

Convenient Reductive Amination of Aldehydes by NaBH₄/Cation Exchange Resin

Davood Setamdideh* and Farhad Sepehraddin

Department of Chemistry, College of Sciences, Mahabad Branch, Islamic Azad University, Mahabad, Iran.
d.setamdideh@iau-mahabad.ac.ir; davood.setamdideh@gmail.com

Received June 10th, 2013; Accepted September 18th, 2013

Abstract. Different secondary amines have been synthesized by reductive amination a variety of aldehydes and anilines with NaBH₄/DOWEX(R)50WX8 as reducing system in THF at room temperature in high to excellent yields of products (85-93%).

Key words: NaBH₄, DOWEX(R)50WX8, Reductive amination, Carbonyl compounds.

Resumen. Se sintetizaron diversas aminas secundarias por aminación reductiva de una variedad de aldehidos y anilinas empleando como sistema reductor NaBH₄/DOWEX(R)50WX8 en THF a temperatura ambiente con rendimientos de altos a excelentes.

Palabras clave: NaBH₄, DOWEX(R)50WX8, aminación reductiva, aminas secundarias.

Introduction

Amines are important in drugs and in active pharmaceutical intermediates. Amines can be achieved by reduction of nitro, cyano, azide, carboxamide derivatives or alkylation of amines (using alkyl halides or sulfonates). On the other hand, direct reductive amination (DRA) is other approach which offers significant advantages. Reductive amination reaction in a single operation can be performed by some non-borohydride reducing system [1]. Also, a variety of borohydrides reducing systems and reducing agents have been used for DRA such as Lewis acid /THF then NH₃BH₃ [2], NaBH₄/cellulose sulfuric Acid/EtOH [3], NaBH₄-silica chloride [4], NaBH₄-silica-gel-supported sulfuric acid [5], [Zr(BH₄)₂(Ph₃P)₂] [6], 2-picoline-BH₃ [7], 5-ethyl-2-methylpyridine borane/ AcOH [8], sodium tetrakis [3,5-di (trifluoromethyl)phenyl]borate (NaBAR^F₄)/ hydrioiridium(III) complex/H₂O [9], NaBH₄-H₃PW₁₂O₄₀ [10], NaBH₄/guanidine hydrochloride/H₂O [11], Cu(PPh₃)₂BH₄, MeOH/NH₂SO₃H [12], NaBH₄/ Brønsted acidic ionic liquid (1-butyl-3-methyl imidazolium tetrafluoroborate [(BMIm)BF₄]) [13], NaBH₄/ LiClO₄/diethyl ether [14], zinc borohydride *N*-methyl piperidine [15], dibutylchlorotin hydride complex [16], NaBH₄-PhCO₂H, NaBH₄/*p*-TsOH [17], Zr[(BH₄)₂(Cl)₂(dabco)₂] [18], benzylamine-BH₃ [19], NaBH₄-NiCl₂ [20], (*t*-Bu)(Me)(*i*-Pr)N-BH₃ [21], silicagel-Zn(BH₄)₂ [22], Ti(O-*i*-Pr)₄-NaBH₄ [23], NaBH₄-wet-clay-microwave [24], NaBH₄-H₂SO₄ [25], NaBH₄/Mg(ClO₄)₂ [26], 2,6-diborane-methanol [27], NaBH₃CN [28] and NaBH₄/X(OH)₃ (X: B, Al, Ga) [29]. These methods have many advantages and some disadvantages such as toxic byproducts, excess amount of reagents, using expensive reagents, prolonged reaction time, higher reaction temperature, acidic conditions and so on. Therefore, there is interest in developing synthesis of secondary amines under new systems. So, in continuing our efforts for the development of new reducing systems [30], we have carried out extensive re-examination of the DRA reaction to develop a convenient system by NaBH₄/DOWEX(R)50WX8 as reducing system in THF at room temperature.

