Tetrahedron Letters 50 (2009) 4054–4057

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A simple, cheap alternative to 'designer convertible isonitriles' expedited with microwaves

Christopher Hulme *, Shashi Chappeta, Justin Dietrich

College of Pharmacy, Department of Pharmacology and Toxicology, Division of Medicinal Chemistry, University of Arizona, Tucson, AZ 85721, United states

ARTICLE INFO

Article history:
Received 7 April 2009
Revised 22 April 2009
Accepted 23 April 2009
Available online 3 May 2009

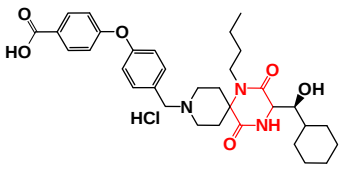
ABSTRACT

Interest in designer convertible isonitriles has increased in recent years with the growing recognition that isonitrile-based multi-component reactions (IMCRs) are highly effective in rapidly accessing, new and pharmacologically relevant diversity space. This Letter reports on the novel use of *n*-butylisonitrile as a cheaper and more atom-economical alternative to currently reported 'designer convertible isonitriles', facilitated by the advent of microwave-assisted organic synthesis (MAOS).

Published by Elsevier Ltd.

Since the completion of the human genome project it has become evident that more efficient, cost-effective exploration of chemical diversity space is required to enable small molecule validation of new macromolecular targets with potential disease modifying effects. As such, the design of new MCRs and post-MCR transformations are now recognized as powerful library generating tools that facilitate the discovery of novel pharmacologically rich molecular probes.[1] Isonitrile-based MCRs (IMCRs)[2] have proven extremely fruitful, and many groups have developed post-condensation strategies with the classical Ugi reaction[3] which employ so-called 'convertible' isonitriles.[4] This set of specialized reagents includes cyclohexynlisonitrile **1**, and close analogs **2**, **3**, and **5** that function as acid activated leaving groups in the Ugi condensation product. Isonitriles **4**, **6**, and **8** utilize 'safety-catch' mechanisms to the same end, Figure 1.[5] Their value was recently nicely exemplified in a report from a clinical candidate development program, where molecules progressed into man without chemistry deviating from original hit generation 'convertible isonitrile' based methodology. One such molecule, Aplaviroc™ **9**, a CCR5 inhibitor developed for the treatment of HIV infection, was discovered from a two-step IMCR based diketopiperazine library using convertible isonitrile **7**.[6] The same strategy with **1** was originally published in 1998[7] at a time when only 12 isonitriles were commercially available and microwave-assisted organic synthesis was in its infancy.[8] This communication follows recent reports from our laboratory that re-examined the application of 'designer convertible isonitriles' in IMCRs. For example, in studies of the Bienayme–Blackburn–Groebke reaction,[9] it was shown that the relatively expensive Walborsky reagent (1,1,3,3-tetramethylbutylisonitrile) was replaceable with trimethylsilylcyanide, rendering deprotection obsolete and free amino bicyclic imidazo[1,2-*x*]-heterocycles directly.[10] Herein, we present studies driven by an observation detailed in a previous article describing a two-step UDC (Ugi/Deprotect/Cyclize)[11] route to benzimidazoles **17** (Pathway A), Scheme 1.[12] It was noted that when sterically hindered acids **11** were used in conjunction with *n*-butylisonitrile **14**, dihydroquinoxalinones **18** emerged from an alternate pathway (Pathway B), Scheme 1.

Aplaviroc™, discontinued Phase II



9

In the majority of reactions monitored Pathway B was insignificant, producing only trace amounts of the side product. Significant however was the new potential application of *n*-butylisonitrile as a simple, cheap, more atom-economical alternative to convertible isonitriles in UDC transformations (note with a >10-fold price differential from isonitriles **1** and **3**)[13]—ironically an isonitrile from the original set of commercially available 12 in the late 1990s. The Aplaviroc™ diketopiperazine ring forming strategy was initially evaluated. Thus, the Ugi reaction was run under microwave-assisted conditions with *N*-Boc-α-amino acids **19**, *n*-butylisonitrile **14** and supporting reagents utilizing a Biotage Initiator8™ system. After solvent evaporation, the crude Ugi product **20** was dissolved in 10% TFA in DCE and was irradiated at 120 °C for 20 min, Scheme 2. Six examples were purified in automated fashion on a Biotage Isolera™, and are shown with reported isolated yields for the overall two-step process, Figure 2.

