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A facile synthesis and thio-Claisen rearrangement of 3-aryl-2-phenyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-ones: regioselective transformation to thieno[3,2-*d*]pyrimidin-4-ones

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Abstract—The synthesis and transformation of previously unknown 3-aryl-2-phenyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-ones **3a**–**e** to novel thieno[3,2-*d*]pyrimidin-4-ones **4a**–**e** are reported.

Pyrimidine and its derivatives are attracting the attention of an increasing number of synthetic organic chemists because of their reported broad range of biological activity and medicinal importance.[1,2] Thus FU (5-fluorouracil) and FUDR (5-fluoro-2′-deoxyuridine) are used in the treatment of cancer.[3] F_3 TDR (trifluorothymidine), BVDU [(*E*)-5-(2-bromovinyl-2′-deoxyuridine)], AZT (3′-azido-3′-deoxythymidine)[4–7] and CEDU[8] 5-(2-chloroethyl-2′-deoxyuridine) are used against viral diseases. Recently the pyrimidinone derivatives 2-methylthio-6-[(2-alkylamino)ethyl]-4(3*H*)-pyrimidinones have been shown to possess activity against positive strand (rubella virus and sindbis virus) and negative strand (vesicular stomatitis virus) RNA virus.[9] A series of 1-(biphenylmethylamidoalkyl)pyrimidinones has also been designed as nanomolar inhibitors of recombinant lipoprotein-associated phospholipase A_2 with high potency in whole human plasma.[10] In recent years the Claisen rearrangement has been utilised for the synthesis of a number of furo[3,2-*d*]pyrimidine, pyrano[3,2-*d*]pyrimidine and dihydrofuro[2,3-*d*]pyrimidine derivatives.[11,12] Although there are numerous reports on Claisen rearrangements involving heterocyclic systems, there are few reports on the thio-Claisen rearrangement of pyrimidinone derivatives. As part of our extensive studies on the synthesis of various substituted pyrimidinone derivatives involving 1,3-diazabuta-1,3-diene-ketene cycloaddition reactions,[13] we report herein a novel methodology towards the synthesis and transformation of pyrimidinones to fused pyrimidinones by the application of thio-Claisen rearrangements. The previously unknown 3-aryl-2-phenyl-5-prop-2-ynylsulfanyl-3*H*-pyrimidin-4-one derivatives were easily obtained by the [4 + 2] cycloaddition reaction of 4-dimethylamino-1-aryl-2-phenyl-1,3-diazabuta-1,3-dienes with prop-2-ynylsulfanyl ketene, generated in situ from the corresponding acid and *p*-toluenesulfonyl chloride in the presence of triethylamine in dry methylene chloride at room temperature (Scheme 1). The prop-2-ynylsulfanyl-acetic acid (**2**) was in turn prepared by the initial esterification of thioglycolic acid followed by its propargylation in the presence of potassium carbonate in dry acetone and its subsequent alkaline hydrolysis. The cycloaddition reactions of 1,3-diazabuta-1,3-dienes with sulfanyl ketenes were found to be efficient and pyrimidinones **3a**–**e** were isolated in excellent yields (80–85%). The structures of pyrimidinones **3a**–**e** were established with the help of analytical and spectroscopic data.

The salient ^{1}H NMR spectral features of pyrimidinone **3a**, for example, involved the appearance of a one proton singlet at δ 2.24 due to the acetylenic proton, a two proton doublet at δ 3.71 ($J = 2.2$ Hz) due to the –SCH_2 group and a characteristic singlet at δ 8.20 due to the olefinic proton. The mass spectrum of **3a** showed a molecular ion peak at m/z 332 (M^+) (Scheme 1).

Refluxing pyrimidinone **3a** in chlorobenzene for 7–8 h, (monitored by TLC), removal of the solvent under reduced pressure and purification of the crude product resulted in the isolation of the previously unknown

