Tetrahedron Letters 50 (2009) 3314–3317

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot assembly of 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes from alkyl aryl(hetaryl) ketoximes, acetylene, and aliphatic ketones: a new three-component reaction

Boris A. Trofimov [a,*], Elena Yu. Schmidt [a], Al'bina I. Mikhaleva [a], Igor A. Ushakov [a], Nadezhda I. Protsuk [a], Elena Yu. Senotrusova [a], Olga N. Kazheva [b], Grigorii G. Aleksandrov [b], Oleg A. Dyachenko [b]

[a] A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., 664033 Irkutsk, Russian Federation
[b] Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 Academician N. N. Semenov Str., 142432 Chernogolovka, Russian Federation

ARTICLE INFO

Article history:
Received 9 January 2009
Revised 27 January 2009
Accepted 11 February 2009
Available online 15 February 2009

Keywords:
4-Methylene-3-oxa-1-azabicyclo[3.1.0]hexanes
Alkyl aryl ketoximes
Acetylene
Acetone
Superbases
Aziridines

ABSTRACT

A new three-component reaction between alkyl aryl(hetaryl)ketoximes, acetylene, and aliphatic ketones in the superbasic systems KOH/DMSO and LiOH/CsF/DMSO (70–90 °C, initial acetylene pressure 13–15 atm, 5–60 min) affords novel 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes in yields of up to 75%. Using KOH/DMSO, the side products of the reaction are *O*-vinylketoximes and 2-aryl(hetaryl)pyrroles, while with LiOH/CsF/DMSO, the reaction proves to be selective, only minor amounts of the corresponding alkyl aryl(hetaryl) ketones being detectable.

© 2009 Elsevier Ltd. All rights reserved.

The reaction of ketoximes with acetylenes in the presence of superbasic systems MOH/DMSO (M = alkaline metal) provides a simple general route to pyrroles[1] and steadily keeps expanding in scope and utility.[2] The key intermediates of the reaction (*O*-vinyloximes,[3] hydroxypyrroline,[1a,4] and 3*H*-pyrroles[1a,5]) are isolable and are themselves interesting for organic synthesis.

Herein, we report on a new reaction between ketoximes **1–6** and acetylene in the presence of aliphatic ketones **7** and **8** using typical pyrrole synthesis conditions. We have made the serendipitous discovery that this three-component reaction affords 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes **9–15**, along with or instead of the expected *O*-vinyloximes and pyrroles, with the yields of the bicyclics reaching 75% (Scheme 1, Table 1).[6]

The reaction proceeds at 70–90 °C in 5–60 min using acetylene gas (autoclave, initial pressure of acetylene at ambient temperature was 13–15 atm which reaches a maximum of 25–30 atm during the reaction). The ketoxime/aliphatic ketone/MOH molar ratio was 1:1:1. When the synthesis was carried out using the KOH/DMSO system, the crude contained the major products **9–15** along with small amounts of the corresponding *O*-vinylketoximes and pyrroles (Scheme 1). With the superbase system LiOH/CsF/DMSO, the reaction was more selective yielding products **9–15** without any *O*-vinyloximes or pyrroles; minor side-products being aryl(hetaryl)ketones instead (Scheme 1).

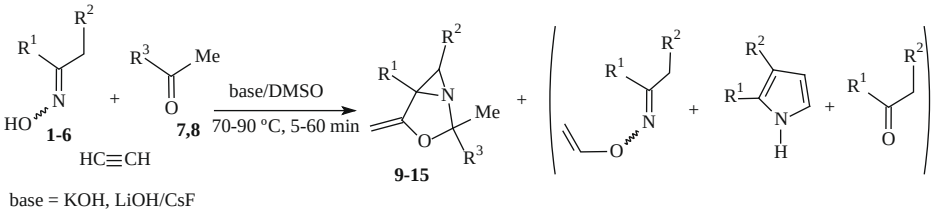
The structures of the 4-methylene-3-oxa-1-azabicyclo[3.1.0]-hexanes **9–15** were assigned unambiguously by X-ray crystallographic analysis of 2,2-dimethyl-4-methylene-5-(1-pyrenyl)-3-oxa-1-azabicyclo[3.1.0]hexane **12** (Fig. 1).

