$ZrCl_4$ Mediated synthesis of 1,2,3-triazoles from vinyl nitrates and their biological evaluation

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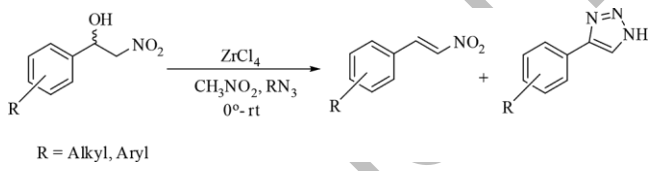
Abstract

A $ZrCl_4$ mediated simple method for the conversion of vinyl nitrates to 1,2,3-triazoles in excellent yields is developed. The obtained new triazoles were evaluated for their anti-microbial activity.

GRAPHICAL ABSTRACT



KEYWORDS: Zirconium(IV)chloride, CH_3NO_2, vinyl nitrates, 1,2,3-triazoles.

INTRODUCTION

1,2,3-Triazoles are very important class of compounds belonging to heterocycles.[1] These compounds found wide use in diverse fields of applications such as pharmaceuticals, agrochemicals and materials.[2] The triazole systems have been implicated in a wide spectrum of biological activities,[3] such as antibacterial,[4] herbicidal, fungicidal,

antiallergic, anti-HIV [5] properties and are expected to become medicines to treat cancers and some other serious diseases.[6]

1,2,3-Triazole moieties are attractive connecting units because they are stable to metabolic degradation and capable of hydrogen bonding, which can be favourable in the binding of bio-molecular targets and can improve the solubility. The 1,2,3-triazole moiety does not occur in nature, although the synthetic molecules that contain 1,2,3-triazole units show diverse biological activities.

Though for the synthesis of triazoles, the copper(I)-catalyzed azide–alkyne cycloaddition reaction has been the method of choice, several new methodologies were developed and have been demonstrated to be powerful alternatives. The strain-promoted azide–alkyne and azide-alkene cycloaddition reaction is one such development under Cu free conditions. Organocatalytic [3+2]-cycloaddition reactions[7] have shown immense potential to become the next generation of preferred method for the metal-free synthesis of triazole. The synthesis of 1,2,3-triazoles, there is still significant room for improvement, both in terms of substrate scope as well as reaction conditions.

Recently sheng *et al*, An efficient, one-pot, three-step, synthesis of 1,2,3-triazoles, has been developed via four-component reaction of phenylselenenyl bromide, cyclohexene, sodium azide and terminal alkynes catalyzed by copper iodide in a mixture of DMF/THF (1:1) at room temperature under mild conditions.

In continuation of our interest on the catalytic applications of $ZrCl_4$[8,9] as a Lewis acid for various organic transformations, herein we report the $ZrCl_4$ mediated synthesis of 1,2,3-triazoles from vinyl nitrates, and their biological evaluation.

Based on our earlier studies on the conversion of benzylic carbinols to azides in the presence of $ZrCl_4$, carbinol **A** was subjected to reaction with $ZrCl_4$ to give **B** (Scheme 1). However, instead reaction of **A** with $ZrCl_4$ gave vinyl nitrate **B**. A method for the conversion of **C** to **D** with PTSA in DMF at 60 ºC was reported,[10] while our work was in progress for the conversion of **C** to **D** with $ZrCl_4$.

RESULTS AND DISCUSSION

Aldehyde **1** on reaction with CH_3NO_2 in the presence of $ZrCl_4$ (5 mol%) for 3 h gave vinyl nitrate **1a**, which on further reaction with NaN_3 in the presence of $ZrCl_4$ (5 mol%) for 18 h at room temperature gave 1,2,3-triazole **14** in 91% of yield (Scheme 2). To standardization of catalyst reaction of **1a** in CH_3NO_2 with different mol% of $ZrCl_4$ (5, 10, 15) revealed that 5 mol% is the optimum quantity.

The two step protocol was extended to aldehydes **2-13** under the above reaction conditions to give the corresponding 1,2,3-triazoles **15** (90%), **16** (94%), **17** (94%), **18** (96%), **19** (92%), **20** (93%), **21** (91%), **22** (93%), **23** (95%), **24** (96%), **25** (95%) and **26** (96%) respectively (Scheme 2). The reaction was found to be very general and irrespective of different functional groups, it was facile to afford the triazoles in high yields.