Results and Discussion

Recently, we have reported that the DOWEX(R)50WX4 (low price cation exchange resin, strong acid) can be used as recyclable catalyst for the regioselective synthesis of Oximes by NH₂OH.HCl/DOWEX(R)50WX4 system [31], reduction of a variety of carbonyl compounds such as aldehydes, ketones, α -diketones, acyloins and α,β -unsaturated carbonyl compounds to their corresponding alcohols by NaBH₄/DOWEX(R)50WX4 system [32] and the synthesis of cyanohydrins by NaCN/DOWEX(R)50WX4 [33]. In this context, we now wish to report an efficient, facile one-pot reductive mono-*N*-alkylation of anilines using aldehydes by NaBH₄/DOWEX(R)50WX8 as reducing system in THF at room temperature. The model reaction has been selected by reductive amination of benzaldehyde with aniline. This reaction was carried out in different solvents, different amounts of the NaBH₄ and DOWEX(R)50WX8 for the selection of appropriate conditions at room temperature. Among the tested different solvents, the reaction was most facile and proceeded to give the highest yield in THF. The optimization reaction conditions showed that using 1 molar equivalents of NaBH₄ and 0.5 g of DOWEX(R)50WX8 in THF were the best conditions to complete the reductive amination of benzaldehyde (1 mmol) and aniline (1 mmol) to *N*-benzylaniline (Table 1, Entry 1). Our observation reveals that reductive amination completes within 20 min with 91% yields of product as shown in scheme 1.

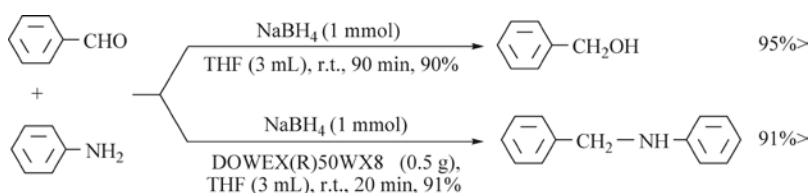
The efficiency of this protocol was further examined by using various structurally different aldehydes and anilines. In this approach, the corresponding secondary amines were obtained in excellent yields (88-93%) and within appropriate times (20-45 min) as shown in Table 2.

Imine formation is usually the rate-determining step for reductive aminations therefore addition of co-reactants is desirable. It is notable, in the absence of DOWEX(R)50WX8, imine formation does not occur and the aldehyde is reduced to benzyl alcohol as shown in scheme 1. Since the insolubility of DOWEX(R)50WX8 in THF, the reaction takes place under

Table 1. Optimization of the Reductive Amination of Benzaldehyde (1 mmol) and Aniline (1 mmol) to Benzylaniline with NaBH₄ and DOWEX(R)50WX8 at Room Temperature.

Entry	NaBH ₄ /mmol	DOWEX(R)50WX8/g	Solvent/3 mL	Time/min	Yields ^a /%
1	1	0.5	THF	20	91
2	1	0.5	CH ₃ CN	50	80
3	1	0.5	EtOH	60	80
4	1	0.5	CH ₃ OH	60	75
5	1	0.5	CH ₂ Cl ₂	60	20
6	1	0.5	Et ₂ O	40	85
7	1	1	THF	15	93
8	1	0.2	THF	60	50
9	0.5	0.5	THF	60	30

^a Yields refer to isolated pure benzylaniline ($\pm 3\%$).



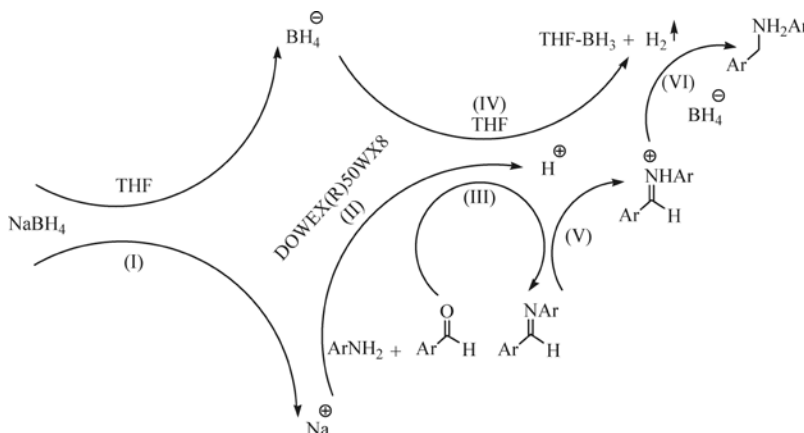
Scheme 1. The Reductive amination of benzaldehyde with aniline to benzylaniline based on optimized reaction conditions.