The oxazolidine heterocycle N(1)C(2)O(3)C(4)C(5) is significantly distorted with maximum deviations of the atoms from the plane being 0.15 Å [O(3)] and −0.11 Å to +0.12 Å [C(2) and C(4)]. The dihedral angle between the planes of the pyrene and oxazolidine units is 113.4°. The aziridine N(1)C(1)C(5) ring and the oxazolidine moiety have a dihedral angle of 101.1°. The dihedral angle between the planes of the pyrene and aziridine units is 122.0°.

The NMR (^{1}H and ^{13}C) spectra were also in agreement with the structures of the 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes. Characteristic signals in the ^{1}H NMR spectra of the bicycles **9–15** are the doublets for the exocyclic double bond protons H_A (3.83–4.16 ppm) and H_B (4.36–4.51 ppm) and the singlets due to the aziridine protons H1 and H2 (2.10–2.58 ppm). Assignments of the ^{13}C signals were based on 2D HSQC and HMBC spectra. The observed correlations (Fig. 2) and the $^1J_{C6-H1}$ ~ 175–176 Hz

* Corresponding author. Tel.: +7 395242 14 11; fax: +7 395241 93 46.
E-mail address: boris_trofimov@irioch.irk.ru (B.A. Trofimov).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.085



Scheme 1.

Table 1
4-Methylene-3-oxa-1-azabicyclo[3.1.0]hexanes **9–15** synthesized according to Scheme 1

R^1, R^2	R^3	Product	Yield (%)
Me, H **1**	Me **7**	**9**	7
, H **2**	Me **7**	**10**	51
, H **3**	Me **7**	**11**	54
, H **4**	Me **7**	**12**	75
, H **5**	Me **7**	**13**	39
, *t*-Bu **6**	Me **7**	**14**	43
, H **5**	*t*-Bu **8**	**15**	27

and $^1J_{C6-H2} \sim 166–167$ Hz coupling values allowed the signals C5 (49.4–52.5 ppm) and C6 (34.6–37.7 ppm) of the aziridine moiety to be assigned. The ^{15}N chemical shift (−300.6 ppm) recorded for compound **14** is typical of an aziridine ring.[7]

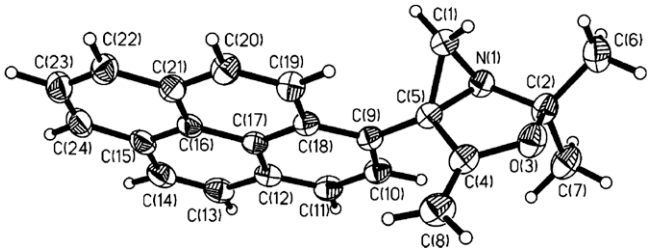


Figure 1. X-ray structure of **12**.

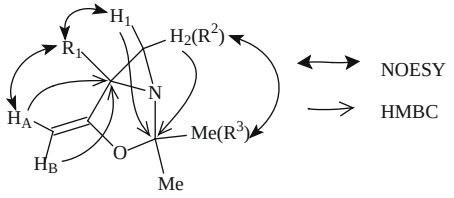
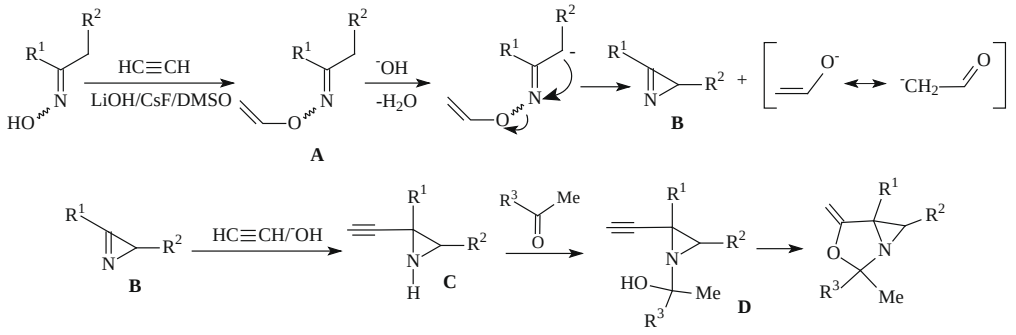


Figure 2. Characteristic NOESY correlation and HMBC of compounds **9–15**.

