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Imino *Diels-Alder* Reactions: Efficient Synthesis of 2-Aryl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinolines catalyzed by Antimony(III) Sulfate

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Summary. Antimony(III) sulfate is found to catalyze the imino *Diels-Alder* reaction of *Schiff*'s bases with *N*-vinylpyrrolidin-2-one to afford 2-aryl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinolines. One-pot synthesis of 1,2,3,4-tetrahydroquinolines from 3-nitro benzaldehyde and aromatic amines with *N*-vinylpyrrolidin-2-one catalyzed by antimony(III) sulfate is also reported. This catalyst is inexpensive, easily available, and it was also found that catalyst could be recovered quantitatively and reused without much loss of catalytic activity.

Keywords. Antimony(III) sulfate; *N*-Vinylpyrrolidin-2-one; *Schiff*'s base; Anilines; 2-Aryl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinolines.

Introduction

The chemistry of tetrahydroquinoline derivatives has long been an area of intense interest for organic chemists due to the presence of these scaffolds within the framework of numerous biologically active natural products and pharmaceutical agents [1]. Tetrahydroquinolines with *N*-heterocycle moiety exhibit interesting properties [2, 3] that make them attractive for synthetic and pharmacological use, while the synthesis of 4-*N*-heterocycle-substituted 1,2,3,4-tetrahydroquinolines has been scarcely explored [3]. The imino *Diels-Alder* reaction is a well-established route for the synthesis of 1,2,3,4-tetrahydroquinolines. *Lewis* acids like $BF_3 \cdot Et_2O$ [4], $GdCl_3$ [5], $InCl_3$ [6], $LiClO_4$ [7], $ZrCl_4$ [8], $BiCl_3$ [9], $SbCl_3$ [10], lanthanide triflates [11], $LiBF_4$ [12], montmorillonite K-10 clay [13], *CAN* [14], and protic acids such as *TFA* [15], p-*Ts*OH [16], or oxalic acid [17] have been found to catalyze the reaction of aldimines with electron rich dienophiles. I_2 [18], $KHSO_4$ [19], and urea nitrate [20] have also been used as efficient catalysts for the imino *Diels-Alder* reaction. Very recently, synthesis of 4-*N*-heterocycle-substituted 1,2,3,4-tetrahydroquinolines *via* imino *Diels-Alder* reaction has been reported [21]. However, most of the these methods involve expensive and more than stoichiometric amounts of *Lewis* acids which are required due to coordination of the *Lewis* acids to imine nitrogen, coupled with longer reaction times and strongly acidic conditions. Hence, a milder and better method is desirable.

In the quest for developing a less toxic, potentially green catalyst, we thought of using $Sb_2(SO_4)_3$ for this reaction. Recently, we have described the synthetic utility of $Sb_2(SO_4)_3$ as catalyst in the synthesis of bis-indoles. The $Sb_2(SO_4)_3$ acid is an inexpensive, stable solid, and easily available. $Sb_2(SO_4)_3$ is easier to handle than metal halides, such as $ZrCl_4$, $BiCl_3$, $SbCl_3$, $InCl_3$, or $GdCl_3$ and protic acids such as *TFA*, *Ts*OH. Since $Sb_2(SO_4)_3$ is insoluble in com-

