinazi, R. F. *J. Med. Chem.* **1991**, *34*, 3305–3309.

(*Received in Japan* 12 *May* 1995; *accepted* 28 *June* 1995)