heterogeneous conditions. The mechanism for the influence of DOWEX(R)50WX8 is not clear, but as shown in scheme 2, we think that with the addition of DOWEX(R)50WX8 (as cation exchange resin, strong acid) to the reaction mixture (substrate & NaBH₄ in THF), Na⁺ with H⁺ slowly being changed and hydrogen ion concentration increase (scheme 2, step II). Therefore, carbonyl group can be protonated, thus it is more readily to attack the nitrogen of aniline for the imine formation (scheme 2, step III). Also, this process causes to protonate nitrogen of the imine as intermediate (scheme 2, step V). Consequently the imine intermediate become more reducible by reducing agents (scheme 2, step VI). On the other hands, we observed

sodium borohydride is decomposed thus, THF-BH₃ complex is formed and hydrogen gas slowly is liberated *in situ* (scheme 2, step IV) [21]. Hydrogen gas generation seems to be directly related to concentration of H⁺ (scheme 2, step II & Table 1, entries 7) and the solubility of the NaBH₄ (scheme 2, step I) in the reaction solvent.

The synergistically generated molecular hydrogen combines with more easily hydride attack to protonated imine intermediate, thus accelerates the rate of reduction reaction (scheme 2, step VI).

The reductive amination of cinnamaldehyde with 1 molar equivalents of aniline and 4-methyl aniline by 1 molar equiva-



Scheme 2. The mechanism for the influence of DOWEX(R)50WX8.

Table 2. Reductive Amination of Aldehydes (1 mmol) with Anilines (1 mmol) by NaBH₄ (1 mmol) in the presence of DOWEX(R)50WX8 (0.5 g) in THF (3 mL) at room temperature.

Entry	Aldehydes	Anilines	Products	δ CH ₂ / ppm	$\bar{\nu}$ NH/ cm ⁻¹	Time/ min	Yields ^a / %
1	benzaldehyde	aniline	<i>N</i> -benzylaniline	4.31	3418	20	91
2	benzaldehyde	4-bromoaniline	<i>N</i> -benzyl-4-bromoaniline	4.28	3427	20	93
3	benzaldehyde	4-methoxyaniline	<i>N</i> -benzyl-4-methoxyaniline	4.28	3411	20	90
4	benzaldehyde	4-methylaniline	<i>N</i> -benzyl-4-methylaniline	4.29	3413	25	90
5	4-bromobenzaldehyde	aniline	<i>N</i> -(4-bromobenzyl)aniline	4.29	3408	20	88
6	4-bromobenzaldehyde	4-methoxyaniline	<i>N</i> -(4-bromobenzyl)-4-methoxyaniline	4.24	3421	40	88
7	4-methylbenzaldehyde	4-bromoaniline	<i>N</i> -(4-methylbenzyl)-4-bromoaniline	4.22	3384	30	93
8	4-methylbenzaldehyde	aniline	<i>N</i> -(4-methylbenzyl)aniline	4.24	3419	40	92
9	4-methylbenzaldehyde	4-methylaniline	<i>N</i> -(4-methylbenzyl)-4-methylaniline	4.23	3416	20	92
10	4-methylbenzaldehyde	4-methoxyaniline	<i>N</i> -(4-methylbenzyl)-4-methoxyaniline	4.22	3390	35	90
11	4-methoxybenzaldehyde	4-methylaniline	<i>N</i> -(4-methoxybenzyl)-4-methylaniline	4.22	3413	20	90
12	4-methoxybenzaldehyde	aniline	<i>N</i> -(4-methoxybenzyl)aniline	4.24	3410	40	93
13	4-nitrobenzaldehyde	aniline	<i>N</i> -(4-nitrobenzyl)aniline	4.47	3427	20	90
14	2-methoxybenzaldehyde	4-bromoaniline	<i>N</i> -(2-methoxybenzyl)-4-bromoaniline	4.29	3388	45	89
15	4-methoxybenzaldehyde	4-methylaniline	<i>N</i> -(4-methoxybenzyl)-4-methylaniline	4.29	3419	40	89
16	4-bromobenzaldehyde	4-methylaniline	<i>N</i> -(4-bromobenzyl)-4-methylaniline	4.27	3410	20	90
17	3-nitrobenzaldehyde	aniline	<i>N</i> -(3-nitrobenzyl)aniline	4.46	3415	20	92
18	2-nitrobenzaldehyde	4-methylaniline	<i>N</i> -(2-nitrobenzyl)-4-methylaniline	4.68	3417	20	89
19	2-methoxybenzaldehyde	4-methoxyaniline	<i>N</i> -(2-methoxybenzyl)-4-methoxyaniline	-	3410	30	85
20	2-methoxybenzaldehyde	aniline	<i>N</i> -(2-methoxybenzyl)aniline	-	3409	30	89
21	2-nitrobenzaldehyde	4-methoxyaniline	<i>N</i> -(2-nitrobenzyl)-4-methoxyaniline	4.66	-	20	92
22	cinnamaldehyde	aniline	<i>N</i> -cinnamylaniline	3.90	3412	20	90
23	cinnamaldehyde	4-methylaniline	<i>N</i> -cinnamyl-4-methylaniline	3.83	3414	20	91

^a Yields referred to isolated pure products ($\pm 3\%$).

