RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2017, **7**, 38830

Free-radical initiated cascade methylation or trideuteromethylation of isocyanides with dimethyl sulfoxides†

Rui Zhang,‡[a] Xiaoqian Shi,‡[a] Qinqin Yan,[a] Zejiang Li,*[ab] Zheng Wang,[a] Haifei Yu,[a] Xiaoke Wang,[a] Jing Qi*[a] and Menglu Jiang[a]

Received 1st August 2017
Accepted 3rd August 2017

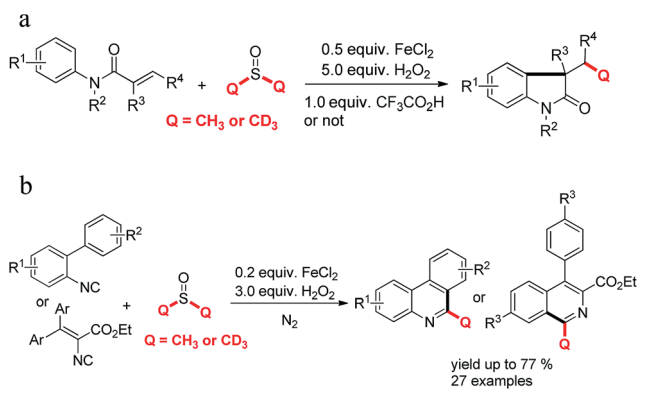
DOI: 10.1039/c7ra08484f

rsc.li/rsc-advances

The methylation or trideuteromethylation reaction of isocyanides with dimethyl sulfoxides in a radical way is developed, which offers a low-cost, easy-operation cascade methylation strategy for the synthesis of phenanthridines or isoquinolines.

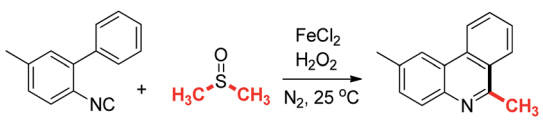
The introduction of methyl or trideuteromethyl groups into organic compounds could affect their biological and chemical properties.[1] Methylation reactions have been widely applied in synthetic organic chemistry.[2] Among them methyl metal reagents,[3] MeI,[4] DMSO,[5] MeCOOH,[6] peroxides[7] *etc.* are usually used as methylating reagents to complete the corresponding reactions. Meanwhile, deuterated iodomethane,[8] deuterated reducing reagents[9] or d^6-DMSO[10] are selected as deuterated methyl sources to develop trideuteromethylation reactions. Although considerable numbers of methods have been developed, more economic and practical methylation or trideuteromethylation strategies are highly desirable.

The preparation of phenanthridines or isoquinolines have been considered as a study topic recently.[11,12] The methyl substituted phenanthridines which were produced by biphenyl isocyanides reacting with peroxides or methyl hydrazine have been developed by Liu,[7] Mao[13] and Cheng,[14] *et al.* Antonchick[15] and our group[16] reported a cascade



Scheme 1 (a) Methylation or trideuteromethylation of *N*-arylacrylamides with dimethyl sulfoxides (previous work). (b) Methylation or trideuteromethylation of isocyanides with dimethyl sulfoxides (this work).

Table 1 Modification of the typical reaction conditions[a]



Entry	Iron(II) chloride (equiv.)	Hydrogen peroxide (30%), (equiv.)	*t*/h	Yield[b] (%)
1	0.5	3	3	52
2	0.5	3	6	55
3	0.5	3	10	52
4[c]	0.5	3	6	30
5[d]	0.5	3	6	40
6[e]	0.5	3	6	50
7	—	3	6	n.r.
8	0.1	3	6	63
9	**0.2**	**3**	**6**	**70**
10	0.3	3	6	55
11	0.4	3	6	55
12	0.2	1	6	20
13	0.2	2	6	36
14	0.2	4	6	56
15[f]	0.2	3	6	60

[a] Reaction conditions: 2-isocyano-5-methyl-1,1′-biphenyl (1 equiv., 0.25 mmol), DMSO (3 mL), 25 °C, N_2. [b] Isolated yields. [c] DMSO (1 mL). [d] DMSO (2 mL). [e] DMSO (4 mL). [f] 50 °C.