* Corresponding author. Tel.: +1 520 626 5322.
E-mail address: hulme@pharmacy.arizona.edu (C. Hulme).

0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.04.095

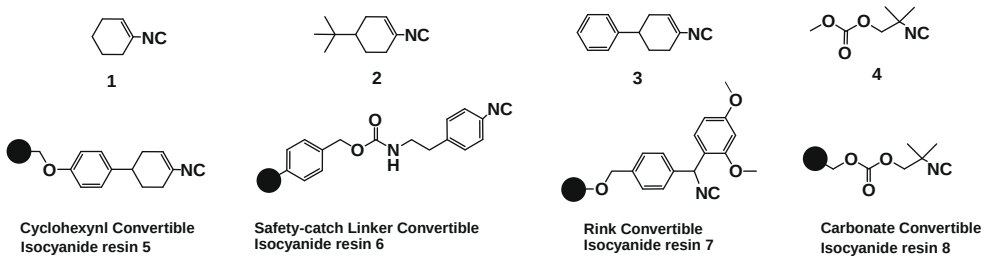
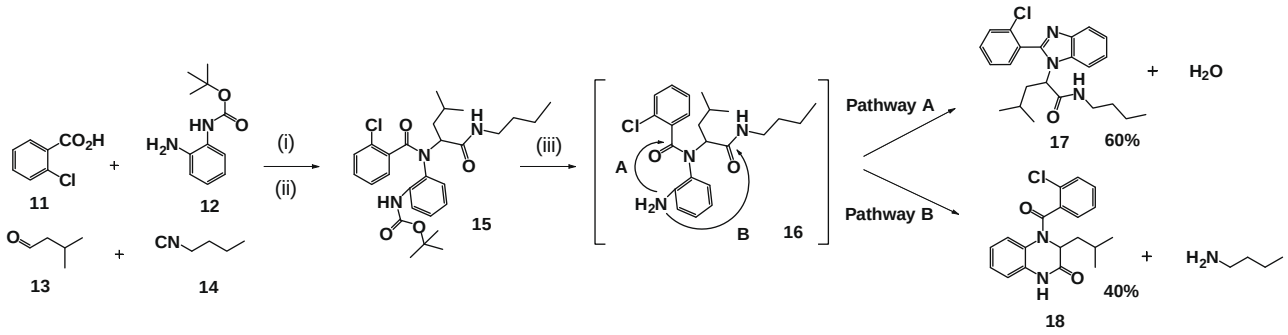
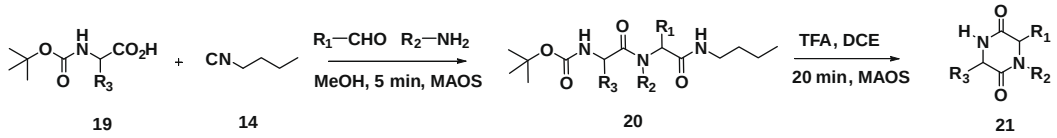


Figure 1. Spectrum of convertible isonitriles.



Scheme 1. Reagents and conditions: (i) **11**, **12**, **1**, **10**, rt, 48 h, MeOH; (ii) PS-tosylhydrazine (3 equiv), PS-*N*-methylmorpholine (3 equiv), THF/CH_2Cl_2, 24 h; and (iii) 20% TFA/CH_2Cl_2, 4 h.



Scheme 2.

Yields were excellent for the two-step process with no intermediate purification of the condensation product **20** required. Observed diastereomeric ratios in molecules **26** and **27** were 1:1.

In similar fashion, *N*-Boc-anthranilic acids **28** were exposed to the same protocol employed in Scheme 2. However, mixtures of the desired 1,4-benzodiazepine-2,4-dione **30** and the trifluoroacetylated analog **31** of the Ugi product **29** were obtained. Conditions were thus slightly modified to use HCl in MeOH with microwave irradiation, Scheme 3.[14] Isolated yields for the two-step process were comparable to those reported with cyclohexynlisonitrile[7,11g] and furthermore the transformation proceeded well without work-up or purification of the intermediate Ugi product via simple addition of a methanolic HCl solution to the on-going Ugi reaction. Seven examples (**32** through **38**) are shown in Figure 3 with isolated yields ranging from <5% to 75% for the microwave mediated ring closing step. The N-methylated anthranilic acid was noticeably a poor performer, **38**.