The formation of 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes **9–15** can be rationalized as depicted in Scheme 2. The initially formed *O*-vinyloxime **A**, a regular primary intermediate of pyrrole synthesis from ketoximes and acetylene,[1] undergoes intermolecular nucleophilic substitution at the nitrogen atom promoted by the adjacent carbanionic center induced by the superbase (Neber[8] or Hoch-Campbell[8b,9] azirine synthesis). The azirine **B**, thus generated, is then attacked by the acetylenic carbanion to give ethynyl aziridine **C** (the nitrogen analog of the Favorsky reaction).[10] The latter is trapped by the ketone (the third component) to form α-amino alcohol **D** which finally cyclizes to the 1,3-oxazolidine via intramolecular nucleophilic addition to the ethynyl group.

In support of this mechanism is the fact that many dialkyl ketoximes only give the expected 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes in smaller yields under the studied conditions. For example, in the case of acetoxime, only negligible amounts of the expected bicycle **9** (7%, Table 1) were detected (^{1}H NMR). This corresponds to the weaker CH-acidity of the dialkyl ketoxime and smaller positive charge at the oxime nitrogen atom owing to the electron-donating effect of both alkyl substituents.

It is worthwhile to note that the 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexane structure has not been studied in detail. To the best of our knowledge, only one publication[11] deals with such a structure which was ascribed to dimers of aziridine aldehydes. 3-Oxa-1-azabicyclo[3.1.0]hexan-2-ones[12] are more well known though they actually belong to the carbamate class of organic compounds. These oxazolidinones are related to many natural and synthetic molecules of significant biological activity, for example, immunomodulators inhibiting intercellular communication between Th1 and Th2 macrophages[13] and antimicrobial agents against multidrug resistant Gram-positive bacteria.[14] An oxazolid-



Scheme 2.

inone analog of the muscarinic agonist pilocarpine is used for the treatment of glaucoma.[15] Other oxazolidinones are strong agonists of α7 nicotinic receptors (a therapy for Alzheimer's disease).[16]

In fact, 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes **9–15** are novel heterocyclic systems in which the exocyclic double bond is conjugated both with the oxygen atom and the aziridine ring. The combination of the three pharmacologically and synthetically important functional groups (aziridine, 1,3-oxazolidine, and enol ether) in one molecule may impart to these heterocyclic systems new properties uncommon for each functionality alone.

In conclusion, a three-component reaction between alkyl-aryl(hetaryl)ketoximes, acetylene, and aliphatic ketones in the presence of the superbases LiOH/CsF/DMSO and KOH/DMSO which affords the novel heterocycles, 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes, has been reported. The LiOH/CsF/DMSO superbase catalyzes the reaction with greater selectively. Being readily available from easily accessible and cheap starting materials, 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes have potential in drug design and as building blocks for organic synthesis.

Acknowledgments

This work has been carried out under financial support of leading scientific schools by the President of the Russian Federation (Grant NSH-263.2008.3) and Russian Foundation for Basic Research (Grants 07-03-92162-PICS and 08-03-00002).

