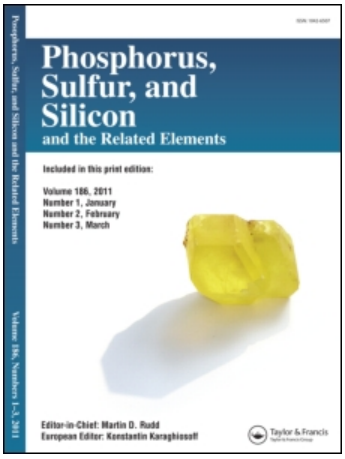


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Some New 3-Oxo-2-[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]-and *N*-Acetylated Pyrimidines

A. Mobinikhaledi[a]; N. Foroughifar[a]; J. Alipour Safari[a]; T. Mosleh[a]
[a] Department of Chemistry, University of Arak, Arak, Iran

To cite this Article Mobinikhaledi, A. , Foroughifar, N. , Safari, J. Alipour and Mosleh, T.(2007) 'Synthesis of Some New 3-Oxo-2-[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]-and *N*-Acetylated Pyrimidines', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 10, 2329 — 2335
To link to this Article: DOI: 10.1080/10426500701441457
URL: http://dx.doi.org/10.1080/10426500701441457

Phosphorus, Sulfur, and Silicon, 182:2329–2335, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701441457

Taylor & Francis
Taylor & Francis Group

Synthesis of Some New 3-Oxo-2-[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]- and *N*-Acetylated Pyrimidines

A. Mobinikhaledi
N. Foroughifar
J. Alipour Safari
T. Mosleh
Department of Chemistry, University of Arak, Arak, Iran

*3-Oxo-2-[(Z)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*] pyrimidine derivatives **2a–f** were synthesized by the reaction of an appropriate 3,4-dihydro-2(*H*)-pyrimidone **1**, chloroacetic acid, sodium acetate and benzaldehyde. Reaction of **1** with acetic anhydride under heating afforded only 3-N-acetylated 3,4-dihydro-2(H)-pyrimidines **3a–f**. The yields of the products after recrystallization from ethanol were of the order of 60–92 %. IR, ^1H NMR spectroscopy, and elemental analysis were used for the identification of these compounds.*

Keywords Acetyl; carboxylate; phenylmethylidene; pyrimidine; thiazolo

INTRODUCTION

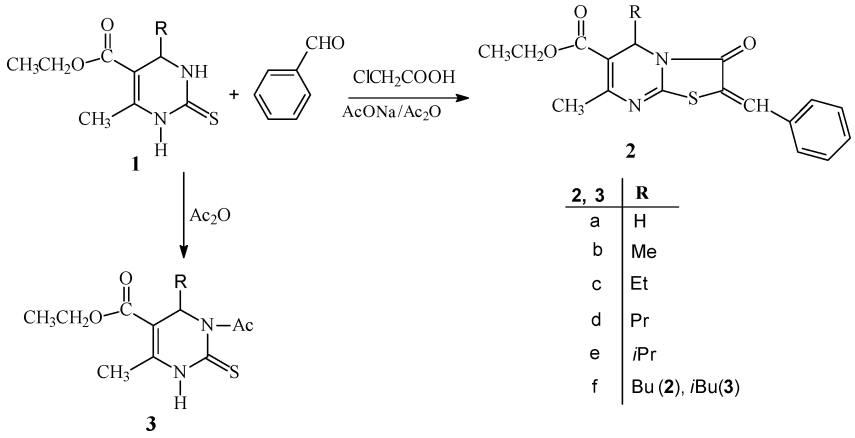
In general, pyrimidines have found much interest for their therapeutic and pharmacological properties.[1–12] They exhibit various interesting pharmacological properties such as antitumor,[3] anticarcinogenic,[4] antiviral,[6] and antifolate activities.[7] Furthermore, several natural marine alkaloids with interesting biological activities contain the dihydropyrimidine-5-carboxylate moiety, which also shows interesting biological properties.[13,14] Some of these alkaloids were found to be potent HIV gp-120-CD4 inhibitors.[15] Several articles report on the synthesis of pyrimidines. The pyrimidine nucleus has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. Various synthetic approaches for the synthesis of pyrimidine derivatives have been reported in the literature.[1,16–22] Due to the versatile biological properties of

Received May 20, 2006; accepted April 27, 2007.
Address correspondence to Akbar Mobinikhaledi, Chemistry Department, Arak University, Dr. Beheshti Avenue, Arak, Iran. E-mail: akbar_mobini@yahoo.com

pyrimidine derivatives and as a continuation of our studies[23] we describe here the synthesis of some new alkyl 3-oxo-2-[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine derivatives, which are prepared in good yields via a cyclocondensation reaction.