Repositioning the internal nucleophile in the condensation product of *mono*-Boc protected diamines **39** and supporting Ugi reagents, followed by acid treatment interestingly gave the acyclic salt **41**, Scheme 4. Desired ketopiperazine **42** was not observed even at reaction temperatures in excess of 200 °C.

In summary, the last ten years has witnessed an explosion of activity in generating new molecular diversity via functional modifications of MCRs.[15] In addition, extensive studies have been performed developing elegant convertible isonitriles that enable production of large arrays of pharmacologically relevant scaffolds. These have been particularly directed toward UDC-like methodologies where an appropriately positioned internal amino nucleophile is utilized to rigidify the flexible Ugi skeleton. Interestingly,

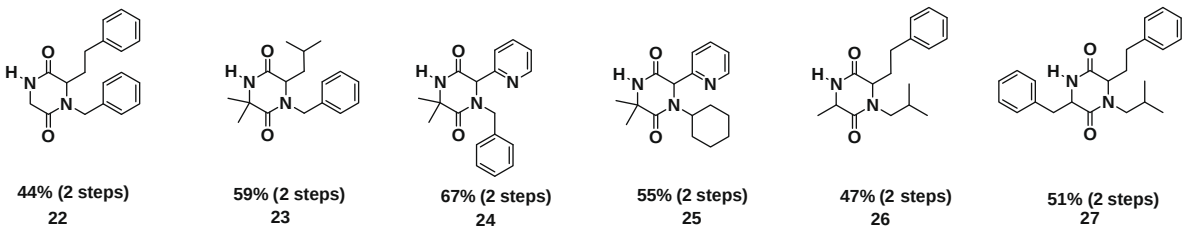
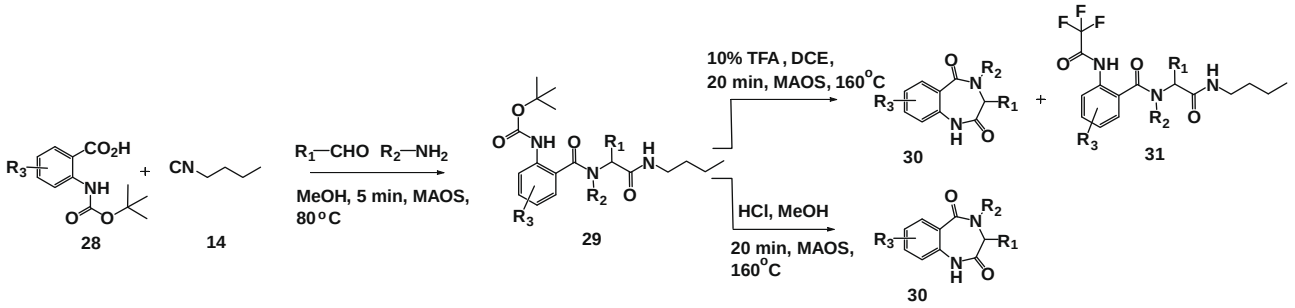


Figure 2.



Scheme 3.

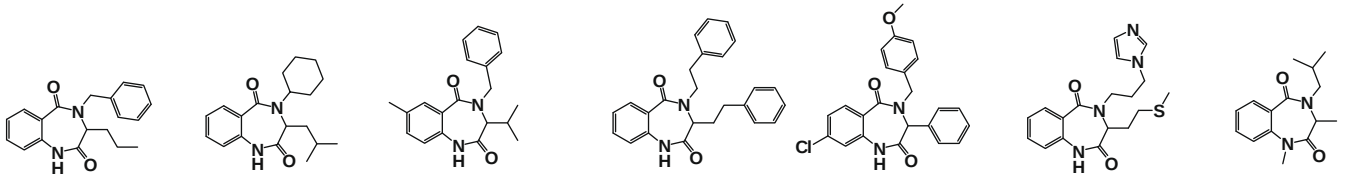
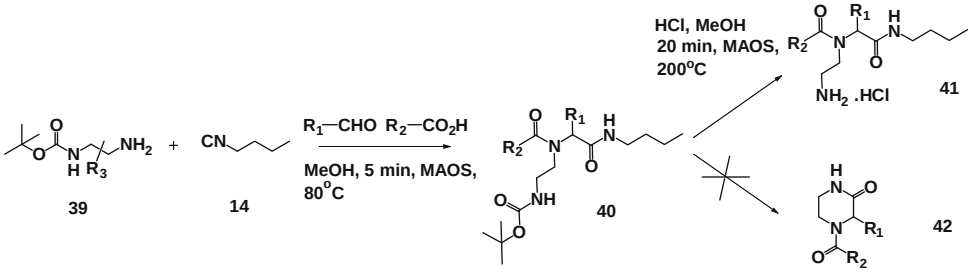


Figure 3. A = Ugi isolated yield, B = cyclization yield.