References and notes

1. (a) Trofimov, B. A. *Adv. Heterocycl. Chem.* **1990**, *51*, 177–301; (b) Trofimov, B. A. *The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles*; Wiley: New York, 1992. pp. 131–298; (c) Mikhaleva, A. I.; Schmidt, E. Yu.. In *Selected Methods for Synthesis and Modification of Heterocycles*; IBS Press: Moscow, 2002; Vol. 1, pp 334–352.
2. (a) Trofimov, B. A.; Schmidt, E. Yu.; Mikhaleva, A. I.; Zorina, N. V.; Ushakov, I. A.; Afonin, A. V.; Vasil'tsov, A. M. *Mendeleev Commun.* **2007**, *17*, 40–42; (b) Trofimov, B. A.; Schmidt, E. Yu.; Zorina, N. V.; Senotrusova, E. Yu.; Protsuk, N. I.; Ushakov, I. A.; Mikhaleva, A. I.; Méallet-Renault, R.; Clavier, G. *Tetrahedron Lett.* **2008**, *49*, 4362–4365.
3. Trofimov, B. A.; Mikhaleva, A. I.; Vasil'tsov, A. M.; Schmidt, E. Yu.; Tarasova, O. A.; Morozova, L. V.; Sobenina, L. N.; Preiss, T.; Henkelmann, J. *Synthesis* **2000**, 1125–1132.
4. Trofimov, B. A.; Korostova, S. E.; Mikhaleva, A. I.; Sobenina, L. N.; Sherbakov, V. V.; Sigalov, M. V. *Khim. Geterotsikl. Soed.* **1983**, *2*, 276.
5. (a) Trofimov, B. A.; Shevchenko, S. G.; Korostova, S. E.; Mikhaleva, A. I.; Sherbakov, V. V. *Khim. Geterotsikl. Soed.* **1985**, *11*, 1573–1574; (b) Trofimov, B. A.; Shevchenko, S. G.; Korostova, S. E.; Mikhaleva, A. I.; Sigalov, M. V.; Krivdin, L. B. *Khim. Geterotsikl. Soed.* **1989**, *11*, 1566–1567.
6. *Synthesis of 2,2-dimethyl-4-methylene-5-(1-pyrenyl)-3-oxa-1-azabicyclo[3.1.0]-hexane* (**12**): A mixture of CsF (293 mg, 1.93 mmol) and LiOH (46 mg, 1.93 mmol) in MeOH (3.0 mL) was stirred at rt for 30 min. Then 1-(1-pyrenyl)-1-ethanone oxime (500 mg, 1.93 mmol) in DMSO (50 mL) was added, and the mixture was distilled (80 °C) with stirring until the MeOH was removed. Next, a vacuum (2 mmHg) at 55 °C was applied to make sure that the mixture was free from MeOH and H_2O. The suspension thus obtained was placed into a 0.25 L steel rotating autoclave and acetone (112 mg, 1.93 mmol) in DMSO (5 mL) was added. The autoclave was charged with acetylene at a pressure of 14 atm and then decompressed to atmospheric pressure to remove air. The autoclave was charged with acetylene again at a pressure of 14 atm and heated (80 °C) whilst rotating for 60 min. The reaction mixture, after cooling to room temperature, was diluted with water (100 mL) and extracted with diethyl ether (20 mL × 5). The combined extract was washed with cold water (20 mL × 3) and dried (K_2CO_3) overnight. After removal of the solvent, 620 mg of a crude residue was obtained. Column chromatography (basic Al_2O_3, benzene or hexene) gave 473 mg (75% yield) of **12** as white crystals (mp 136–137 °C). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.48 (d, 1H, *J* = 9.0 Hz, H_{pyr}), 8.25–8.15 (m, 4H, H_{pyr}), 8.13 (d, 1H, *J* = 9.0 Hz, H_{pyr}), 8.10–8.00 (m, 3H, H_{pyr}), 4.43 (d, 1H, *J* = 2.0 Hz, H_B), 3.83 (d, 1H, *J* = 2.0 Hz, H_A), 2.58 (s, 1H, H2), 2.28 (s, 1H, H1), 1.77 (s, 3H, Me), 1.63 (s, 3H, Me). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 159.5 (C4), 132.0–123.1 (16 C_{pyr}), 99.0 (C2), 86.1 (=CH_2), 51.5 (C5), 36.6 (C6), 28.1, 22.7 (2Me). IR (KBr) ν_{max}: 1667, 1460, 1371, 1289, 1226, 1093, 1075, 1036, 1003, 988, 960, 843, 829, 821, 808, 798, 756, 721, 681, 621. Anal. Calcd for $C_{23}H_{19}NO$ (325.40): C, 84.89; H, 5.89; N, 4.30. Found: C, 85.01; H, 5.99; N, 4.11.
Compounds **10, 11,** and **13–15** were obtained analogously.