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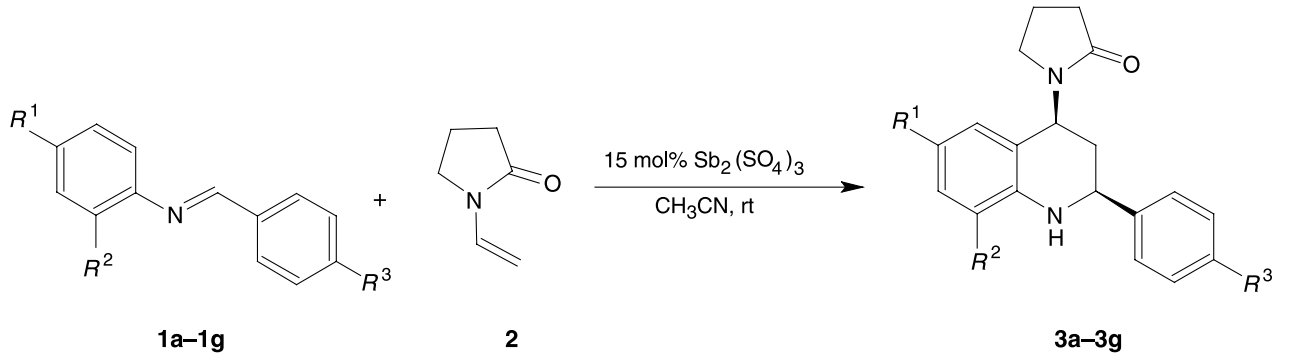


Scheme 1

mon organic solvents, it can be filtered off after the reaction and is suited for recycling. In this communication we report the synthesis of substituted 1,2,3,4-tetrahydroquinolines *via* an imino *Diels-Alder* reaction using $Sb_2(SO_4)_3$ as a catalyst. To the best of our knowledge there is no report of the use of $Sb_2(SO_4)_3$ as a mild and inexpensive catalyst for this type of reactions.

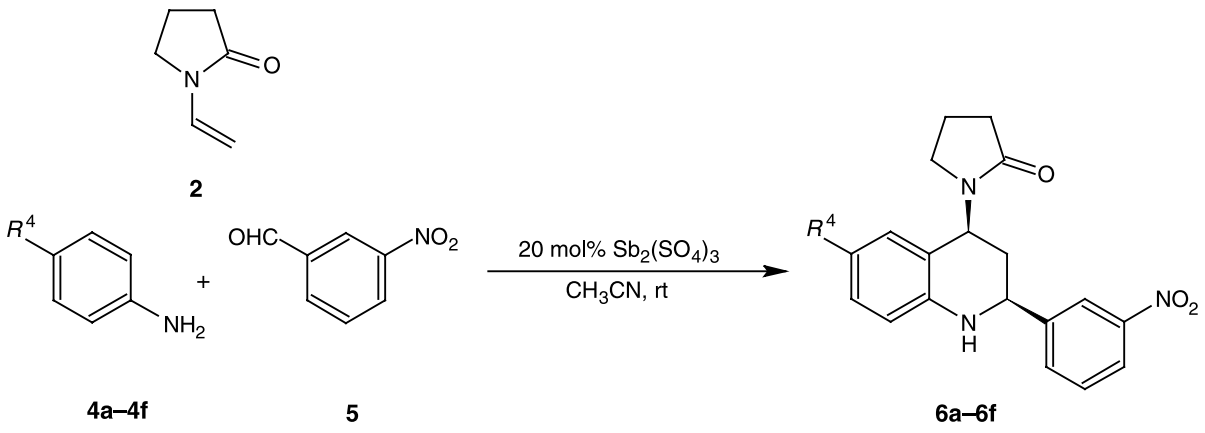
Results and Discussion

Thus to begin our study, first we employed 15 mol% $Sb_2(SO_4)_3$ in the imino *Diels-Alder* reaction between *N*-benzylideneaniline derivatives **1** and *N*-vinylpyrrolidin-2-one **2** in acetonitrile as solvent. This afforded the corresponding tetrahydroquinolines **3** in good yields at room temperature (Scheme 1); the results are summarized in Table 1. Another advantage of the use of $Sb_2(SO_4)_3$ was that it could be easily recovered and recycled in subsequent reactions without significant decrease in the catalytic activity. $Sb_2(SO_4)_3$ was easily separated from the reaction mixture by simple filtration as it is sparingly soluble in acetonitrile. The catalyst could be recycled three times without obvious loss of activity (Table 1, entry 2: 92%, 1st run; 87%, 2nd run; 80%, 3rd run).