Encouraged by the above synthetic transformation by the use of $ZrCl_4$ (5 mol%), the study was then extended to sugar derived aldehydes. Accordingly, reaction of aldehydes **27**, **28**, and **29** (Schemes 3) with CH_3NO_2 in the presence of $ZrCl_4$ at room temperature furnished the vinyl nitrates **27a**-**29a**. Further, treatment of **27a**-**29a** with $ZrCl_4$ (5 mol%) and NaN_3 afforded the corresponding 1,2,3-triazoles **30** (93%), **31** (93%) and **32** (95%) respectively (Scheme 3). Likewise **28a** on reaction with $PMBN_3$ in CH_3NO_2 at room temperature gave **31a** in 91% of yield.

Similarly, $ZrCl_4$ catalyzed reactions of several vinyl nitrates with benzyl and PMB azides for 24 h in CH_3NO_2 at room temperature furnished 1,2,3-triazoles **33-40** respectively (Scheme 4).

Antimicrobial Activity Of Triazoles

As the triazoles are known to be powerful antimicrobial agents,[11] the synthetic triazoles were evaluated for their antibacterial behavior (Table 1) against Gram-negative (*P. aeruginosa, S. typhi*) and Gram-positive (*B. subtilis*, *S. aureus*) microbial strains. All the synthetic triazoles showed intreasting antibacterial activity against the tested cultures. Maximum activity was indicated for triazole **40** against *P. aeruginosa* (30 mm), and *B. subtilis* (29 mm), whereas, minimum activity observed was for triazole **20**. Further observations revealed that the triazoles, **21**, **35**, **37**, and **39** showing good intensity of antibacterial activity compared with others.

In summary a $ZrCl_4$ mediated conversion of vinyl nitrates to triazole has been developed. The present method is simple, efficient and high yielding. The new triazole have shown moderate to weak anti microbial activity.

Experimental Section

4-(3-(Benzyloxy)-4-Methoxyphenyl)-1H-1,2,3-Triazole (14)

To a stirred solution of **1a** (0.2 g, 0.7 mmol) in nitromethane (2 mL), NaN_3 (0.05 g, 0.84 mmol) and $ZrCl_4$ (0.06 g, 0.28 mmol) was stirred at room temperature for 18 h. The reaction mixture was treated with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The organic layers were dried (Na_2SO_4), evaporated under reduced pressure and purified the residue by column chromatography (60-120 mesh silica gel, 14% ethyl acetate in pet. ether) to furnish **14** (0.18 g, 91%) as a white solid. m.p. 137-139 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO): δ 7.80 (s, 1H, Olefinic), 7.52-7.44 (m, 3H, ArH-Bn), 7.42- 7.30 (m, 4H, ArH-Bn), 6.96 (d, 2H, *J* = 8.4 Hz, ArH-Bn), 5.20 (s, 2H, benzylic), 3.90 (s, 3H, -OCH_3); ^{13}C NMR ($CDCl_3$ + DMSO, 75 MHz): δ 148.6, 147.2, 135.8, 127.3, 126.8, 126.5, 117.9, 111.1, 110.6, 69.7, 54.8; IR (neat): 3273, 3137, 3064, 3008, 2924, 2652, 1611, 1588, 1506, 1458, 1422, 1379, 1313, 1252, 1176, 1140, 1079, 992, 770, 667 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{16}H_{15}O_2N_3$ Na $[M+Na]^+$ 304.1165, found 304.1170.

1-Benzyl-4-(2,4-Dimethoxyphenyl)-1H-1,2,3-Triazole (33)

To a stirred solution of **3a** (0.2 g, 0.9 mmol) in nitromethane (3 mL) was treated with benzyl azide (0.15 g, 1.14 mmol), $ZrCl_4$ (0.08 g, 0.38 mmol) and at room temperature in air for 24 h. The reaction mixture was treated with H_2O (10 mL) and extracted with

EtOAc (3×10 mL). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and purified the residue by column chromatography (60-120 mesh silica gel, 20% ethyl acetate in pet. ether) to furnish **33** (0.26 g, 92%) as a white solid. m.p. 125-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO): δ 7.61 (s, 1H, Olefinic), 7.25-7.19 (m, 3H, Aromatic), 7.05-6.94 (m, 3H, Aromatic), 6.54-6.47 (m, 2H, Aromatic), 5.40 (s, 2H, benzylic), 3.84 (s, 3H, -OCH_3), 3.67 (s, 3H, -OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO): δ 161.3, 156.8, 134.6, 133.8, 132.6, 130.9, 127.3, 126.6, 126.3, 106.6, 104.0, 97.6, 54.4, 50.7; IR (neat): 3448, 3005, 2938, 2840, 1616, 1579, 1492, 1458, 1302, 1264, 1240, 1209, 1161, 1121, 1074, 1028, 973, 933, 832, 717, 638 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{17}H_{17}N_3O_2Na$ $[M+Na]^+$ 318.1320, found 318.1326.

