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Alternative Solvents for Elevated-Temperature Solid-Phase Parallel Synthesis. Application to Thionation of Amides

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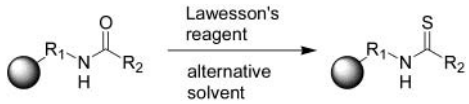
ABSTRACT



A new class of higher-boiling solvents was investigated for elevated-temperature solid-phase parallel synthesis. Extremely low vapor pressures at high temperature and a broader range of solvent effect tuning make this new class of solvents an ideal choice for high-temperature parallel solid-phase synthesis. Benzyl benzoate is identified as a superior high-boiling solvent for parallel solid-phase Lawesson's thionation reactions.

Solid-phase organic synthesis (SPOS) has undergone a transformation from a specialized method for peptide synthesis to a powerful tool for synthetic chemists in all fields of chemistry.[1] An ever-increasing number of chemical reactions have been demonstrated in parallel with SPOS.[2] One limitation of SPOS is the need for a large excess of reagents and/or elevated temperatures to increase reaction rates and drive reactions to completion. The number of high-boiling solvents used for traditional organic synthesis is quite limited and all have significant vapor pressure at temperatures over 100 °C. The increasing recognition that polystyrene resins are stable at temperatures in excess of 150 °C will continue to broaden the use of temperature to drive solid-phase reactions.[3]

In our experience, elevated temperatures for SPOS work well on single reactions or small numbers of reactions where the conditions and the apparatus are easy to control. When applied to the parallel synthesis of larger numbers, the vapor pressure of the solvent causes a multitude of problems depending on the equipment utilized. These problems include (1) solvent evaporation, (2) solvent migration, (3) flash point of escaping vapor, (4) leaking of reaction solution and/or reaction vessel failure, and (5) scientist exposure to escaping solvent vapor. Parallel synthesis equipment manufacturers have addressed these problems with varying degrees of success. Due to these factors, chemists often need to develop conditions that avoid elevated temperatures in parallel applications of SPOS, which limits the scope of these reactions.

Typically, SPOS reaction conditions are developed using the conventional solvents that have been routinely used in solution-phase organic synthesis. With SPOS, the reaction solvent is washed away upon completion of the reaction, and we reasoned that a much broader class of compounds should be considered as solvents. As a result a new and very large arsenal of solvents is available for SPOS reaction

(1) For recent reviews see: (a) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 2415−2437. (b) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607−2624. (c) Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61−91. (d) Orain, D.; Ellard, J.; Bradley, M. *J. Comb. Chem.* **2002**, *4*, 1−16. (e) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125−150.

(2) Library synthesis: (a) Dolle, R. E. *J. Comb. Chem.* **2002**, *4*, 369−418. (b) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477−517. (c) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385−15443. (d) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214. (e) Dolle, R. E. *Mol. Diversity* **1998**, *3*, 199−233.

(3) (a) Pérez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 501−510. (b) Ley, S. V.; Leach, A. G.; Storer, R. I. *J. Chem. Soc., Perkin Trans. 1* **2001**, 358−361. (c) Stadler, A.; Kappe, C. O. *Eur. J. Org. Chem.* **2001**, 919−925.

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Table 1. Swelling Properties of Five Resins in Alternative Solvents (Volume in mL/g of resin)