Table 1. Synthesis of tetrahydroquinolines **3a**–**3h** at room temperature using 20 mol% of antimony sulfate as catalyst

Entries	Product	R^1	R^2	R^3	Reaction time/min	Yields[a]/%
1	**3a**	H	H	H	80	92
2	**3a**	H	H	H	80	92, 87, 80[b]
3	**3b**	Cl	H	H	90	95
4	**3c**	OCH_3	H	H	75	90
5	**3d**	H	H	NO_2	75	90
6	**3e**	CH_3	H	H	75	88
7	**3f**	H	CH_3	H	75	85
8	**3g**	H	H	Cl	80	92
9	**3h**	Br	H	H	90	90

[a] Isolated yields
[b] Reaction was carried out in presence of recycled antimony sulfate



Scheme 2

Table 2. One pot synthesis of tetrahydroquinolines **6a–6f** at room temperature using antimony sulfate as catalyst

Entries	Product	R^4	Reaction time/h	Yields[a]/%
1	**6a**	H	4.3	80
2	**6b**	Cl	4.3	82
3	**6c**	CH_3	4.0	85
4	**6d**	OCH_3	4.0	83
5	**6e**	F	5.0	76
6	**6f**	Br	6.0	75

[a] Isolated yields

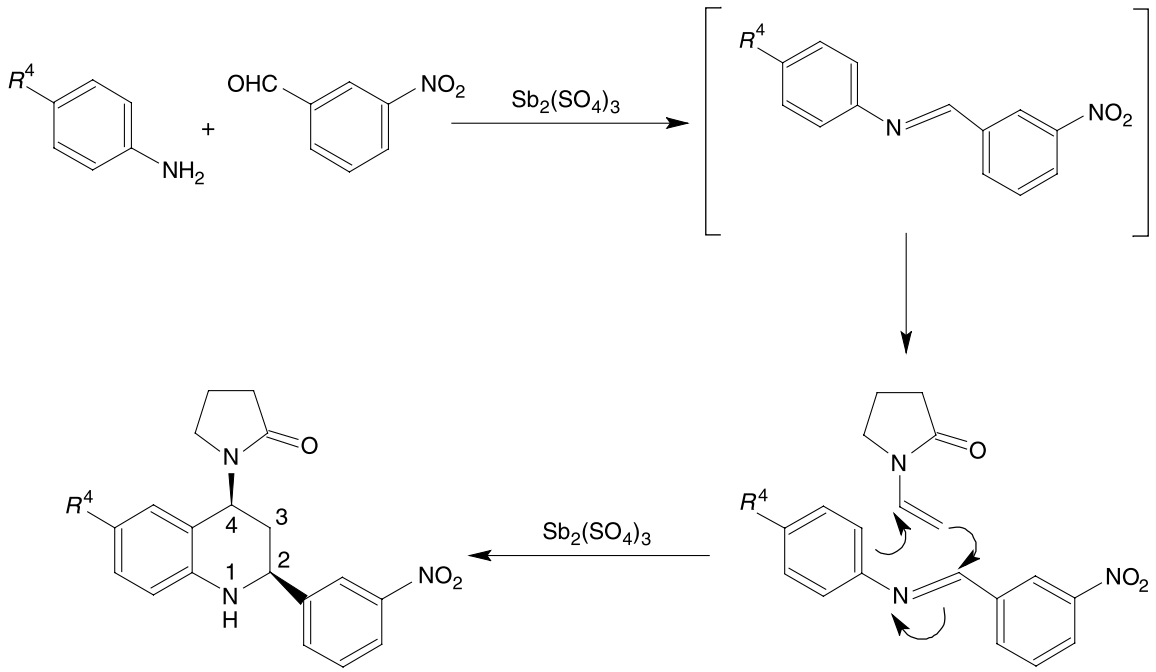
Similarly, imino *Diels-Alder* reaction were known to proceed through three component reaction systems with 3-nitro benzaldehyde, aryl amines, and **2** in presence of $BiCl_3$ [9]. Hence we expect the same reaction with $Sb_2(SO_4)_3$ also. Thus, various anilines and 3-nitrobenzaldehyde were reacted with **2** in presence of 20 mol% $Sb_2(SO_4)_3$ (Scheme 2) and the reaction proceeded smoothly to afford the expected tetrahydroquinolines **6** in good yields (Table 2). Through this reaction it was noticed that the $Sb_2(SO_4)_3$ facilitates the *Schiff*'s base formation in the initial stage (monitored by TLC) followed by cycloaddition with **2** to afford tetrahydroquinolines. These coupling reactions were performed under mild conditions (room temperature, 4–6 h) in the presence of 20 mol% $Sb_2(SO_4)_3$ in acetonitrile (Scheme 2). All the substituted tetrahydroquinolines **3** and **6** obtained were purified by SiO_2 column chromatography and exist as the *cis*-diastereomers. Their structural elucidation was based on ^{1}H NMR. The relative *trans* orientation of H_2, H_3, and H_4 was established from the large vicinal coupling $J_{2,3} = 9.0–11.2$ and $J_{3,4} = 9.8–11.5$ Hz.