[a]*College of Chemistry & Environmental Science, Hebei University, Baoding, Hebei, 071002, P. R. China. E-mail: lizejiang898@126.com; qijinghbu2013@126.com*

[b]*Key Laboratory of Medicinal Chemistry and Molecular Diagnosis of Ministry of Education, Baoding, Hebei, 071002, P. R. China*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra08484f

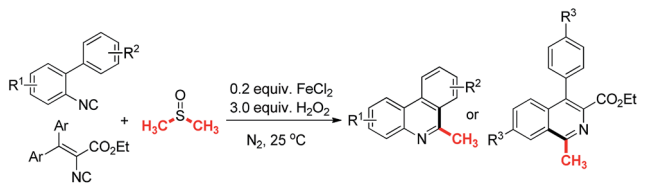
‡ These authors contributed equally.

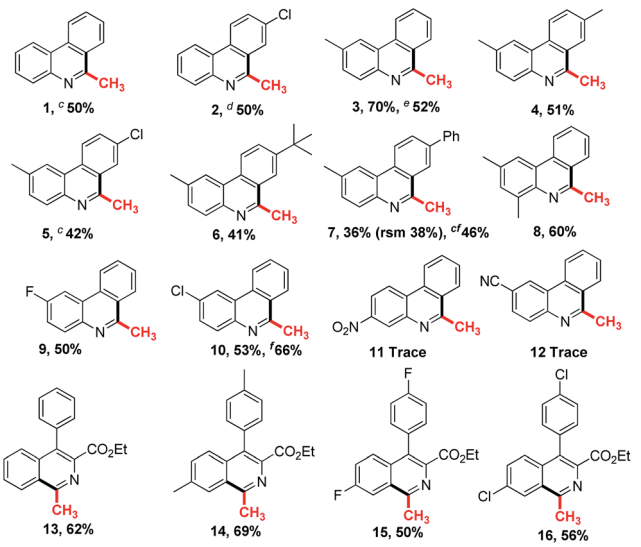
trideuteromethylation or methylation reaction of *N*-arylacrylamides with dimethyl sulfoxides respectively (Scheme 1a). However, a free radical cascade methylation or trideuteromethylation of isocyanides with dimethyl sulfoxides under analogous Fenton reaction condition was not finished now (Scheme 1b).[17] Combined with our previous study,[18] we wish to accomplish this reaction system.

Initially, 2-isocyano-5-methyl-1,1′-biphenyl and dimethyl sulfoxide were selected as model substrates to optimize the reaction systems (Table 1, also see ESI for detail†). It was shown that the yield of the final product in 6 hour is better than that in 3 and 10 hour (entries 1–3). Adding 1 mL, 2 mL and 4 mL of dimethyl sulfoxide gained the product in 30%, 40%, 50% yields, respectively (entries 4–6). No reaction was found without any iron salts (entry 7). Variation of the amount of iron(II) chloride and hydrogen peroxide greatly affected reaction efficiency (entries 8–14). Higher temperature slightly reduced reaction yield (entry 15). Finally, 2,6-dimethylphenanthridine was isolated in 70% yield under the optimum conditions: isonitriles (1 equiv., 0.25 mmol), $FeCl_2$ (0.2 equiv., 0.05 mmol), H_2O_2 (30%, 3 equiv., 0.75 mmol) and DMSO (3 mL), 25 °C, N_2, 6 h, sealed tube.