entry	solvent	bp (°C)	mp (°C)	Wang	REM	Merrifield	Rink	Tentagel S AM
1	dichloromethane	40	−97	5.7	5.8	5.8	5.8	5.8
2	toluene	111	−93	4.9	4.3	5.4	5.2	4.3
3	silicon oil	>250		2.2	1.6	2.1	2.1	2.0
4	corn oil	>250		2.2	1.6	1.6	1.6	2.0
5	diethylene glycol dibutyl ether	256	−60	3.3	3.2	2.2	3.6	2.4
6	diphenylmethane	264	22	5.0	5.2	5.2	4.2	5.3
7	*n*-hexadecane	287	18	1.7	1.6	2.1	1.9	2.0
8	adiponitrile	295	1	1.9	1.7	2.0	3.0	3.9
9	dibenzyl ether	298	2	5.1	4.9	5.1	5.2	4.3
10	*n*-dodecylbenzene	300	−7	1.7	2.0	1.7	2.0	2.1
11	*N*-cyclohexyl-2-pyrrolidone	154 (7 Torr)	12	6.1	1.8	2.2	1.7	2.0
12	benzyl benzoate	323	19	5.1	5.1	3.5	6.4	5.0
13	1-phenylnaphthalene	325	19	1.8	1.7	1.8	1.7	2.0
14	*N*-benzyl-2-pyrrolidone	205 (6 Torr)	0	4.0	1.8	1.9	1.7	2.0
15	light mineral oil	∼360		1.8	1.7	2.0	1.9	1.9
16	4-benzylpyridine	287	9	5.8	4.2	5.1	3.9	5.0
17	4-(3-phenylpropyl)pyridine	322		5.2	4.3	3.0	4.3	3.6
18	tris[2-(2-methoxyethoxy)ethyl]amine	330	0	5.0	4.2	5.0	5.0	2.5
19	tri-*N*-octylamine	366	−35	2.0	2.0	2.2	2.0	1.8

development and clearly would provide a unique level of solvent effect fine-tuning for both room-temperature and elevated-temperature reactions.[4] This study focuses on low-vapor pressure nonstandard solvents for elevated-temperature parallel SPOS.

We chose "solvents" based on the following criteria: (1) vapor pressure less than 0.01 mmHg at 25 °C, (2) boiling point greater than 250 °C, (3) low chemical reactivity, (4) good thermal stability, (5) melting point less than 25 °C, (6) resin swelling ability, (7) health hazard, (8) disposal issues, (9) viscosity, and (10) cost. NFPA hazard classification and toxicity data obtained from the solvent's MSDS was used to evaluate potential health effects and disposal issues. The chemical stability of each solvent was determined by analysis of the proton NMR spectra after heating at 150 °C under nitrogen for 24 h.

We first examined the swelling ability of several alternative solvents utilizing the protocol previously described (Table 1).[5a] We chose five commonly utilized resins[6] and included dichloromethane and toluene for comparison in our swelling study. Solvents are listed by increasing boiling point with several high-boiling organic bases listed last. As was found earlier,[5] we observed different trends for the swelling with Tentagel resin relative to other resins. Although we observed good swelling of Tentagel resin in adiponitrile (Table 1, entry 8) relative to other resins, we cannot recommend this solvent due to its highly toxic nature. Silicon oil, corn oil, and mineral oil (Table 1, entries 3, 4, and 15) all have poor swelling characteristics; but we have had some preliminary successes with these unusual solvents.[7] 4-(3-Phenylpropyl) pyridine and tris[2-(2-methoxyethoxy)ethyl]-amine are high-boiling bases (Table 1, entries 17 and 18) that display good swelling profiles across all resins, while tri-*N*-octylamine (Table 1, entry 19) has less swelling ability. At elevated temperatures, the swelling ability of a given solvent may be less important due to the increased energy in the system.[4]

Our interest in resin-bound 1,3-dipoles, derived from thioamides, led us to first explore the synthetic usefulness of these solvents with the thionation of resin-bound amides. Lawesson's reagent[8] **1** contains four sulfur atoms, three of which have been shown to exchange with the oxygen of a carboxamide.[8b]