The tentative mechanism to rationalize the three component one pot synthesis of tetrahydroquinolines is as shown in Scheme 3.

In conclusion, the synthesis of tetrahydroquinolines *via* imino *Diels-Alder* reaction was successfully carried out in presence of a catalytic amount of reusable antimony(III) sulfate at room temperature. This method offers several significant advantages, such as high conversions, easy handling, cheap catalyst, cleaner reaction profiles, short reaction time, and the reaction conditions are environmental friendly and might be amenable for upscaling.

Experimental

All the melting points were recorded in open capillaries. The purity of the compounds was checked by TLC on silica gel and they were purified by column chromatography. ^{1}H NMR spectra were recorded on a Bruker-400 Hz spectrometer using *TMS* as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra were recorded



Scheme 3

on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer. The compounds **3a–3d** [21a] and **6a–6f** [21b] are known, their identity were proven by means of IR, NMR, and mass spectra. Herein we describe melting points and spectral data for **3e–3h**, which could not be found in literature.

*Synthesis of 2-Aryl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinolines **3***

To a mixture of 1.0 mmol arylamines **1** and 122.3 mg *N*-vinylpyrrolidin-2-one (**2**) (1.1 mmol) in 10 cm^3 acetonitrile, 791.5 mg $Sb_2(SO_4)_3$ (0.15 mmol) was added. The reaction mixture was stirred at room temperature for the appropriate time. The reaction was monitored by TLC (petroleum ether:-ethyl acetate). After completion of reaction, the reaction mixture was filtered to remove the catalyst and washed with 3 cm^3 of acetone. Then the clear filtrate was poured into 50 cm^3 water and extracted with ethyl acetate (3×10 cm^3). The combined organic layer washed with 10 cm^3 brine, followed by 10 cm^3 water and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue, thus obtained was purified by column chromatography using silica gel (60–120 mesh) and eluted with petroleum ether:ethyl acetate to afford tetrahydroquinolines **3**.

cis-6-Methyl-2-phenyl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinoline (**3e**, $C_{20}H_{22}N_2O$)

Colorless crystalline solid, mp 164–166°C; IR (KBr): $\bar{\nu} =$ 3356 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.96$–2.01 (m, 2H), 2.05–2.09 (m, 2H), 2.26 (s, 3H), 2.41–2.52 (m, 2H), 3.17–3.28 (m, 2H), 4.02 (brs, NH), 4.55 (dd, $J = 9.0$, 3.9 Hz, 1H), 5.22 (dd, $J = 10.8$, 6.4 Hz, 1H), 6.61 (d, $J = 8.1$ Hz, 1H), 6.99 (dd, $J = 8.1$, 2.8 Hz, 1H), 7.25 (d, $J = 6.6$ Hz, 1H), 7.33–7.51 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 175.6$, 143.1, 142.5, 129.5, 129.4, 128.7, 127.9, 127.7, 126.6, 122.2, 121.8, 118.4, 55.3, 48.1, 42.8, 35.5, 31.3, 21.4, 18.2 ppm; MS: $m/z = 306$ (M+).