To investigate the substrate scope, a variety of isocyanides were prepared and tested in Table 2. As can be seen, many

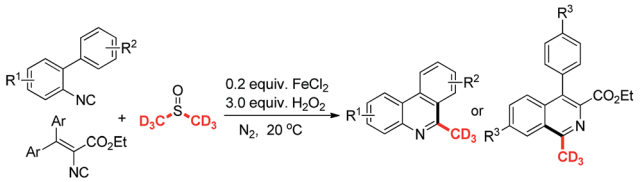
Table 2 Iron-promoted free radical cascade methylation of isocyanides with dimethyl sulfoxide

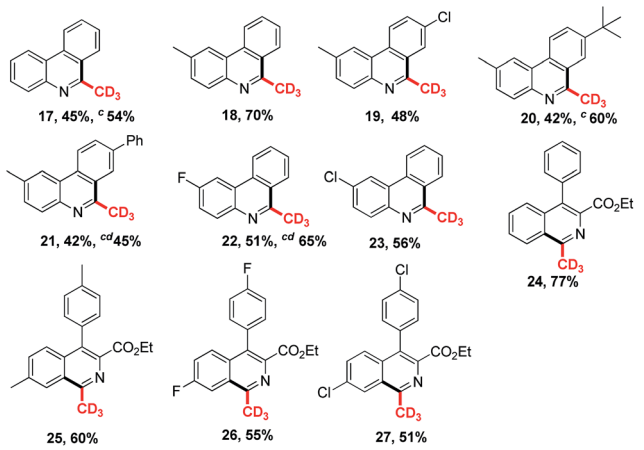




[a] Reaction conditions: isocyanide (1 equiv., 0.25 mmol), iron(II) chloride (0.2 equiv., 0.05 mmol), hydrogen peroxide (30%, 3 equiv., 0.75 mmol), DMSO (3 mL), 25 °C, N_2, 6 h. [b] Isolated yields. [c] 10 h. [d] 21 h. [e] Isocyanide (1 equiv., 5.20 mmol, 1.0 g). [f] Adding 1 equiv. K_2CO_3 in the system.

Table 3 Iron-promoted free radical cascade trideuteromethylation of isocyanides with deuterated dimethyl sulfoxide

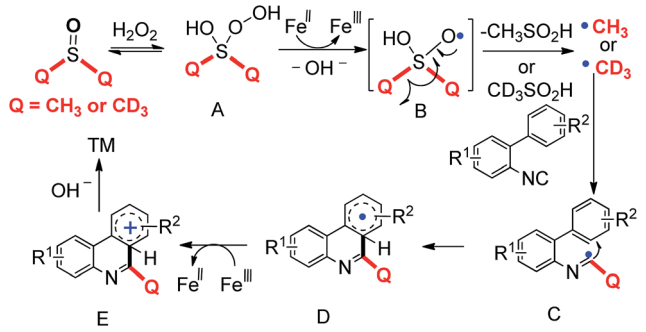




[a] Reaction conditions: 2-isocyano-5-methyl-1,1′-biphenyl (1 equiv., 0.25 mmol), DMSO-d^6 (1 mL), 20 °C, N_2, 12 h. [b] Isolated yields. [c] Adding 1 equiv. K_2CO_3 in the system. [d] 21 h.

functional groups substituted substrates could react well in this reaction system (1–10). Halogen atoms such as F, Cl substituted isocyanides gave the corresponding products in moderate yields, respectively (2, 5, 9–10). The substrates with large groups such as *t*-butyl and phenyl on 4′-position of the aromatic ring obtained the product 6 and 7 in 41% and 36% yields, which indicate that the steric effect is slightly obvious. The products 7 and 10 were isolated in 46% and 66% yields respectively by adding potassium carbonate in the system. It indicates potassium carbonate could weaken the impact on the yields of final products from methylsulfinyl acid as the side product. The electronic effect also influences the reaction yields, and the raw material with electron-withdrawing group such as nitro, cyano could not result the desirable product (11–12). And vinyl isocyanides gained the desired isoquinolines in 50–69% yields (13–16). Notably, the product 3 was isolated in 52% yield, when the reaction system was scaled up to the gram level.

As can be seen in Table 3, diverse aryl isocyanides could react well with deuterated dimethyl sulfoxide in the typical condition (17–23). The halogen atoms such as F, Cl were tolerant in the system and gave the corresponding products in good yields (19, 22, 23). The *t*-butyl and phenyl substituted substrates obtained the product 20 and 21 both in 42% yields. Notably, the products 17, 20, 21 and 22 gave better yields by adding the base in the system under typical conditions. And vinyl isocyanides produced the trideuteromethyl substituted isoquinolines in 51–77% yields (24–27).