RESULTS AND DISCUSSION

The reaction of **1** with chloroacetic acid and benzaldehyde in a solution of anhydrous sodium acetate in dioxane under reflux gave compounds **2a–f**, which contain a thiazole ring (Scheme 1). Two isomeric products may be expected for this reaction. In each case only the *Z*-isomer was obtained, most probably due to the lower sterical interaction between the carbonyl group of thiazole ring and the phenyl ring compared to the *E*-isomer. Reaction of **1** in acetic anhydride alone under reflux yielded the 3-*N*-acylated derivatives **3a–f** as the result of a nucleophilic attack of the nitrogen atom in 3–position at the CO group of Ac_2O.



SCHEME 1

In the synthesis of oxothiazolopyrimidines and *N*-acetylated pyrimidines, two isomeric products may be expected resulting from the nucleophilic attack of N-1 and N-3 of the starting pyrimidine **1**. It is well known, that the N-3 position in the pyrimidines **1** is more reactive towards electrophiles than the N-1 position, which is conjugated with the ester group in 5-position of the pyrimidine ring.[24,25] Also, the low field shift of the pyrimidine proton(s) in the 3-oxothiazolopyrimidines **2a–f** and in the *N*-acetylated 3,4-dihydro-2(*H*)-pyrimidines **3a–f** compared to that of the starting material, is a good support of the nucleophilic attack of the nitrogen atom at N-3 position. The low field shift (more

than 1 ppm) of the pyrimidine proton(s) in these products is due to a deshielding effect of the neighboring carbonyl group.

The ^{1}H NMR spectra of the compounds are consistent with their structures. For example, in the ^{1}H NMR spectrum of **2a** the two singlets at 2.43 and 7.85 ppm are due to resonances of the pyrimidine and vinyl protons, respectively. The triplet at 1.34 ppm and the quartet at 4.28 ppm are attributed to the resonances of the CH_2 and CH_3 protons of the ester group, respectively. The resonance of the aromatic protons appears at 7.56 ppm as a multiplet. The absence of one or both NH protons in the ^{1}H NMR spectra of **3a–f** and **2a–f,** respectively compared to the spectra of the staring materials is a good support of the observed reactions.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus Mettler Toledo Type FP62. ^{1}H NMR spectra were recorded with a Bruker Avance (300 MHz) spectrometer. The IR spectra were recorded on Unicom Galaxy series FT-IR 5000 spectrometer. Microanalyses were performed by the Microanalytical Lab at the Arak petrochemical company. Reactions were monitored by thin layer chromatography using silica gel F_{254} aluminum sheets (Merck).

Synthesis of 2a–f: General Procedure

A mixture of the corresponding pyrimidine derivative **1** (1.25 mmol) prepared according to the procedures described in the literature,[19–21] benzaldehyde (1.25 mmol), chloroacetic acid (1.25 mmol) and anhydrous sodium acetate (1.25 mmol) in dioxane (5 mL) was refluxed for 3–5 h. The crude product was dissolved in boiling ethanol and filtered. From the resulting solution yellow crystals of **2a–f** separated after 12 h, which were collected by filtration.

Synthesis of 3a–f: General Procedure

A mixture of the respective pyrimidine derivative **1** (1.25 mmol), acetic anhydride (10.0 mmol), and glacial acetic acid (10.0 mmol) in DMF (5 mL) was refluxed for 12–14 h. The reaction mixture was poured in 10 mL of ice-cooled water. The precipitate was separated by filtration and recrystallized from ethanol to give the white pure compounds **3a–f**.

Ethyl 7-Methyl-3-oxo-2-[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6(3*H*)-carboxylate (2a)

Yield 266.5 mg, 65%; m.p. 186–188°C; IR (KBr): $\upsilon = 3110, 2960, 1709, 1626, 1559\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.34$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.28 (q, $J = 7.1$ Hz, 2H, CH_2), 4.57 (d, $J = 1.6$ Hz, 2H, CH_2), 7.56 (m, 5H, arom-H), 7.85 (s, 1H, vinylic-H); Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.98; N, 8.53%. Found: C, 62.10; H, 4.98; N, 8.65%.