2,2-Dimethyl-4-methylene-5-phenyl-3-oxa-1-azabicyclo[3.1.0]hexane **10**: Oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.44 (m, 2H, H_o), 7.35 (m, 2H, H_m), 7.31 (m, 1H, H_p), 4.42 (d, 1H, *J* = 1.7 Hz, H_B), 3.88 (d, 1H, *J* = 1.7 Hz, H_A), 2.21 (s, 1H, H1), 2.10 (s, 1H, H2), 1.56 (s, 3H, Me), 1.47 (s, 3H, Me). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 160.4 (C4), 135.9 (C_i), 129.0 (C_o), 128.5 (C_m), 128.2 (C_p), 98.9 (C2), 85.0 (=CH_2), 52.2 (C5), 34.6 (C6), 28.2, 22.6 (2Me). IR (film) ν_{max}: 2989, 2933, 1678, 1500, 1448, 1385, 1372, 1285, 1226, 1152, 1087, 1027, 1005, 963, 850, 821, 755, 698, 531. Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.71; H, 7.69; N, 6.90.
2,2-Dimethyl-4-methylene-5-(2-naphthyl)-3-oxa-1-azabicyclo[3.1.0]hexane **11**: White crystals (mp 89–92 °C). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.90–7.80 (m, 4H, H_{naphth}), 7.56 (m, 1H, H_{naphth}), 7.47 (m, 2H, H_{naphth}), 4.45 (d, 1H, *J* = 1.8 Hz, H_B), 3.91 (d, 1H, *J* = 1.8 Hz, H_A), 2.32 (s, 1H, H1), 2.19 (s, 1H, H2), 1.62 (s, 3H, Me), 1.50 (s, 3H, Me). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 160.3 (C4), 133.4–126.3 (10 C_{naphth}), 99.1 (C2), 85.3 (=CH_2), 52.5 (C5), 34.9 (C6), 28.3, 22.6 (2Me). IR (KBr) ν_{max}: 2987, 2931, 1678, 1633, 1505, 1452, 1434, 1380, 1370, 1291, 1224, 1188, 1144, 1126, 1087, 1063, 1001, 984, 967, 952, 914, 870, 844, 808, 750, 696, 523, 478. Anal. Calcd for $C_{17}H_{17}NO$ (251.32): C, 81.24; H, 6.82; N, 5.57. Found: C, 81.43; H, 7.00; N, 5.41.
2,2-Dimethyl-4-methylene-5-(2-thienyl)-3-oxa-1-azabicyclo[3.1.0]hexane **13**: Oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.26 (dd, 1H, *J* = 5.2 Hz, *J* = 1.1 Hz, H5'), 7.09 (dd, 1H, *J* = 3.6 Hz, *J* = 1.1 Hz, H3'), 6.97 (dd, 1H, *J* = 5.2 Hz, *J* = 3.6 Hz, H4'), 4.51 (d, 1H, *J* = 1.9 Hz, H_B), 4.16 (d, 1H, *J* = 1.9 Hz, H_A), 2.39 (s, 1H, H1), 2.17 (s, 1H, H2), 1.51 (s, 3H, Me), 1.43 (s, 3H, Me). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 159.3 (C4), 139.2 (C2'), 127.4 (C3'), 127.0 (C4'), 126.0 (C5'), 98.8 (C2), 85.4 (=CH_2), 47.6 (C5), 36.4 (C6), 27.9, 22.5 (2Me). IR (film) ν_{max}: 2926, 2854, 1653, 1459, 1375, 1282, 1225, 1152, 1107, 920, 831, 815, 736, 700. Anal. Calcd for $C_{11}H_{13}NOS$ (207.29): C, 63.74; H, 6.32; N, 6.76; S, 15.47. Found: C, 63.75; H, 6.37; N, 6.71; S 15.30.
6-tert-Butyl-2,2-dimethyl-4-methylene-5-(2-thienyl)-3-oxa-1-azabicyclo[3.1.0]-hexane **14**: Oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.21 (dd, 1H, *J* = 5.2 Hz, *J* = 1.1 Hz, H5'), 7.05 (dd, 1H, *J* = 3.4 Hz, *J* = 1.1 Hz, H3'), 6.97 (dd, 1H, *J* = 5.2 Hz, *J* = 3.4 Hz, H4'), 4.36 (d, 1H, *J* = 2.0 Hz, H_B), 4.08 (d, 1H, *J* = 2.0 Hz, H_A), 1.97 (s, 1H, H1), 1.54 (s, 3H, Me), 1.46 (s, 3H, Me), 0.78 (s, 9H, *t*-Bu). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 160.8 (C4), 138.9 (C2'), 127.4 (C3'), 126.9 (C4'), 125.8 (C5'), 99.4 (C2), 83.5 (=CH_2), 55.8 (C6), 52.4 (C5), 31.6 (C-Me_3), 27.6 (C-Me_3), 28.3, 22.1 (2Me). IR (film) ν_{max}: 2962, 2927, 2870, 1639, 1385, 1364, 1287, 1169, 1150, 1002, 887, 849, 832, 700. Anal. Calcd for $C_{15}H_{21}NOS$ (263.39): C, 68.40; H, 8.04; N, 5.32; S, 12.17. Found: C, 68.45; H, 7.97; N, 5.19; S 11.99.
2-tert-Butyl-2-methyl-4-methylene-5-(2-thienyl)-3-oxa-1-azabicyclo[3.1.0]-hexane **15**: Oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.21 (dd, 1H, *J* = 5.4, *J* = 1.2 Hz, H5'), 7.10 (dd, 1H, *J* = 3.7 Hz, *J* = 1.2 Hz, H3'), 6.94 (dd, 1H, *J* = 5.4 Hz, *J* = 3.7 Hz, H4'), 4.38 (d, 1H, *J* = 2.0 Hz, H_B), 4.03 (d, 1H, *J* = 2.0 Hz, H_A), 2.45 (s, 1H, H1), 2.12 (s, 1H, H2), 1.31 (s, 3H, Me), 1.00 (s, 9H, *t*-Bu). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 161.3 (C4), 139.4 (C2'), 127.5 (C3'), 126.8 (C4'), 125.4 (C5'), 105.8 (C2), 81.5 (=CH_2), 49.4 (C5), 37.7 (C6), 40.4 (C-Me_3), 25.9 (C-Me_3), 18.3 (Me). IR (film) ν_{max}: 2961, 2923, 2875, 1673, 1639, 1598, 1394, 1364, 1284, 1172, 1149, 1018, 975, 889, 855, 832, 811, 705. Anal. Calcd for $C_{14}H_{19}NOS$ (249.37): C, 67.43; H, 7.68; N, 5.62; S, 12.86. Found: C, 67.61; H, 7.80; N, 5.44; S 12.78.