1-(4-Methoxybenzyl)-4-(2,3,4-Trimethoxyphenyl)-1H-1,2,3-Triazole (37)

To a stirred solution of **4a** (0.2 g, 0.83 mmol) in CH_3NO_2 (3 mL) was treated with *p*-methoxybenzyl azide (0.16 g, 1.0 mmol) and $ZrCl_4$ (0.07 g, 0.33 mmol) and at room temperature in air for 24 h. The reaction mixture was treated with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The organic layers were dried (Na_2SO_4), evaporated under reduced pressure and purified the residue by column chromatography (60-120 mesh silica gel, 21% ethyl acetate in pet. ether) to furnish **37** (0.279 g, 94%) as a white solid. m.p. 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO): δ 7.62 (s, 1H, Olefinic), 6.93 (d, 2H, *J* = 8.4 Hz, Aromatic), 6.82-6.78 (m, 1H, Aromatic), 6.76-6.70 (m, 3H, Aromatic), 5.42 (s, 2H, benzylic), 3.91 (s, 6H, 2 x -CH_3), 3.73 (s, 3H, -OCH_3), 3.58 (s, 3H, -OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO): δ 158.1, 154.3, 141.3, 133.1, 132.7, 128.0, 126.4, 124.4, 112.8, 112.3, 106.6, 59.9, 55.0, 54.1, 50.5; IR (neat): 3448, 2935,

2841, 1610, 1555, 1513, 1485, 1464, 1324, 1292, 1247, 1177, 1099, 1078, 1008, 979, 917, 768, 694 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{19}H_{21}N_3O_4Na$ $[M+Na]^+$ 378.1531, found 378.1537.

SUPPORTING INFORMATION

Full experimental details, spectral data of the products, ^1H NMR and ^{13}C NMR of all the new compounds can be found via the Supplementary Content section of this article's Web page.

CONCLUSION

In conclusion, an efficient method for the conversion of vinyl nitrates to 1,2,3-triazoles catalyzed by $ZrCl_4$ has been developed in good yields. The derived triazoles were evaluated for their antimicrobial activity against Gram-positive and Gram-negative bacteria.

ACKNOWLEDGEMENTS

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REFERENCES

1. (a) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (c) Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso,

C. A. M.; Trindade, A. F. *Chem. Rev.* **2009**, *109*, 2703. (d) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.

2. (a) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev*. **2013**, *113*, 4905. (b) Wang, K.; Chen, M.; Wang, Q.; Shi, X.; Lee, J. K. *J. Org. Chem*. **2013**, *78*, 7249. (c) Chen, C. Y.; Lee, P. H.; Lin, Y. Y.; Yu, W. T.; Hu, W. P.; Hsu, C. C.; Lin, Y. T.; Chang, L. S.; Hsiao, C. T.; Wang, J. J.; Chung, M. I. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 6854. (d) Lau, Y.; Rutledge, P. J.; Watkinson, M.; Todd, M. H. *Chem. Soc. Rev*. **2011**, *40*, 2848. (e) Liu, Y. H.; Zhang, L.; Xu, X. N.; Li, Z. M.; Zhang, D. W.; Zhao, X.; Li, Z. T. *Org. Chem. Front*. **2014**, *1*, 494.

3. (a) Chabre, Y. M.; Roy, R. *Curr. Top. Med. Chem.* **2008**, *8*, 1237. (b) Colombo, M.; Peretto, I. *Drug Discovery Today* **2008**, *13*, 677. (c) Hanselmann, R.; Job, G. E.; Johnson, G.; Lou, R. L.; Martynow, J. G.; Reeve, M. M. *Org. Process Res. Dev.* **2010**, *14*, 152. (d) Moumne, R.; Larue, V.; Seijo, B.; Lecourt, T.; Micouin, L.; Tisne, C. *Org. Biomol. Chem.* **2010**, *8*, 1154.

4. (a) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; J. Morris, J.; Reischer, R. D.; Stper, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953. (b) Li, W.; Xia, Y.; Fan, Z.; Qu, F.; Wu, Q.; Ling, P. *Tetrahedron Lett.* **2008**, *49*, 2804.

5. (a) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; C. F. Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (b) da Silva, F.; De Souza, M. C. B. V.; Frugulhetti, I. I. P.; Castro, H. C.; De Souza, O. S. L.; De Souza, T. M. L.; Rodrigues, D. Q.; Souza, A. M. T.; Abreu, P. A.; Passamani, F.; Rodrigues, C. R.; Ferreira, V. F. *Eur. J. Med. Chem.* **2009**, *44*, 373.