Scheme 4.

the work described herein, reveals that many of the same transformations are feasible with one of the original commercially available isonitriles, namely *n*-butylisonitrile and expedited by MAOS to reduce reaction times. As such, this represents a cost effective[13] and more atom-economical alternative to the use of more complex designer isonitriles and will be a particularly welcome addition to early stage medicinal chemistry projects developing convertible isonitrile UDC-derived hits or leads.

Acknowledgments

We would like to thank the Abbott Laboratories Scaffold Oriented Synthesis group for support via a New Faculty Award to C.H.

References and notes

1. (a) For relevant reviews see: *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005; (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472; (c) Hulme, C. *Multicomponent Reactions* **2005**, 311–341.
2. (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80; (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Eur. J. Chem.* **2000**, *6*, 3321–3329; (d) Hulme, C.; Nixey, T. *Curr. Opin. Drug Disc. Dev.* **2003**, *6*, 921–929; (e) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147; (f) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*; (g) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171.
3. (a) Ugi, I. *Angew. Chem.* **1962**, *74*, 9–22; (b) Ugi, I.; Steinbrucker, C. *Chem. Ber.* **1961**, *94*, 734–742; (c) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8; (d) Ugi, I.; Domling, A.; Horl, W. *Endeavor* **1994**, *18*, 115.
4. (a) Rosendahl, F. K.; Ugi, I. *Ann. Chem.* **1963**, *666*, 65; (b) Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149–1152; (c) Pirrung, M. C.; Ghorai, S. *J. Am. Chem. Soc.* **2006**, *128*, 11772–11773; (d) Hulme, C.; Ma, L.; Cherrier, M-P.; Romano, J. J.; Morton, G.; Duquenne, C.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1883–1887; (e) Kennedy, A. L.; Fryer, A. M.; Josey, J. A. *Org. Lett.* **2002**, *4*, 1167–1170; (f) Chen, J. J.; Golebiowski, A.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2002**, *43*, 4083–4085; (g) Keating, Thomas A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574–2583; (h) Maison, W.; Schlemminger, I.; Westerhoff, O.; Martens, J. *Bioorg. Med. Chem.* **2000**, *8*, 1343–1360; (i) Keating, T. A.; Armstrong, R. W. J. *Am. Chem. Soc.* **1995**, *117*, 7842–7843.
5. (a) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227; (b) Backes, B. J.; Virgflio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055; (c) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636.
6. Aplaviroc: (a) Habashita, H.; Kokubo, M.; Hamano, S-I.; Hamanaka, N.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *J. Med. Chem.* **2006**, *49*, 4140–4152; (b) Nishizawa, R.; Nishiyama, T.; Hisaichi, K.; Matsunaga, N.; Minamoto, C.; Habashita, H.; Takaoka, Y.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 727–731; (c) Crabb, C. *AIDS* **2006**, *20*, 641.
7. Hulme, C.; Morrissette, M.; Volz, F.; Burns, C. *Tetrahedron Lett.* **1998**, *39*, 1113.
8. Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Disc.* **2006**, *5*, 51–63.