Ethyl 5,7-Dimethyl-3-oxo-2[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6(3*H*)-carboxylate (2b)

Yield 256.5 mg, 60%; m.p. 135–137°C; IR (KBr): $\upsilon = 3050, 2950, 1709, 1608, 1548\ cm^{-1}$; ^1H NMR (CD_3COCD_3): $\delta = 1.33$ (m, 6H, CH_3), 2.43 (s, 3H, CH_3), 4.28 (m, 2H, CH_2), 5.35 (q, $J = 5.4$ Hz, 1H, CH), 7.51 (m, 5H, arom-H), 7.86 (s, 1H, vinylic-H); Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18%. Found: C, 63.31; H, 5.45; N, 8.41%.

Ethyl 5-Ethyl-7-methyl-3-oxo-2[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6(3*H*)-carboxylate (2c)

Yield 311.5 mg, 70%; m.p. 120–122°C; IR (KBr): $\nu = 3050, 2976, 1720, 1714, 1604, 1548\ cm^{-1}$; ^1H NMR: (CD_3COCD_3): $\delta = 0.80$ (t, $J = 7.5$ Hz, 3H, CH_3), 1.32 (t, $J = 7.1$ Hz, 3H, CH_3), 1.33 (m, 1H, CH_2), 1.92 (m, 1H, CH_2), 2.37 (s, 3H, CH_3), 4.24 (m, 2H, CH_2), 5.34 (t, $J = 3.8$ Hz, 1H, CH), 7.61 (m, 5H, arom-H), 7.87 (s, 1H, vinylic-H); Anal. Calcd. for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86%. Found: C, 64.31; H, 5.49; N, 7.66%.

Ethyl 7-Methyl-3-oxo-2-[(*Z*)-1-phenylmethylidene]-5-propyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6(3*H*)-carboxylate (2d)

Yield 346.9 mg, 75%; m.p. 107–109°C; IR (KBr): $\nu = 3034, 2953, 1709, 1604, 1537\ cm^{-1}$; ^1H NMR: ($CDCl_3$): $\delta = 0.89$ (t, $J = 7.3$ Hz, 3H, CH_3), 1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 1.72 (m, 4H, CH_2), 2.47 (s, 3H, CH_3), 4.30 (m, 2H, CH_2), 5.46 (t, $J = 4.5$ Hz, 1H, CH), 7.61 (m, 5H, arom-H), 7.92 (s, 1H, vinylic-H); Anal. Calcd. for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56%. Found: C, 64.96; H, 5.71; N, 7.81%.

Ethyl 5-Isopropyl-7-methyl-3-oxo-2[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidine-6(3*H*)-carboxylate (2e)

Yield 277.5 mg, 60%; m.p. 137–139°C; IR (KBr): ν =3060, 2980, 1710, 1697, 1599, 1543 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 0.75$ (d, $J = 6.9$ Hz, 3H, CH_3), 0.79 (d, $J = 6.9$ Hz, 3H, CH_3), 1.26 (t, $J = 7.1$ Hz, 3H, CH_3), 1.94 (m, 1H, CH), 2.30 (s, 3H, CH_3), 4.19 (m, 2H, CH_2), 5.18 (d, $J = 3.2$ Hz, 1H, CH), 7.59 (m, 5H, arom-H), 7.91 (s, 1H, vinylic-H); Anal. Calcd-for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56%. Found: C, 64.89; H, 5.65; N, 7.69%.

Ethyl 5-Butyl-7-methyl-3-oxo-2[(*Z*)-1-phenylmethylidene]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6(3*H*)-carboxylate (2f)

Yield 268.8 mg, 56%; m.p. 97–99°C; IR (KBr): $\nu = 3060$, 2986, 1710, 1703, 1619, 1548 cm^{-1}; ^1H NMR (CD_3COCD_3): $\delta = 0.84$ (t, $J = 7.1$ Hz, 3H, CH_3), 1.31 (m, 9H, CH_3, CH_2), 2.36 (s, 3H, CH_3), 4.25 (m, 2H, CH_2), 5.34 (t, $J = 2.8$ Hz, 1H, CH), 7.62 (m, 5H, arom-H), 7.87 (s, 1H, vinylic-H); Anal. Calcd. for $C_{21}H_{24}N_2O_3S$: C, 65.60; H, 6.29; N, 7.29%. Found: C, 65.39; H, 5.91; N, 7.36%.