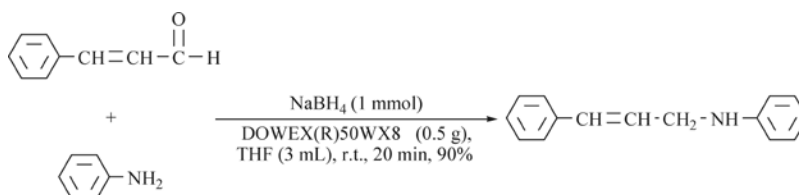
lents of NaBH₄ in the presence of 0.5 g of DOWEX(R)50WX8 was carried out exclusively in 1,2-reduction manner within 20 minutes at room temperature as shown in scheme 3. In these reactions the corresponding cinnamylanilines were obtained in 90-91% yields (Table 2, entries 22-23).

The reductive amination of aldehyde in the presence of ketones was 100%. So, this is a general trend for the reductive amination of various aldehydes in the presence of ketones (scheme 4).

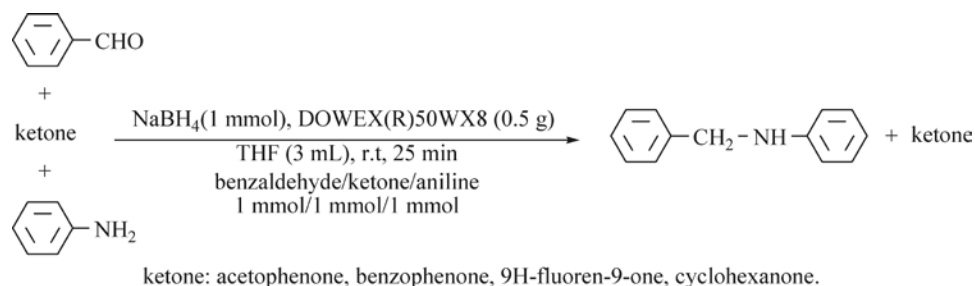
We have also checked the reusability of the catalyst using the recovered DOWEX(R)50WX8 from the reductive

amination reaction. It was observed that recovered catalyst could be satisfactorily used for the second run without regeneration. Whereas, third run of the recovered catalyst leads to poor yields and longer reaction times. After regeneration of DOWEX(R)50WX8 (It was stirred in HCl 10-5% for 30-60 minutes, then washed with distilled water), the reduction reaction has been carried out like the first run in the presence of the regenerated DOWEX(R)50WX8.

The products were determined from the ¹H-chemical shift of the CH₂ group which appeared around 4.22-4.68 ppm as a singlet. Also the NH stretching frequency in FT-



Scheme 3. The reductive amination of cinnamaldehyde with aniline to cinnamylaniline based on optimized reaction conditions.



Scheme 4. Comparison of the reductive amination of aldehyde and ketones based on optimized reaction conditions.

IR spectrum appeared around 3380-3427 cm^{-1} as shown in table 2.

Experimental

General

All substrates and reagents were purchased from commercially sources with the best quality and used without further purification. IR and ¹H NMR spectra were recorded on PerkinElmer FT-IR RXI, 100 and 400 MHz Bruker spectrometers, respectively. The products were characterized by their ¹H NMR or IR spectra and comparison with authentic samples (melting or boiling points). Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F₂₅₄ aluminum sheet.

Reductive amination of benzaldehyde and aniline with NaBH₄/DOWEX(R)50WX8, A typical procedure

In a round-bottomed flask (10 mL) equipped with a magnetic stirrer, a solution of benzaldehyde (0.106 g, 1 mmol), aniline (0.093 g, 1 mmol) and DOWEX(R)50WX8 (0.5 g) in THF (3 mL) was prepared. The resulting mixture was stirred for 5 min at room temperature. Then the NaBH₄ (0.036 g, 1 mmol) was added to the reaction mixture and stirred at room temperature. TLC monitored the progress of the reaction (eluent; CCl₄/Ether: 5/2). The reaction was filtered after completion within 20 min. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent; CCl₄/Ether: 5/2) afforded the *N*-benzylaniline (0.166 g, 91% yield, Table 2, entry 1).