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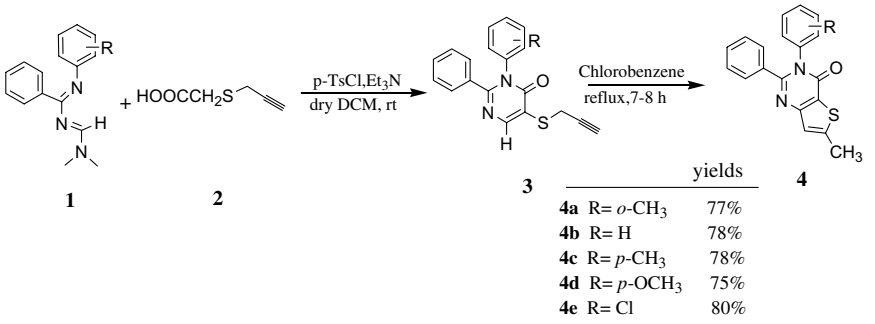
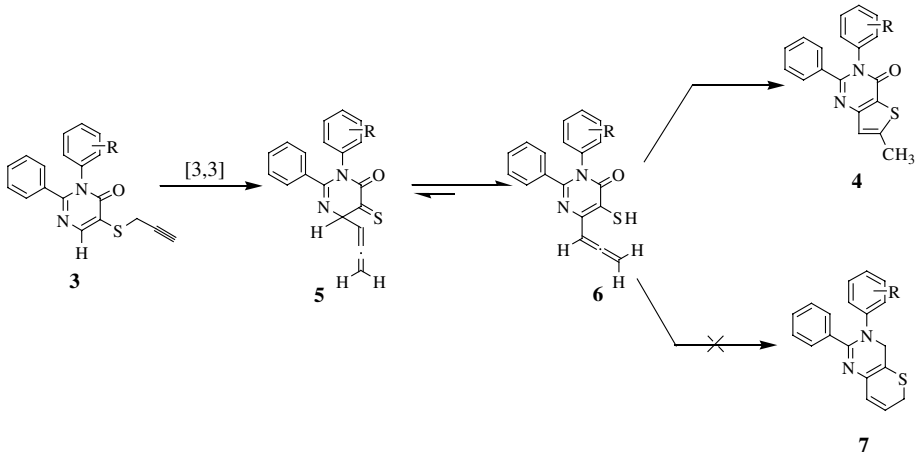


Scheme 1.



Scheme 2.

thieno-pyrimidinone **4a** in good yield (75–80%). Pyrimidinone **4a** was characterised by its analytical and spectroscopic data. The ^{1}H NMR spectrum of **4a** showed a three proton singlet at δ 2.34 due to the *o*-substituted –CH_3, a three proton singlet at δ 2.87 due to a –CH_3 indicated the formation of a five-membered thiophene ring, and a ten proton multiplet due to the nine aromatic and one olefinic protons at δ 7.23–7.52. Moreover, thermal treatment of the substrates **3** resulted in the loss of terminal acetylene absorptions in the IR. The mass spectrum of **4a** showed a molecular ion peak at m/z 332 (M^+). The reaction was successfully generalised by the thermal rearrangement of four other sulfides **3b**–**e** and resulted in good yields of the corresponding thieno[3,2-*d*]pyrimidin-4-ones **4b**–**f**.[14,15]

The plausible mechanism for the formation of 3-aryl-6-methyl-2-phenyl-3*H*-thieno[3,2-*d*] pyrimidinone involves an initial [3,3] thio-Claisen rearrangement to form an intermediate allene **5** followed by its enolisation to enethiol **6**. The thiol **6** can then yield either the product **7** usually obtained or thieno[3,2-*d*]pyrimidinone **4**, via the reported rearrangements.[16,17] However, none of the substrates **3a**–**e** gave products of the type **7** (Scheme 2). Thus the thermal rearrangement of sulfides (**3a**–**e**) interestingly resulted in regioselective ring closure leading to thieno[3,2-*d*]pyrimidinone derivatives (**4a**–**e**) in excellent yields.

In conclusion we have devised a novel and regioselective approach towards the synthesis of five-membered fused thieno[3,2-*d*]pyrimidinones via a thermal thio-Claisen rearrangement.

References and notes

1. (a) Lunt, E. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1974; Vol. 4, p 493; (b) Brown, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 57; (c) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, *36*, 865; (d) Bradshaw, T. K.; Hutchison, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43.
2. (a) Maumato, R.; Farukawa, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2974; (b) Cheng, C. C.; Roth, B. *Progr. Med. Chem.* **1971**, *8*, 61; (c) Jones, A. S.; Swgers, J. R.; Walker, R. T.; Clercq, E. D. *J. Med. Chem.* **1988**, *31*, 268; (d) Griengl, H. H.; Wanck, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; Clercq, E. D. *J. Med. Chem.* **1987**, *30*, 1199; (e) Clercq, E. D.; Benaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905.
3. Heidelberger, C. In *Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicine*; Holland, J. F., Frei, E., Eds.; Lea Febiger: Philadelphia, 1984; p 801.
4. Clercq, E. D.; Descamps, J.; Somer, P. D.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2974.