6. (a) Kallander, L. S.; Lu, Q.; Chen, W.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fisher, P. D.; Mattern, M. R.; Johnson, R. K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. *J. Med. Chem.* **2005**, *48*, 5644. (b) Rohrig, U. F.; Awad, O. L.; Grosdidier, O. A.; Larrieu, P.; Stroobant, V.; Colau, D.; Cerundolo, V.; Simpson, A. J. G.; Vogel, P.; Van den Eynde, B. J.; Zoete, V.; Michielin, O. *J. Med. Chem*. **2010**, *53*, 1172. (c) Huang, Q.; Zheng, M.; Yang, S.; Kuang, C.; Yu, C.; Yang, Q. *Eur. J. Med. Chem*. **201**1, *46*, 5680. (d) Rohrig, U.; Majjigapu, S.; Grosdidier, A.; Bron, S.; Stroobant, V.; Pilotte, L.; Colau, D.; Vogel, P.; Eynde, B. J. V.; Zoete, V.; Michielin, O. J. *Med. Chem*. **2012**, *55*, 5270.

7. Ramasastry, S. S. V. *Angew. Chem., Int. Ed.*, **2014**, ***53***, 14310.

8. Sharma, G. V. M.; Kumar, K. S.; Kumar, B. S.; Reddy, S. V.; Prakasham, R. S.; Hugel, H. *Synth. Commun.* **2014**, *44*, 3156.

9. (a) Sharma, G. V. M.; Reddy, Ch. G.; Krishna, P. R. *J. Org. Chem.* **2003**, *67*, 4574. (b) Sharma, G. V. M.; Srinivas, B.; Krishna, P. R. *Tetrahedron Lett.* **2003**, *44*, 4689. (c) Sharma, G. V. M.; Reddy, Ch. G.; Krishna, P. R. *Synlett.* **2003**, 1728. (d) Zhang, Z.-H.; Li, T. S. *Curr. Org. Chem.* **2004**, *13*, 1. (e) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. *Tetrahedron Lett.* **2005**, *46*, 6119. (f) Sharma, G. V. M.; Jyothi, Y.; Lakshmi, P. S. *Synth. Commun.* **2006**, *36*, 2991. (g) Sharma, G. V. M.; Krishna, D.; Reddy, K. L. *Lett. Org. Chem.* **2009**, *5*, 151.

10. Quan, X. J.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Org. Lett*. **2014**, *16*, 5728.

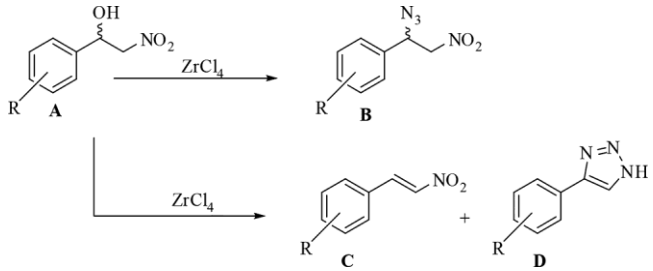
11. Isloo, A. M.; Kalluraya, B.; Shetty, P. Eur. *J. Med. Chem*. **2009**, *44*, 3784.

Table 1. Antibactirial activity of triazole derivatives

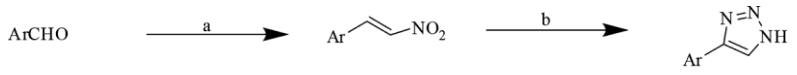
Entry	Triazoles	*B.subtilis*	*P.aeruginosa*	*S.typhi*	*S.aureus*
1	**14**	19.5	18	16	18.5
2	**15**	17	16	15	11.5
3	**16**	12	-	-	-
4	**17**	14.5	13.5	14.5	-
5	**18**	12.5	12.5	11	-
6	**19**	18.5	20.5	21	-
7	**20**	10.5	12.5	11.5	-
8	**21**	24.5	23.5	19	18.5
9	**22**	11	11.5	11.5	-
10	**23**	10	12.5	11	-
11	**24**	12	19.5	12.5	-
12	**25**	14.5	14.5	19.5	-
13	**26**	14.5	14.5	12	11
14	**30**	15.5	11.5	11	-
15	**31**	12.5	12.5	12.5	-
16	**32**	13.5	11	-	-
17	**33**	13.5	12.5	13	12
18	**34**	18.5	20	12.5	14.5
19	**35**	20	14	12.5	14.5
20	**37**	24.5	17.5	11.5	11.5
21	**38**	15.5	14.5	14.5	-

22	**39**	21.5	24.5	22.5	22.5
23	**40**	29	30	26.5	26.5
24	**31a**	12.5	11	13	11.5
Standard		21	25.5	21	20.5

Scheme 1.