Conclusions

In this investigation, we have shown that the NaBH₄/DOWEX(R)50WX8 is suitable for the reductive amination of a variety of aldehydes and anilines to their corresponding sec-

ondary amines in high to excellent yields. Reduction reactions were carried out with 1 molar equivalents of NaBH₄ in the presence of 0.5 g DOWEX(R)50WX8 in THF at room temperature. High efficiency of the reductions, shorter reaction times and easy work-up procedure makes as an attractive new protocol for reductive amination of aldehydes and it could be a useful addition to the present methodologies.

Acknowledgments

The authors gratefully appreciated the financial support of this work by the research council of Islamic Azad University branch of Mahabad.

References

1. a) Nador, F.; Moglie, Y.; Ciolino, A.; Pierini, A.; Dorn, V.; Yus, M. *Tetrahedron Lett.* **2012**, *53*, 3156-3160. b) Cano, R.; Yus, M.; Ramon, D. J. *Tetrahedron* **2011**, *67*, 8079-8085. c) Connor, D.; Lauria, A.; Bondi, S. P.; Saba, S. *Tetrahedron Lett.* **2011**, *52*, 129-132. d) Azizi, N.; Khajeh Amiri, A. R.; Ghafuri, H.; Saidi, M. R.; Bolourtchian, M. *J. Iran. Chem. Soc.* **2010**, *7*, 428-431. e) Patel, J. P.; Li, A. H.; Dong, H.; Korlipara, V. L.; Mulvihill, M. J. *Tetrahedron Lett.* **2009**, *50*, 5975-5977. f) Bhor, M. D.; Bhanushali, M. J.; Nandurkar, N. S.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 965-969. g) Byun, E.; Hong, B.; De Castro, K. A.; Lim, M.; Rhee, H. J. *Org. Chem.* **2007**, *72*, 9815-9817. h) Gnanamgari, D.; Moores, A.; Rajaseelan, E.; Crabtree, R. H. *Organometallics* **2007**, *26*, 1226-1230. i) Robichaud, A.; Ajjou, A. N. *Tetrahedron Lett.* **2006**, *47*, 3633-3636. j) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. *Adv. Synth. Catal.* **2006**, *348*, 1289-1299. k) Matsushita, T. I. K.; Shinozawa, J.; Yada, S.; Takagi, Y. *Tetrahedron* **2005**, *61*, 2105-2109. l) Cho, B. T.; Kang, S. K. *Tetrahedron* **2005**, *61*, 5725-5734. m) Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, *60*, 6649-6655. n) Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, *43*, 3105-3108. o) Chen, B. C.; Sundeen, J. E.; Guo, P.; Bednarz, M. S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245-1246. p) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745-1748. q) Chandrasekhar, S.; Raji Reddy, C.; Ahmed, M. *Synlett* **2000**, 1655-1657. r) Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* **2000**, 556-558. s) Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* **1999**, 1579-1581. t) Piennemann, T.; Schäfer, H. J. *Synthesis* **1987**, *11*, 1005-1007.
2. Ramachandran, V.; Gagare, P. D.; Sakavuyi, K.; Clark, P. *Tetrahedron Lett.* **2010**, *51*, 3167-3169.