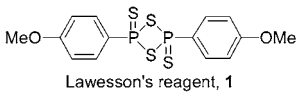
(4) For some discussions of solvent effects, resin kinetics, and resin reaction rates see: (a) Gerritz, S. W.; Trump, R. P.; Zuercher, W. J. *J. Am. Chem. Soc.* **2000**, *122*, 6357−6363. (b) Li, W.; Xiao, X.; Czarnik, A. W. *J. Comb. Chem.* **1999**, *1*, 127−129. (c) Li, W.; Czarnik, A. W.; Lillig, J.; Xiao, X.-Y. *J. Comb. Chem.* **2000**, *2*, 224−227. (d) Merrifield, B. *Br. Polym. J.* **1984**, *16*, 173−178. (e) Li, W.; Yan, B. *J. Org. Chem.* **1998**, *63*, 4092−4097. (f) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R.; Jewell, C. F., Jr.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736−5738. (g) Yan, B.; Fell, J. B.; Kumaravel, G. *J. Org. Chem.* **1996**, *61*, 7467−7472.

(5) (a) Santini, R.; Griffith, M. C.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 8951−8954. (b) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329−6332. (c) Adams, J. H.; Cook, R. M.; Hudson, D.; Jammalamadaka, V.; Lyttle, M. H.; Songster, M. F. *J. Org. Chem.* **1998**, *63*, 3706−3716.

(6) Wang resin, 200−400 mesh, 0.97 mmol/g, Novabiochem catalog no. 01-64-0001; REM resin, 100−200 mesh, 0.84 mmol/g, Novabiochem catalog no. 01-64-0302; Merrifield resin, 100−200 mesh, 1.34 mmol/g, Novabiochem catalog no. 01-64-0104; Rink resin, 100−200 mesh, 0.7 mmol/g, Advanced ChemTech catalog no. SA5030; Tentagel S AM, 0.24 mmol/g, Rapp Polymere catalog no. S30 022

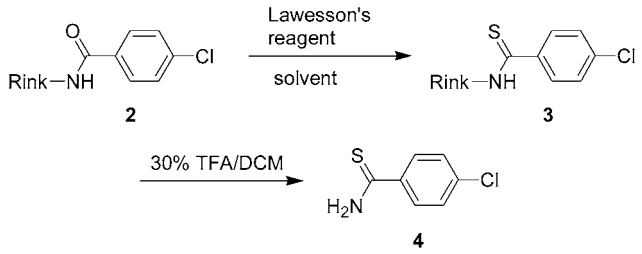
(7) (a) Formation of thiazoles from α-bromo ketones and resin-bound thioamides in silicon oil and mineral oil. (b) Stille reaction with a resin-bound stannane and 4-bromoanisole in silicon oil; comparable yield to NMP. (c) 1,3-Dipolar cycloaddition of a resin-bound alkyne with benzyl azide in silicon oil, mineral oil, Edwards pump oil (ultra grade), and corn oil; yields were comparable to those in toluene.

(8) (a) Pederson, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223−228. (b) Scheibye, S.; Pederson, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229−238. (c) Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S.-O.; Lawesson, S.-O. *Nouv. J. Chim.* **1980**, *4*, 47−51. (d) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061−5087 and references therein.



Lawesson's reagent, **1**

Scheme 1. Preparation of Thioamide **3**



Lawesson found that complete conversion of amides to thioamides in solution-phase reactions was realized when 0.5 mol of **1** was allowed to react with 1.0 mol of amide.[8b] An earlier report of resin-bound amide to thioamide conversion with Lawesson's reagent utilized THF as the solvent and required 4 h at reflux for complete conversion.[9] In addition, this reaction used a 6-fold excess of Lawesson's reagent relative to that necessary in solution.

Our desire to perform this thionation reaction in parallel necessitated our investigation of higher-boiling solvents. Toluene and xylenes have been used as the solvent with Lawesson's reagent in solution, but more electron-deficient amides require long reaction times and temperatures at or near the boiling point of these solvents in order to effect complete conversion.

We chose the relatively electron-rich resin-bound amide **2** (Scheme 1) for our initial studies due to its facile conversion to the corresponding thioamide **3** and because of the stability of solution-phase thioamide **4** to the TFA cleavage conditions. Rink amide resin was converted to Rink 4-chlorobenzamide **2** by reaction with 4-chlorobenzoyl chloride by standard procedures.