Scheme 2 Plausible mechanism.

No reaction was deuterated when TEMPO was added to the reaction system, which suggests the reaction would be in process through a free radical way. According to the precedent literature[15,16,19] and experimental study, we design a possible mechanism in Scheme 2. First, dimethyl sulfoxide or deuterated dimethyl sulfoxide reacts with hydrogen peroxide and generates the intermediate **A**. With the induction of iron(II) chloride, free radical **B** and hydroxyl ion are produced by intermediate **A** occurring heterolysis reaction. Radical **B** gives methyl radical or trideuteromethyl radical along with methylsulfinyl acid or detected methylsulfinyl acid produced in the process of β-cleavage reaction. Next, radical **C** is formed from adding methyl radical or trideuteromethyl radical to the isocyanides. Then, radical **C** adds to the aromatic ring and generates radical **D**. Radical **D** can be oxidized by iron and yields the carbocation **E**, which is pulled the proton by hydroxyl ion and gains the terminal product.

In summary, we have accomplished a free radical triggered cascade methylation or trideuteromethylation/cyclization reaction of isocyanides with dimethyl sulfoxides. It offers an economical and convenient protocol for preparing phenanthridines or isoquinolines. Further studies on cyclization reactions in a novel free radical way are ongoing in our laboratory.

Acknowledgements

This project is supported by the Natural Science Foundation of Hebei Province (B2017201043), the Fundamental Research Funds for The Midwest Universities Comprehensive Strength Promotion Project, Key Laboratory of Medicinal Chemistry and Molecular Diagnosis of Ministry of Education, Key Laboratory of Chemical Biology of Hebei Province and College of Chemistry & Environmental Science, Hebei University.

Notes and references

1 (*a*) E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga, *Chem. Rev.*, 2011, **111**, 5215; (*b*) T. G. Gant, *J. Med. Chem.*, 2014, **57**, 3595; (*c*) I. Kheterpal and R. Wetzel, *Acc. Chem. Res.*, 2006, **39**, 584; (*d*) I. Lee, *Chem. Soc. Rev.*, 1995, **24**, 223.

2 H. Schönherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256.

3 (*a*) R. Giri, N. Maugel, J. Li, D. Wang, S. P. Breazzano, L. B. Saunders and J.-Q. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3510; (*b*) J. A. Romero-Revilla, A. Garcia-Rubia, R. G. Arrayas, M. A. Fernandez-Ibanez and J. C. Carretero, *J. Org. Chem.*, 2011, **76**, 9525; (*c*) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7222; (*d*) X. Chen, J. Li, X. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 78; (*e*) S. R. Neufeldt, C. K. Seigerman and M. S. Sanford, *Org. Lett.*, 2013, **15**, 2302; (*f*) Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, *Org. Lett.*, 2011, **13**, 3232.

4 (*a*) L. Barsky, H. W. Gschwend, J. McKenna and H. R. Rodriguez, *J. Org. Chem.*, 1976, **41**, 3651; (*b*) S. J. Tremont and H. U. Rahman, *J. Am. Chem. Soc.*, 1984, **106**, 5759; (*c*) Z. Zhao and G. Chen, *Org. Lett.*, 2011, **13**, 4850; (*d*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788.

5 B. Yao, R.-J. Song, Y. Liu, Y.-X. Xie, J.-H. Li, M.-K. Wang, R.-Y. Tang, X.-G. Zhang and C.-L. Deng, *Adv. Synth. Catal.*, 2012, **354**, 1890.

6 F. Pan, Z.-Q. Lei, H. Wang, H. Li, J. Sun and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 2063.

7 Z. Xu, C. Yan and Z.-Q. Liu, *Org. Lett.*, 2014, **16**, 5670.

8 (*a*) S. Komarapuri, K. Krishnan and D. F. Covey, *J. Labelled Compd. Radiopharm.*, 2008, **51**, 430; (*b*) R. G. Gillis, *Tetrahedron Lett.*, 1968, **9**, 1413.