3. Heshmatollah, A.; Zakieh, T. *Bull. Korean Chem. Soc.* **2010**, 31, 1927-1930.
4. Alinezhad, H.; Tajbakhsh, M.; Hamidi, N. *Turk. J. Chem.* **2010**, 34, 307-312.
5. Alinezhad, H.; Tajbakhsh, M.; Zare, M. *Synth. Commun.* **2009**, 39, 2907-2916.
6. Firouzabadi, H.; Iranpoora, N.; Alinezhadb, H. *J. Iran. Chem. Soc.* **2009**, 6, 177-186.
7. Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Tetrahedron* **2004**, 60, 7899-7906.
8. Burkhardt, E. R.; Coleridge, B. M. *Tetrahedron Lett.* **2008**, 49, 5152-5155.
9. Lai, R. Y.; Lee, C. I.; Liu, S. T. *Tetrahedron* **2008**, 64, 1213-1217.
10. Heydari, A.; Khaksar, S.; Akbari, J.; Esfandyari M.; Pourayoubia, M.; Tajbakhsh, M. *Tetrahedron Lett.* **2007**, 48, 1135-1138.
11. Heydari, A.; Arefi, A.; Esfandyari, M. *J. Mol. Catal. A: Chem.* **2007**, 169-172.
12. Bhanushali, M. J.; Nandurkar, N. S.; Bhor, M D.; Bhanage, B. M. *Tetrahedron Lett.* **2007**, 48, 1273-1278.
13. Reddy, P. S.; Kanjilal, S.; Sunitha, S.; Prasad, R. B. N. *Tetrahedron Lett.* **2007**, 48, 8807-8810.
14. Saidia, M. R.; Brownb, R. S.; Ziyaei-Halimjani, A. *J. Iran. Chem. Soc.* **2007**, 4, 194-198.
15. Alinezhad, H.; Tajbakhsh, M.; Zamani, R. *Synlett* **2006**, 431-434.
16. Kato, H.; Shibata, I.; Yasaka, Y.; Tsunoi, S.; Yasuda, M.; Baba, A. *Chem. Commun.* **2006**, 4189-4191.
17. Cho, B. T.; Kang, S. K. *Tetrahedron* **2005**, 61, 5725-5734.
18. Firouzabadi, H.; Iranpoor, N.; Alinezhad, H. *Bull. Chem. Soc. Jpn.* **2003**, 76, 143-151.
19. Peterson, M. A.; Bowman, A.; Morgan, S. *Synth. Commun.* **2002**, 32, 443-448.
20. Saxena, I.; Borah, R.; Sarma, J. C. *J. Chem. Soc. Perkin Trans. I* **2000**, 503-504.
21. Brown, H. C.; Kanth, J. V. B.; Dalvi, P. V.; Zaidlewicz, M. *J. Org. Chem.* **1999**, 64, 6263-6274.
22. Ranu, B. C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, 63, 370-373.
23. Neidigh, K. A.; Avery, M. A.; Williamson, J. C.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans. I* **1998**, 2527-2532.
24. Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, 54, 6293-6298.
25. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, 61, 3849-3869.
26. Brussee, J.; van Benthem, R. A. T. M.; Kruse, C. G.; van der Gen, A. *Tetrahedron Asymmetry* **1990**, 1, 163-166.
27. Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1980**, 34, 4817-4820.
28. Lane, C. F. *Synthesis* **1975**, 135-146.
29. a) Setamdideh, D.; Hasani, S.; Noori, S. *J. Chin. Chem. Soc.* **2013**, 60, 1267-1271. b) Pourhanafi, S.; Setamdideh, D.; Khezri, B. *Orient. J. Chem.* **2013**, 29, 709-712.
30. a) Setamdideh, D.; Rafigh, M. *E-J. Chem.* **2012**, 4, 2338-2345. b) Setamdideh, D.; Rahmatollahzadeh, M. *J. Mex. Chem. Soc.* **2012**, 56, 169-175. c) Setamdideh, D.; Ghahremani, S. *S. Afr. J. Chem.* **2012**, 65, 91-97. d) Setamdideh, D.; Khezri, B.; Rahmatollahzadeh, M. *J. Serb. Chem. Soc.* **2013**, 78, 1-13 e) Mo-hamadi, M.; Setamdideh, D.; Khezri, B. *Org. Chem. Inter.* **2013**, 2, doi:10.1155/2013/127585. f) Setamdideh, D.; Khaledi, L. *S. Afr. J. Chem.* **2013**, 66, 150-157. g) Kamari, R.; Setamdideh, D. *Orient. J. Chem.* **2013**, 29, 497-499. h) Latifi Mamaghani, E.; Setamdideh, D. *Orient. J. Chem.* **2013**, 29, 953-955.
31. Setamdideh, D.; Khezri, B.; Esmaeilzadeh, S. *J. Chin. Chem. Soc.* **2012**, 59, 1119-1124.
32. Setamdideh, D.; Karimi, Z.; Alipouramjad, A. *J. Chin. Chem. Soc.* **2013**, 60, 590-596.
33. Sophighaderi, S.; Setamdideh, D. *Orient. J. Chem.* **2013**, 29, 1135-1137.