cis-8-Methyl-2-phenyl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinoline (**3f**, $C_{20}H_{22}N_2O$)

Colorless crystalline solid, mp 172–174°C; IR (KBr): $\bar{\nu} =$ 3348 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.01$–2.05 (m, 2H), 2.09–2.15 (m, 3H), 2.45–2.55 (m, 2H), 3.18–3.33 (m, 2H), 4.09 (brs, NH), 4.35 (dd, $J = 8.6$, 3.8 Hz, 1H), 5.24 (dd, $J = 11.2$, 2.8 Hz, 1H), 6.65 (t, $J = 7.6$ Hz, 1H), 7.12 (d, $J =$ 7.8 Hz, 1H), 7.29–7.42 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 175.4$, 141.9, 141.0, 129.3, 129.2, 128.8, 128.1, 127.8, 121.9, 118.1, 117.0, 55.1, 47.6, 42.1, 34.6, 31.1, 20.9, 18.22 ppm; MS: $m/z = 322$ (M+).

cis-2-(4-Chlorophenyl)-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinoline (**3g**, $C_{19}H_{19}ClN_2O$)

Colorless crystalline solid, mp 148–150°C; IR (KBr): $\bar{\nu} = 3328$ (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.04$–2.09 (m, 2H), 2.11–2.15 (m, 2H), 2.45–2.52 (m, 2H), 3.19–3.34 (m, 2H), 4.10 (brs, NH), 4.26 (dd, $J = 8.8$, 3.8 Hz, 1H), 5.21 (dd, $J = 11.8$, 2.6 Hz, 1H), 6.77 (t, $J = 7.4$, 1.0 Hz, 1H), 7.13 (dt, $J = 7.4$, 1.7 Hz, 1H), 7.25–7.54 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 175.4$, 144.7, 140.6, 132.2, 130.0, 129.5, 128.7, 128.3, 122.5, 119.7, 114.9, 55.5, 47.2, 42.3, 34.4, 32.1, 18.2 ppm; MS: $m/z = 327$ (M + 1).

cis-6-Bromo-2-phenyl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinoline (**3h**, $C_{19}H_{19}BrN_2O$)

Colorless crystalline solid, mp 185–187°C; IR (KBr): $\bar{\nu} =$ 3315 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.08$–2.22 (m, 4H), 2.29–2.48 (m, 2H), 3.15–3.21 (m, 2H), 4.12 (brs, NH), 4.38 (dd, $J = 10.6$, 2.8 Hz, 1H), 5.38 (dd, $J = 11.6$, 5.9 Hz, 1H), 6.50 (d, $J = 7.8$ Hz, 1H), 7.2 (dd, $J = 7.6$, 2.6 Hz, 1H), 7.32–7.44 (m, 5H), 7.48 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 175.8$, 144.1, 140.7, 128.3, 127.9, 127.6, 127.2, 126.9, 123.1, 121.6, 116.6, 56.6, 49.1, 42.3, 35.1, 31.6, 18.8 ppm; MS: $m/z = 373$ (M + 1).

*One-Pot Synthesis of 2-(3-Nitrophenyl-4-(2′-oxopyrrolidinyl-1′)-1,2,3,4-tetrahydroquinoline **6***

A mixture of 1.0 mmol arylamines **4** and 151.1 mg 3-nitrobenzaldehyde (**5**) (1.0 mmol) in 10 cm^3 CH_3CN was stirred at room temperature for 1 h in presence of 166.3mg $Sb_2(SO_4)_3$ (0.20 mmol), followed by addition of 111.0 mg **2** (1.0 mmol) drop by drop over a period of 2 min. The resulting reaction mixture were stirred at room temperature for the appropriate time. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered to remove the catalyst and washed with 3 cm^3 of acetone. Then the clear filtrate was poured into 50 cm^3 water and extracted with ethyl acetate (3×10 cm^3). The combined organic layer was washed with 10 cm^3 brine, followed by 10 cm^3 water, and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using silica gel (60–120 mesh) and eluted with petroleum ether:ethyl acetate to afford tetrahydroquinolines **6**.