5. Heidelberger, C.; King, D. H. In *Antiviral Agents in Pharmacology and Therapeutics*; Shugar, D., Ed.; Pergamon: Oxford, 1979; 6, p 427.
6. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; Clair, M. H.; Lehraman, S. N.; Gallo, C.; Bolognesi, D.; Barry, D. W.; Boder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
7. Fischl, M. A.; Richman, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberdin, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King, D. N. *Eng. J. Med.* **1987**, *317*, 185.
8. Griengl, H.; Bodenteich, M.; Hayden, W.; Wanek, E.; Steicher, W.; Stutz, P.; Bachmayer, H.; Ghazzouli, I.; Rosenwirth, B. *J. Med. Chem.* **1985**, *28*, 1679.
9. Botta, M.; Occhionero, F.; Nicoletti, R.; Mastromarino, P.; Conti, C.; Margini, M. *Saladino. Bioorg. Med. Chem.* **1999**, *7*, 1925.
10. Boyd, H. F.; Fell, S. C. M.; Hickey, D. M. B.; Ife, R. J.; Leach, C. A.; Macphee, C. H.; Milliner, K. J.; Pinto, I. L.; Rawlings, D. A.; Smith, S. A.; Stansfield, I. G.; Stanway, S. J.; Theobald, C. J.; Whittaker, C. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 51.
11. Kawahara, N.; Nakajima, T.; Itoh, T.; Ogura, H. *Chem. Pharm. Bull.* **1985**, *33*, 4740.
12. (a) Majumdar, K. C.; Das, U. *J. Chem. Res. (S)* **1997**, 309; (b) Majumdar, K. C.; Das, U. *Synth. Commun.* **1997**, *27*, 4013.
13. (a) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471; (b) Sharma, A. K.; Jayakumar, S.; Hundal, M. S.; Mahajan, M. P. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 774–784, and references cited therein.
14. *Compound* **3d**: Mp 160–161 °C; IR (KBr) v_{max}; 2120, 1690 cm^{-1}; δ_H (200 MHz): 2.35 (t, 1H, $J = 2.6$ acetylenic); 3.57–3.84 (dABq, 2H, $J_1 = 2.6$ Hz, $J_2 = 16.9$ Hz); 3.86 (s, 3H, $-OCH_3$); 6.87–6.91 (d, 2H, $J = 8.6$ Hz, ArH); 7.09–7.13 (d, 2H, $J = 8.6$ Hz, ArH); 7.15–7.29 (m, 5H, ArH); 8.29 (s, 1H, -olefinic); δ_c: 24.3 ($-CH_2$); 55.0 ($-OCH_3$); 115.2, 120.7, 123.5, 124.7, 127.5, 128.9, 129.0, 129.5, 130.3, 133.4, 150.3, 155.7, 157.8, 159.1: m/z 348 (M^+). Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94%; H, 4.63%; N, 8.04%. Found: C, 68.72%; H, 4.70%; N, 8.20%.
15. *Compound* **4d**: Mp 220–221 °C; IR (KBr) v_{max}; 1680 cm^{-1}; δ_H (200 MHz): 2.64 (s, 3H, $-CH_3$); 3.74 (s, 3H, $-OCH_3$); 6.74–6.78 (d, 2H, $J = 8.8$ Hz, ArH); 6.97–7.02 (d, 2H, $J = 8.8$ Hz, ArH); 7.05–7.33 (m, 6H, ArH); δ_c: 16.7 ($-CH_3$); 55.2 ($-OCH_3$); 114.1, 120.8, 123.5, 127.9, 128.9, 129.0, 129.9, 130.1, 135.5, 150.2, 156.6, 157.0, 157.8, 159.1: m/z 348 (M^+). Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94%; H, 4.63%; N, 8.04%. Found: C, 68.73%; H, 4.73%; N, 8.19%.
16. Majumdar, K. C.; Ghosh, M.; Jana, M.; Saha, D. *Tetrahedron Lett.* **2002**, *43*, 2111.
17. Majumdar, K. C.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 2115.