Several solvents (Table 2) were studied in order to determine their chemical compatibility with Lawesson's reagent and their effect on conversion to the thioamide **3**.

Initially, we utilized the more forcing conditions of 3 equiv of **1** relative to resin amide **2** and heated the mixtures for 2 h at 65 °C (Table 2, method A).

All reactions could be performed in open vessels except the control reactions in THF and toluene, which were tightly sealed to avoid solvent loss. Reactions were monitored by removal of a small portion of resin that was subjected to a standard DCM/MeOH wash sequence and then cleaved with 30% TFA/DCM (5−10% TFA/DCM solutions provided only partial cleavage of the thioamide **3**).[10] We found that silicon oil, corn oil, mineral oil, and 4-(3-phenylpropyl)pyridine (Table 2, entries 5, 6, 14, and 20) all gave poor results and, in some cases, were clearly substrates for Lawesson's reagent. *n*-Hexadecane and *n*-dodecylbenzene (Table 2, entries 11 and 21) were also poor solvents for this conversion, most likely due to the extremely poor solubility of Lawesson's reagent in these solvents.

Table 2. Effect of Alternative Solvents on Lawesson's Thionation Reaction (Scheme 1)

entry	solvent	method[a]	% conversion[b]
1	THF	A	100
2	THF	B	95
3	toluene	A	100 (88)[c]
4	toluene	B	82
5	silicon oil	A	0
6	corn oil	A	0
7	bis(2-butoxyethyl)ether	A	93
8	bis(2-butoxyethyl)ether	B	60
9	diphenylmethane	A	100
10	diphenylmethane	B	0
11	*n*-hexadecane	A	0
12	dibenzyl ether	A	100
13	dibenzyl ether	B	0
14	mineral oil	A	0
15	benzyl benzoate	A	100 (98)[c]
16	benzyl benzoate	B	91
17	benzyl benzoate	C	100 (99)[d]
18	1-phenylnaphthalene	B	74
19	1-phenylnaphthalene	C	100
20	4-(3-phenylpropyl) pyridine	C	38
21	*n*-dodecylbenzene	A	5

[a] Method A: 3 equiv of **1**, 65 °C, 2 h. Method B: 1 equiv of **1**, 65 °C, 30 min. Method C: 3 equiv of **1**, 115 °C, 5 min. [b] Based on total absorption chromatogram from 190 to 360 nm; % purity was equivalent to % conversion except for entries 9 and 12, which were each 77% pure. [c] Conditions: 3 equiv of **1**, 90 °C, 1 h; isolated yield by flash silica chromatography. [d] Conditions: 1 equiv of **1**, 115 °C, 5 min; isolated yield by flash silica chromatography; cf. ref 12.

The remaining solvents, which were successful in the thionation reaction, were then investigated with 1 equiv of **1** relative to resin amide **2** and heated for 30 min at 65 °C (Table 2, method B). Bis(2-butoxyethyl)ether, diphenylmethane, and dibenzyl ether (Table 2, entries 8, 10, and 13) displayed a much slower rate of conversion with only 1 equiv of Lawesson's reagent. However, we found that benzyl benzoate (entry 16) provided a higher conversion of amide **2** to thioamide **3** compared to toluene (entry 4) and comparable conversions to that observed with THF (entry 2).

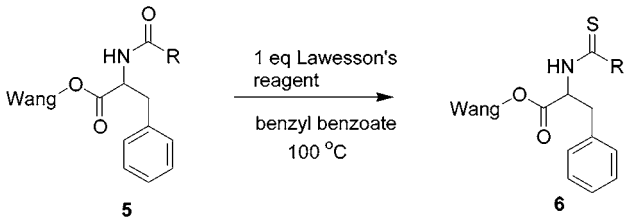
It is interesting to note that conversion to thioamide **3** works almost equally well in 1-phenylnaphthalene (Table 2, entries 18 and 19), which is a poor swelling solvent (Table 1, entry 13).