9 For selected reviews, see: (*a*) J. H. Gui, Q. H. Zhou, C. M. Pan, Y. Yabe, A. C. Burns, M. R. Collins, M. A. Ornelas, Y. Ishihara and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 4853; (*b*) V. A. Khripach, V. N. Zhabinskii, A. P. Antonchick, O. V. Konstantinova and B. Schneider, *Steroids*, 2002, **67**, 1101; (*c*) M. Adamczyk, J. R. Fishpaugh and D. Johnson, *J. Labelled Compd. Radiopharm.*, 1993, **33**, 153.

10 (*a*) E. Jones-Mensah, M. Karki and J. Magolan, *Synthesis*, 2016, **48**, 1421; (*b*) X. F. Wu and K. Natte, *Adv. Synth. Catal.*, 2016, **358**, 336; (*c*) X. Jiang, C. Wang, Y. W. Wei, D. Xue, Z. T. Liu and J. L. Xiao, *Chem.–Eur. J.*, 2014, **20**, 58; (*d*) K. Kawai, Y. S. Li, M. F. Song and H. Kasai, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 260; (*e*) S. W. Peabody, B. Breiner, S. V. Kovalenko, S. Patil and I. V. Alabugin, *Org. Biomol. Chem.*, 2005, **3**, 218.

11 For selected reviews on phenanthridine, see: (*a*) R. S. Theobald and K. Schofield, *Chem. Rev.*, 1950, **46**, 170; (*b*) S. Simeon, J. L. Rios and A. Villar, *Pharmazie*, 1989, **44**, 593; (*c*) W. K. Brewster, D. E. Nichols, R. M. Riggs, D. M. Mottola, T. W. Lovenberg, M. H. Lewis and R. B. Mailman, *J. Med. Chem.*, 1990, **33**, 1756; (*d*) T. Nakanishi, M. Suzuki, A. Saimoto and T. Kabasawa, *J. Nat. Prod.*, 1999, **62**, 864; (*e*) L. Sripada, J. A. Teske and A. Deiters, *Org. Biomol. Chem.*, 2008, **6**, 263; (*f*) G. Qiu, Q. Ding and J. Wu, *Chem. Soc. Rev.*, 2013, **42**, 5257; (*g*) B. Zhang, C. Mück-Lichtenfeld, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2013, **52**, 10792; (*h*) D. Leifert, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2013, **15**, 6286; (*i*) Q. Wang, X. Dong, T. Xiao and L. Zhou, *Org. Lett.*, 2013, **15**, 4846; (*j*) Y. Cheng, H. Jiang, Y. Zhang and S. Yu, *Org. Lett.*, 2013, **15**, 5520; (*k*) B. Zhang, C. G. Daniliuc and