Scheme 2.



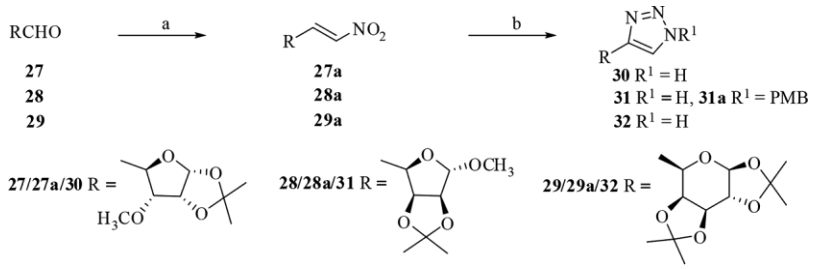
1 Ar = 3-OBn-4-OMe-Ph
2 Ar = 3,4 di-Cl-Ph
3 Ar = 2,4 di-OMe-Ph
4 Ar = 2,3,4 tri-OMe-Ph
5 Ar = 3,4,5 tri-OMe-Ph
6 Ar = 3-OMe-4-OBn-Ph
7 Ar = 3,4 di-OMe-Ph
8 Ar = 2-CN-Ph
9 Ar = 1-naphthalenyl-Ph
10 Ar = 4-OMe-Ph
11 Ar = 9-anthracenyl-Ph
12 Ar = 4-pyrenyl-Ph
13 Ar = 4-methylthiazole-5-yl

1a Ar = 3-OBn-4-OMe-Ph
2a Ar = 3,4 di-Cl-Ph
3a Ar = 2,4 di-OMe-Ph
4a Ar = 2,3,4 tri-OMe-Ph
5a Ar = 3,4,5 tri-OMe-Ph
6a Ar = 3-OMe-4-OBn-Ph
7a Ar = 3,4 di-OMe-Ph
8a Ar = 2-CN-Ph
9a Ar = 1-naphthalenyl-Ph
10a Ar = 4-OMe-Ph
11a Ar = 9-anthracenyl-Ph
12a Ar = 4-pyrenyl-Ph
13a Ar = 4-methylthiazole-5-yl

14 Ar = 3-OBn-4-OMe-Ph
15 Ar = 3,4 di-Cl-Ph
16 Ar = 2,4 di-OMe-Ph
17 Ar = 2,3,4 tri-OMe-Ph
18 Ar = 3,4,5 tri-OMe-Ph
19 Ar = 3-OMe-4-OBn-Ph
20 Ar = 3,4 di-OMe-Ph
21 Ar = 2-CN-Ph
22 Ar = 1-naphthalenyl-Ph
23 Ar = 4-OMe-Ph
24 Ar = 9-anthracenyl-Ph
25 Ar = 4-pyrenyl-Ph
26 Ar = 4-methylthiazole-5-yl

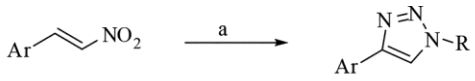
Reagents and conditions: a) $ZrCl_4$, CH_3NO_2, 0ºC-rt, 3 h; b) $ZrCl_4$, NaN_3, CH_3NO_2, 35ºc, 18 h.

Scheme 3.



Reagents and conditions; a) $ZrCl_4$, CH_3NO_2, 0 °C-rt, 3 h; b) $ZrCl_4$, NaN_3, CH_3NO_2, 0 °C-rt, 18 h

Scheme 4.



3a Ar = 2,4 di-OMe-Ph
6a Ar = 3-OMe-4-OBn-Ph
9a Ar = 1-naphthalenyl-Ph
4a Ar = 2, 3, 4 tri-OMe-Ph
6a Ar = 3-OMe-4-OBn-Ph
12a Ar = 4-pyrenyl-Ph
36 Ar = 2, 6 di-Cl-Ph

33 Ar = 2,4 di-OMe-Ph, R = Bn
34 Ar = 3-OMe-4-OBn-Ph, R = Bn
35 Ar = 1-naphthalenyl-Ph, R = Bn
37 Ar = 2, 3, 4 tri-OMe-Ph, R = PMB
38 Ar = 3-OMe-4-OBn-Ph, R = PMB
39 Ar = 4-pyrenyl-Ph, R = PMB
40 Ar = 2, 6 di-Cl-Ph, R= PMB

Reagents and conditions; a) $ZrCl_4$, NaN_3, BnN_3 or $PMBN_3$, 0 °C-rt, 24 h