Ethyl 3-Acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (3a)

Yield 260.2 mg, 86%; m.p. 134–136°C; IR (KBr): $\nu = 3203$, 3148, 2984, 1710, 1658, 1512 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.32$ (t, $J = 7.1$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.23 (q, $J = 7.1$ Hz, 2H, CH_2), 4.54 (s, 2H, CH_2), 8.21 (bs, 1H, NH); Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56%. Found: C, 49.65; H, 5.86; N, 11.34%.

Ethyl 3-Acetyl-4,6-dimethyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (3b)

Yield 294.5 mg, 92%; m.p. 179–181°C; IR (KBr): $\nu = 3180$, 3134, 2972, 1709, 1649 cm^{-1}; ^1H NMR (CD_3COCD_3): $\delta = 1.18$ (d, $J = 6.6$ Hz, 3H, CH_3), 1.29 (t, $J = 7.1$ Hz, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.21 (m, 2H, CH_2), 5.39 (q, $J = 6.6$ Hz, 1H, CH), 10.26 (bs, 1H, NH); Anal. Calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93%. Found: C, 51.41; H, 6.43; N, 11.18%.

Ethyl 3-Acetyl-4-ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (3c)

Yield 310.5 mg, 92%; m.p. 140–142°C; IR (KBr): $\nu = 3234, 3153, 2960, 1710, 1668, 1518\ cm^{-1}$; ^1H NMR (CD_3COCD_3): $\delta = 0.87$ (t, $J = 7.5$ Hz, 3H, CH_3) 1.27 (t, $J = 5.9$ Hz, 3H, CH_3), 1.59 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.20 (m, 2H, CH_2), 5.45 (t, $J = 6.4$ Hz, 1H, CH), 10.31 (bs, 1H, NH); Anal. Calcd. for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36%. Found: C, 53.08; H, 6.50; N, 10.49%.

Ethyl 3-Acetyl-6-methyl-4-propyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (3d)

Yield 312.5 mg, 88%; m.p. 118–120°C; IR (KBr): $\nu = 3190, 3140, 2980, 1707, 1653, 1516\ cm^{-1}$; ^1H NMR (DMSO-d_6): $\delta = 0.84$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.17–1.41 (m, 7H, CH_3, CH_2), 2.25 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.12 (m, 2H, CH_2), 5.36 (t, $J = 6.9$ Hz, 1H, CH), 11.63 (bs, 1H, NH); Anal. Calcd. for $C_{13}H_{20}N_2O_3S$: C, 54.91; H, 7.09; N, 9.85%. Found: C, 55.11; H, 7.20; N, 9.93%.

Ethyl 3-Acetyl-4-isopropyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (3e)

Yield 287.5 mg, 81%; m.p. 176–178°C; IR (KBr): $\nu = 3188, 3146, 2995, 1709, 1651, 1516\ cm^{-1}$; ^1H NMR (CD_3COCD_3): $\delta = 0.86$ (d, $J = 3.9$ Hz, 3H, CH_3), 0.87 (d, $J = 3.9$ Hz, 3H, CH_3), 1.29 (t, $J = 7.1$ Hz, 3H, CH_3), 1.84 (m, 1H, CH), 2.07 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.20 (m, 2H, CH_2), 5.39 (d, $J = 9.3$ Hz, 1H, CH), 10.49 (bs, 1H, NH); Anal. Calcd. for $C_{13}H_{20}N_2O_3S$: C, 54.91; H, 7.09; N, 9.85%. Found: C, 55.23; H, 7.31; N, 9.71%.

Ethyl 3-Acetyl-4-isobutyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (3f)

Yield 272.0 mg, 80%; m.p. 128–130°C; IR (KBr): $\nu = 3209, 3157, 2986, 1710, 1660, 1520\ cm^{-1}$; ^1H NMR (CD_3COCD_3): $\delta = 0.91$ (d, $J = 5.7$ Hz, 3H, CH_3), 0.97 (d, $J = 6.4$ Hz, 3H, CH_3), 1.27–1.32 (m, 6H, CH_3, CH_2, CH), 2.38 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.21 (m, 2H, CH_2), 5.64 (t, $J = 5.6$ Hz, 1H, CH), 10.48 (bs, 1H, NH); Anal. Calcd. for $C_{14}H_{22}N_2O_3S$: C, 56.35; H, 7.43; N, 9.39%. Found: C, 56.89; H, 7.52; N, 9.15%.