In subsequent experiments, we found that an open vessel containing the resin-bound amide **2** and Lawesson's reagent in benzyl benzoate heated to 90 °C for 1 h gave a 98% isolated yield of the corresponding thiourea **4** after 30% TFA/DCM cleavage from Rink resin and normal-phase purification (Table 2, entry 15).[11] The same reaction run in toluene at 90 °C for 1 h provided an 88% isolated yield of **3** (entry 3). In fact, similar yields were obtained at 115 °C in benzyl benzoate after 5 min when only 1 equiv of Lawesson's reagent was used (Table 2, entry 17).[12] Proton NMR analysis of the crude thioamide **3** (Table 2, entries 15 and 17) confirmed the HPLC conversions and purities listed in Table

(9) Pons, J. F.; Mishir, Q.; Nouvet, A.; Brookfield, F. *Tetrahedron Lett.* **2000**, *41*, 4965−4968.

(10) Solvents were dispensed without special equipment or requirements. Diphenylmethane was warmed gently before dispensing. In the case of solvents that have higher viscosity, we found it useful to add dichloromethane or another appropriate solvent to the cooled reaction slurry prior to filtration.

Scheme 2. Preparation of Thioamides **6**



2. Thionation reactions performed at 140 °C gave lower isolated yields, presumably due to premature cleavage of the amide from resin.

Although benzyl thionobenzoate could not be detected when the temperature was kept below 120 °C, we were interested in determining if benzyl benzoate could be acting as a sulfur transfer agent in these reactions. Benzyl thionobenzoate was prepared as previously described,[13] and upon exposure of 4-chlorobenzamide Rink resin **2** to 3 equiv of benzyl thionobenzoate in benzyl benzoate at 90 °C for 1 h, no thioamides **3** or **4** could be detected.

To further define the scope of these new thionation conditions, we evaluated the conversion of acylated Wang-bound phenylalanine with 1 equiv of **1** in benzyl benzoate at 100 °C in a glass vial with magnetic stirring and oil bath heating (Scheme 2). Amides **5** were prepared from the corresponding acid chlorides in the presence of DIPEA by standard procedures.

We found that the thionation reaction worked quite well in all cases, although the electron-deficient aromatics (Table 3, entries 2 and 6) did require longer reaction times due to their lower nucleophilicity toward **1**. Reactions were monitored at 1 h intervals by removal of a portion of resin, which was subsequently washed and dried under vacuum. The resulting resins were evaluated by FT-IR, cleaved with 50% TFA/DCM, and then analyzed by HPLC/MS. The product thioamides, as previously noted,[9] were not stable to TFA cleavage conditions (except entry 3). The percent conversion was estimated on the basis of the disappearance of starting material by HPLC analysis of the cleaved material and by FT-IR analysis of the loss of the amide stretch at ~1663 cm^{-1} relative to the polystyrene aromatic ring stretch at 1600 cm^{-1}. It is important to note that all reactions were driven to completion with 1 equiv of Lawesson's reagent at 100 °C with reaction times that are comparable to those observed in solution.[8b]

Table 3. Reaction Time Necessary for Conversion of Amides **5** to Thioamides **6** (Scheme 2)

entry	R	complete conversion time (vials)[a,b]	parallel reaction % conversion (at 8 h)[b,c]
1	Ph	2 h	90%
2	2-NO_2-Ph	3 h	80% (45%)[e]
3	3-Pyr	1 h (89%)[d]	95% (65%)[e]
4	$(Ph)_2CH_2$	1 h	90%
5	acetyl	4 h	95%
6	2,6-difluoro-Ph		65%
7	$(CH_3)_2CHCH_2$		90%

[a] Conditions: 1 equiv of **1**, 100 °C, glass vial, oil bath heating, magnetic stirring. [b] Estimated values; see text. [c] Conditions: 2 equiv of **1**, 97 °C well temperature, Bohdan Miniblock, Bohdan/Labline orbital shaker setting = 7.5. [d] Resin **5** (0.5 g); isolated yield after RP purification; cf. ref 15. [e] % Conversion at 4 h.