A. Studer, *Org. Lett.*, 2014, **16**, 250; (*l*) L. Gu, C. Jin, J. Liu, H. Ding and B. Fan, *Chem. Commun.*, 2014, **50**, 4643; (*m*) T.-H. Zhu, S.-Y. Wang, Y.-Q. Tao, T.-Q. Wei and S.-J. Ji, *Org. Lett.*, 2014, **16**, 1260; (*n*) L. Wang, W. Sha, Q. Dai, X. Feng, W. Wu, H. Peng, B. Chen and J. Cheng, *Org. Lett.*, 2014, **16**, 2088; (*o*) J.-J. Cao, T.-H. Zhu, S.-Y. Wang, Z.-Y. Gu, X. Wang and S.-J. Ji, *Chem. Commun.*, 2014, **50**, 6439; (*p*) T. Xiao, L. Li, G. Lin, Q. Wang, P. Zhang, Z.-W. Mao and L. Zhou, *Green Chem.*, 2014, **16**, 2418; (*q*) J. Liu, C. Fan, H. Yin, C. Qin, G. Zhang, X. Zhang, H. Yi and A. Lei, *Chem. Commun.*, 2014, **50**, 2145; (*r*) Z. Xia, J. Huang, Y. He, J. Zhao, J. Lei and Q. Zhu, *Org. Lett.*, 2014, **16**, 2546; (*s*) J. Lei, J. Huang and Q. Zhu, *Org. Biomol. Chem.*, 2016, **14**, 2593; (*t*) B. Zhang and A. Studer, *Chem. Soc. Rev.*, 2015, **44**, 3505; (*u*) B.-R. Song and B. Xu, *Chem. Soc. Rev.*, 2017, **46**, 1103; (*v*) Z.-G. Xie, P.-H. Li, Y. Hu, N. Xu and L. Wang, *Org. Biomol. Chem.*, 2017, **15**, 4205; (*w*) H. Cao, S. Lei, N.-Y. Li, L.-B. Chen, J.-Y. Liu, H.-Y. Cai, S.-X. Qiu and J.-W. Tan, *Chem. Commun.*, 2015, **51**, 1823; (*x*) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang and S. Yu, *Angew. Chem., Int. Ed.*, 2013, **52**, 13289; (*y*) W. Sha, J.-T. Yu, Y. Jiang, H. Yang and J. Cheng, *Chem. Commun.*, 2014, **50**, 9179; (*z*) H.-Y. Tu, Y.-R. Liu, J.-J. Chu, B.-L. Hu and X.-G. Zhang, *J. Org. Chem.*, 2014, **79**, 9907.

12 For selected examples of preparation of isoquinolines and its derivatives, see: (*a*) P. Villuendas and E. P. Urriolabeitia, *J. Org. Chem.*, 2013, **78**, 5254; (*b*) J. Jayakumar, K. Parthasarathy and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 197; (*c*) Y.-F. Wang, K. K. Toh, J.-Y. Lee and S. Chiba, *Angew. Chem., Int. Ed.*, 2011, **50**, 5927; (*d*) P. C. Too, S. H. Chua, S. H. Wong and S. Chiba, *J. Org. Chem.*, 2011, **76**, 6159; (*e*) N. Guimond and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 12050; (*f*) P. C. Too, Y.-F. Wang and S. Chiba, *Org. Lett.*, 2010, **12**, 5688; (*g*) R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Org. Lett.*, 2012, **14**, 3032; (*h*) H. Jiang, Y. Cheng, R. Wang, Y. Zhang and S.-Y. Yu, *Chem. Commun.*, 2014, **50**, 6164.

13 T. Xiao, L. Li, G. Lin, Q. Wang, P. Zhang, Z.-W. Mao and L. Zhou, *Green Chem.*, 2014, **16**, 2418.

14 Q. Dai, J. Yu, X. Feng, Y. Jiang, H. Yang and J. Cheng, *Adv. Synth. Catal.*, 2014, **356**, 3341.

15 R. Caporaso, S. Manna, S. Zinken, A. R. Kochnev, E. R. Lukyanenko, A. V. Kurkin and A. P. Antonchick, *Chem. Commun.*, 2016, **52**, 12486.

16 Z.-J. Li, X. Cui, L. Niu, Y. Ren, M. Bian, X. Yang, B. Yang, Q.-Q. Yan and J. Zhao, *Adv. Synth. Catal.*, 2017, **359**, 246.

17 H. Fenton, *J. Chem. Soc., Trans.*, 1984, **65**, 899.

18 (*a*) Z. J. Li, Y. Zhang, L. Z. Zhang and Z.-Q. Liu, *Org. Lett.*, 2014, **16**, 382; (*b*) Z. J. Li, F. H. Fan, J. Yang and Z.-Q. Liu, *Org. Lett.*, 2014, **16**, 3396; (*c*) L. Z. Zhang, Z. J. Li and Z.-Q. Liu, *Org. Lett.*, 2014, **16**, 3688.

19 K.-U. Schoening, W. Fischer, S. Hauck, A. Dichtl and M. Kuepfert, *J. Org. Chem.*, 2009, **74**, 1567.