REFERENCES

[1] C. O. Kappe, *Tetrahedron*, **49,** 6937 (1993).
[2] R. S. Varma, *Green Chem*., **43,** (1999).
[3] P. G. Baraldi, M. G. Pavani, M. Nunez, P. Brigidi, B. Vitali, R. Gambari, and R. Romagnoli, *Bioorg. Med. Chem.*, **10,** 449 (2002).
[4] S. M. Sondhi, M. Johar, S. Rajvanshi, S. G. Dastidar, R. Shukla, R. Raghubir, and J. W. Lown, *Aust. J. Chem.*, **54,** 69 (2001).
[5] A. Kumar, S. Sinhah, and M. S. Chauhan,*Bioorg. Med. Chem. Lett*., **12,** 667 (2002).
[6] M. N. Nasr and M. M. Gineinah, *Arch. Pharm.,* **335,** 289 (2002).
[7] A. Gangjee, A. Vidwans, E. Elzein, J. J. Mc Guire, S. F. Queener, and R. L. Kisliuk, *J. Med*. *Chem*., **44,** 1993 (2001).
[8] C. O. Kappe and F. S. Falsone, *Synlett,* **718,** (1998).
[9] G. J. Grover, S. Dzwonczyk, D. M. McMullen, C. S. Normadinam, P. G. Sleph, and S. J. Moreland, *Cardiovasc*. *Pharmacol*., **26,** 289 (1995).
[10] N. Foroughifar; A. Mobinikhaledi, S. M. Shariatzadeh, and M. Masoudnia, *Asian J. Chem.*, **14,** 782 (2002).
[11] M. M. Ghorba, Y. A. Mohamed, S. A. Mohamed, and Y. A. Ammar. *Phosphorus*, *Sulfur*, *and Silicon*, **108,** 249 (1996).
[12] K. Tsuji and H. Ishikawa, *Bioorg. Med. Chem. Lett.*, **4,** 1601 (1994).
[13] L. E. Overman, M. H. Rabinowitz, and P. A. Renhowe,*J. Am. Chem*. *Soc.*, **117,** 1657 (1995).
[14] B. B. Snider and Z. Shi, *J. Org. Chem.*, **58,** 3828 (1993).
[15] B. B. Snider, J. Chen, A. D. Patil, and A. Freyer, *Tetrahedron Lett.*, **37,** 6977 (1996).
[16] P. Biginelli, *Gazz. Chim, Ital*., **23,** 360 (1893).
[17] C. O. Kappe and P. Rochger, *J. Heterocycl. Chem*., **26,** 55 (1989).
[18] H. Lin, J. Ding, X. Chen, and Z. Zhang, *Molecules*, **5,** 1240 (2000).
[19] N. Foroughifar, A. Mobinikhaledi, and H. Fathinejad Jirandehi, *Phosphorus, Sulfur, and Silicon*, **178,** 495 (2003).
[20] N. Foroughifar, A. Mobinikhaledi, and H. Fathinejad Jirandehi, *Phosphorus, Sulfur, and Silicon,* **178,** 1241 (2003).
[21] N. Foroughifar, A. Mobinikhaledi, and H. Fathinejad Jirandehi, *Phosphorus, Sulfur, and Silicon,* **178,** 1269 (2003).
[22] A. D. Shutalev, E. A. Kishko, N. Sivova, and A. Y. Kuznetsov, *Molecules*, **3,** 100 (1989).
[23] M. Amrollahi, A. Mobinikhaled, and N. Foroughifar, *Asian J. Chem.*, **17,** 902 (2005).
[24] N. Foroughifar, A. Mobinikhaledi, and F. Goodarzi, *Phosphorus, Sulfur, and Silicon,* **178,** 2539 (2003).
[25] A. Mobinikhaledi, N. Foroughifar, and F. B. Ahmadi, *Phosphorus, Sulfur, and Silicon,* **180,** 339 (2005).