9. (a) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635; (b) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234; (c) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661–663; (d) Zanchini, C. *Chem. Phys.* **2000**, *254*, 187; (e) Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469–5472; (f) Blackburn, C.; Guan, B. *Tetrahedron Lett.* **2000**, *41*, 1495.
10. Hulme, C.; Lee, Y.-S. *Mol. Div.* **2008**, *12*, 1–15.
11. (a) Hulme, C.; Peng, J.; Louridas, B.; Menard, P.; Krolikowski, P.; Kumar, N. V. *Tetrahedron Lett.* **1998**, *39*, 8047; (b) Nixey, T.; Tempest, P.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 1637; (c) Hulme, C.; Ma, L.; Romano, J.; Cherrier, M. P.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1889; (d) Hulme, C.; Cherrier, M. P. *Tetrahedron Lett.* **1999**, *40*, 5295; (e) Hulme, C.; Ma, L.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1509; (f) Hulme, C.; Ma, L.; Romano, J.; Morton, G.; Tang, S.-Y.; Cherrier, M-P.; Choi, S.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1883; (g) Hulme, C.; Peng, J.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, *63*, 8021–8023; (h) Nixey, T.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 6833–6835; (i) Hulme, C.; Chappeta, S.; Griffith, C.; Lee, Y.-S.; Dietrich, J. *Tetrahedron Lett.* **2009**, *50*, 1939–1942.
12. Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4959–4962.
13. *Scifinder reagent costs were as follows*: (a) *n*-butylisonitrile, **14**, $132/5 g. (b) Cyclohexynl isonitrile, **1**, 1060 EUR (~$1300)/5 g. (c) 4-Phenylcyclohexynl isonitrile, **3**, 1060 EUR (~$1300)/5 g. (d) Prices for **2** and **4** were not available requiring specific custom synthesis.
14. *For the preparation of* **34**: To a solution of isobutyraldehyde (86 mg, 109 μL, 1.194 mmol) in methanol (3 mL) contained in a 2.0–5.0 mL microwave vial were added benzylamine (85 mg, 0.843 mmol), *n*-butylisonitrile (67.0 mg, 89 μL, 0.843 mmol), and *N*-Boc-3-methyl-anthranilic acid (200 mg, 0.796 mmol). The reaction mixture was irradiated for 10 min at 90 °C with a Biotage Initiator8™ system on a low absorption setting. After heating, the mixture was washed with water and saturated sodium bicarbonate. The crude material was purified by flash chromatography on a Biotage Isolera™ automated system equipped with a 25 g silica column and a gradient of 10–39% EtOAc/Hex. The Ugi product was collected and dried to yield 365 mg product (93% yield). The Ugi product was dissolved in 3 N HCl/MeOH (5 mL) in 2–5 mL microwave vial and was then irradiated for 20 min at 160 °C. Upon completion of the reaction, the solvent was evaporated *in vacuo* and crude material partitioned between $NaHCO_3$ (20 mL) and ethyl acetate (20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), and pre-absorbed onto flash silica. Column purification on a Biotage Isolera system (20–60% EtOAc/Hex) afforded the desired benzodiazepine, which was concentrated and dried under high vacuum to yield **34** as a white solid (174 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (br s, 1H, –NH), 7.82 (s, 1H, –NH), 7.39 (d, 1H, J = 7.6 Hz), 7.19–7.32 (m, 6H), 6.78 (d, 1H, J = 8.1 Hz), 5.29 (d, 1H, J = 14.4 Hz, benzyl), 4.47 (d, 1H, J = 14.4 Hz, benzyl), 3.62 (d, 1H, J = 11.5 Hz), 2.40 (s, 3H), 1.70 (m, 1H), 0.84 (d, 3H, J = 6.5 Hz), 0.69 (d, 3H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCL_3$): δ 172.12, 166.69, 136.91, 135.13, 133.79, 132.67, 131.96, 129.18 (2C), 129.02 (2C), 128.27, 126.93, 120.23, 71.83, 55.74, 27.93, 21.09, 19.99, 19.82.
15. (a) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119–5122; (b) Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Tetrahedron Lett.* **2007**, *48*, 3549–3552; (c) Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 1299–1302; (d) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439–8441; (e) Akritopoulou-Zanze, I.; Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 3421–3423; (f) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575–579; (g) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587–590; (h) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron* **2006**, *62*, 8830–8837; (i) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 6637–6640; (j) Ilyn, A. P.; Kuzovkova, J. A.; Shkirando, A. M.; Ivachtchenko, A. V. *Heterocycl. Commun.* **2005**, *11*, 523–526; (k) Ilyin, A.; Kobak, V.; Dmitrieva, I.; Peregudova, Y.; Kustova, V.; Mishunina, Y.; Tkachenko, S.; Ivachtchenko, A. *Synth. Commun.* **2006**, *36*, 903–910; (l) Ilyn, A. P.; Trifilenkov, A. S.; Tsirulnikov, S. A.; Kurashvily, I. D.; Ivachtchenko, A. V. *J. Comb. Chem.* **2005**, *7*, 806–808; (m) Nenajdenko, V. G.; Reznichenko, A. L.; Balenkova, E. S. *Tetrahedron* **2007**, *63*, 3031–3041; (n) Ilyin, A. P.; Trifilenkov, A. S.; Kurashvili, I. D.; Krasavin, M.; Ivachtchenko, A. V. *J. Comb. Chem.* **2005**, *7*, 360–363.