7. Witanovski, M.; Stefaniak, L.; Webb, G. A.. In *Annual Reports on NMR Spectroscopy*; Academic Press: London, 1981; Vol. 11B. pp. 34–35.
8. (a) Neber, P. W.; Uber, A. *Justus Liebigs Ann. Chem.* **1928**, *467*, 52; (b) Mikhaleva, A. I.; Zaitzev, A. B.; Trofimov, B. A. *Russ. Chem. Rev.* **2006**, *75*, 797–823.
9. (a) Hoch, J. *Compt. Rend.* **1934**, *198*, 1865–1868; (b) Campbell, K. N.; McKenna, J. F. *J. Org. Chem.* **1939**, *4*, 198–205.
10. Trofimov, B. A. *Curr. Org. Chem.* **2002**, *6*, 1121–1162.
11. Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772–14773.
12. Bergmeier, S. C.; Katz, S. J. *J. Comb. Chem.* **2002**, *4*, 162–166.
13. Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T. I.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052–1053.
14. Kearney, J. A.; Barbadora, K.; Mason, E. O.; Wald, E. R.; Green, M. *Int. J. Antimicrob. Agents* **1999**, *12*, 141–144.
15. Sauerberg, P.; Chen, J.; WoldeMussie, E.; Rapoport, H. *J. Med. Chem.* **1989**, *32*, 1322–1326.
16. Muller, G.; Napier, J.; Balestra, M.; DeCory, T.; Hale, G.; Macor, J.; Mack, R.; Loch, J.; Wu, E.; Kover, A.; Verhoest, P.; Sampognaro, A.; Phillips, E.; Zhu, Y.; Murray, R.; Griffith, R.; Blosser, J.; Gurley, D.; Machulskis, A.; Zongrone, J.; Rosen, A.; Gordon, J. *J. Med. Chem.* **2000**, *43*, 4045–4050.