References

[1] a) Aslokar NR, Schroder D, Heckmann R, Lang S, Wagner I (2004) J Antibiot **57**: 17; b) Omura S, Nakagama A (1981) Tetrahedron Lett **22**: 2199; c) Kumar MB, Potter DW, Hormann RE, Edwards A, Tice CM, Smith HC, Dipietro MA, Polley M, Wolohan PRN, Kethidi DR, Palli SR (2004) J Biol Chem **279**: 27211; d) Smith HC, Cavanaugh CK, Friz JL, Thompson CS, Saggers JA, Michelotti EL, Tice CM (2003) Bioorg Med Chem Lett **13**: 1943

[2] Leeson PD, Carling RW, Moore KW, Moseley AM, Smith JD, Stevenson G, Chan T, Baker R, Foster AC, Grimwood S, Kemp JA, Marshall GR, Hoogsteen K (1992) J Med Chem **35**: 1954

[3] a) Katritzky AR, Rachwal B, Rachwal S (1995) J Org Chem **60**: 3993; b) Kametani T, Furuyama H, Fukuoka Y, Takeda H, Suzuki Y, Honda T (1986) J Heterocycl Chem **23**: 185; c) Babu G, Nagarajan R, Natarajan R, Perumal PT (1999) Synthesis 661

[4] Kametani T, Takeda H, Suzuki Y, Honda T (1985) Synth Commun **15**: 499

[5] Ma Y, Qian C, Xie M, Sun J (1999) J Org Chem **64**: 6462

[6] a) Babu G, Perumal PT (1997) Tetrahedron Lett **38**: 5025; b) Zhang J, Li C-J (2002) J Org Chem **67**: 3969
[7] Yadav JS, Subba Reddy BV, Srinivas R, Madhuri C, Ramalingam T (2001) Synlett: 1089
[8] Mahesh M, Venkateshwar Reddy C, Srinivasa Reddy K, Raju PVK, Narayana Reddy VV (2004) Synth Commun **34**: 4089
[9] Kouznetsov VV, Astrudillosaavedra L, Vargas Mendez LY, Ramirez MC (2004) J Chil Chem Soc **49**: 319
[10] Maiti G, Kundu P (2006) Tetrahedron **62**: 349
[11] a) Habben M, Stevenson PJ (1999) Tetrahedron Lett **40**: 1215; b) Makioka Y, Taniguchi Y, Takaki K, Fuliwara Y (1995) Synthesis 801; c) Kobayashi S, Ishitani H, Nagayama S (1995) Chem Lett **6**: 423
[12] Yadav JS, Subba Reddy BV, Srinivas R, Madhuri C, Ramalingam T (2001) Synlett 240
[13] Jadav JS, Reddy BVS, Sadasiv K, Reddy PSR (2002) Tetrahedron Lett **43**: 3853
[14] Sridharan V, Avendaño C, Menéndez JC (2007) Tetrahedron **63**: 673
[15] a) Boger DL, Weinreb SM (1987) Hetero *Diels-Alder* Methodology in Organic Synthesis. Academic Press, San Diego, p 9; b) Mellor JM, Merriman GD, Riviere P (1991) Tetrahedron Lett **32**: 7103
[16] Grieco PA, Bahasas A (1988) Tetrahedron Lett **29**: 5855
[17] Nagarajan R, Perumal PT (2001) Synth Commun **31**: 1733
[18] Xia M, Lu Y-D (2005) Synlett: 2357
[19] Kumar RS, Nagarajan R, Perumal PT (2004) Synthesis: 949
[20] Anniyappan M, Nagarajan R, Perumal PT (2002) Synth Commun **32**: 99
[21] a) Zhang W, Guo Y, Liu Z, Jin X, Yang L, Liu Z-L (2005) Tetrahedron Lett **61**: 1325; b) Kouznetsov VV, Bohorquez ARR, Saavedra LA, Medina RF (2006) Mol Div **10**: 29