When the same reactions were run in a parallel manner,[14] we found that much longer reaction times were required due to the length of time necessary for the reactions to reach temperature combined with much less efficient mixing. In parallel, we found that 1 equiv of **1** required reaction times of 8−36 h in order to effect complete thionation. In addition, significant cleavage of the Wang ester linkage was observed by FT-IR analysis (loss of the ester stretch at ~1735 cm^{-1} relative to the polystyrene aromatic ring stretch at 1600 cm^{-1}) after 24−36 h of heating in the presence of **1**. When the experiments were repeated with 2 equiv of **1**, all reactions except the electron-deficient aromatics (Table 3, entries 2 and 6) were near completion after 8 h at 97 °C. The significantly longer reaction times observed in parallel highlight the utility of high-boiling solvents for parallel applications of SPOS.

In conclusion, we have introduced the concept of using a much broader range of solvents for parallel solid-phase synthesis. As part of our study, we identified high-boiling solvents with good swelling ability that we expect will find broad use in thermally driven SPOS reactions. In this study, we have demonstrated that, at least for the Lawesson's thionation reaction, room-temperature swelling is not an important solvent selection criteria. Extremely low vapor pressures at high temperature combined with flash points greater than 100 °C make this new class of solvents an ideal choice for high-temperature parallel solid-phase synthesis.

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(11) Resin loading was determined as follows: 0.5 g of amide resin **2** was exposed to 6 mL of 10% TFA/DCM for 1 h. The solution was removed by filtration, and the resin was washed three times with 6 mL of 1% TFA in DCM. The TFA cleavage and wash cycle was repeated, and the combined filtrates were concentrated and purified by MPLC on silica gel to give 41 mg (0.264 mmol) of 4-chlorobenzamide as an off-white solid.

(12) Rink amide **2** (0.25 g, 0.132 mmol), Lawesson's reagent **1** (107 mg, 0.132 mmol), and benzoyl benzoate (1.5 mL) were placed in a vial with a magnetic stir bar. The vial was placed in an oil bath preheated to 115 °C and allowed to react for 5 min with magnetic stirring. The resulting slurry was cooled, filtered, and washed three times with DCM/MeOH and three times with DCM. The resin **3** was cleaved with 30% TFA/DCM for 1.5 h, filtered, washed 3 × 1% TFA/DCM. The combined filtrate and washings were concentrated under vacuum and then purified on silica gel (10−30% EtOAc/Hex) to give 4-chlorothiobenzamide **4** (22.4 mg, 99%) as a yellow solid.

(13) Pederson, B. S.; Scheibye, S.; Clausen, K.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 293−297.

(14) Bohdan Miniblock in the 48 position configuration with 4 mL sintered glass vessels was utilized. Mixing was performed on a Bohdan/Labline orbital shaker set at 7.5.

(15) 3-Phenyl-2-[(pyridine-3-carbothioyl)-amino]-propionic acid (Table 3, entry 3): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.87 (br, 1H), 9.36 (d, J = 6.8 Hz, 1H), 8.82 (d, J = 7.9 Hz, 1H), 8.71 (s, 1H), 7.82 (s, 1H), 7.15−7.32 (m, 5H), 5.57−6.62 (m, 1H), 3.46 (dd, J = 4.9, 14.2 Hz, 1H), 2.93 (dd, J = 7.3, 14.2 Hz, 1H), 2.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.46, 173.37, 146.32, 142.39, 139.93, 139.02, 135.29, 129.39, 128.89, 127.67, 126.19, 59.68, 36.52; HRMS (FAB) calcd for $C_{15}H_{15}N_2O_2S$ $[M + H]^+$ 287.0854, found 287.0863.