Send Orders of Reprints at reprints@benthamscience.net

P_2O_5/SiO_2 : A Simple and Effective Catalyst for the Synthesis of *N*-substituted 1-Alkyl and 1-Aryl 3-Aminoisoquinolines

Leticia J. Méndez, Alicia S. Cánepa*, Ruben Rimada and Rodolfo D. Bravo

Laboratorio de Estudio de Compuestos Orgánicos, Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, 47 y 115, 1900.La Plata-Argentina

Received November 26, 2012: Revised January 17, 2013: Accepted February 25, 2013

Abstract: A synthesis of *N*-substituted 1-alkyl and 1-aryl 3-aminoisoquinolines by cyclocondensation of 2-acylphenylacetonitriles with aliphatic and aromatic amines using P_2O_5/SiO_2 as catalysts is described. Selectivity, simplicity of operation and easy work-up are some advantages of this method.

Keywords: P_2O_5/SiO_2, 3-aminoisoquinolines, 2-acylphenylacetonitriles.

INTRODUCTION

Aminoisoquinolines are widely known elements in natural products as well as in agents with potential therapeutic utility. These derivatives possess versatile type of biological activities. Among these, 3-amino, 5-amino and 8-aminoisoquinolines have been studied initially as antimalarials [1,2]. On the other hand, 3-amino-4-arylisoquinolines, 3-amino-4-(*p*-aminophenyl)-isoquinoline and 3-amino-4-(*p*-acetamidophenyl)isoquinoline are well known for their central nervous system activity, characterized by general CNS depression and anticonvulsant activity [3]. More recently 5-substituted 1-aminoisoquinolines have been investigated as inhibitors of tumor growth [4]. As well, 6-substituted 1-aminoisoquinolines were studied as Rho-associated protein kinase inhibitors (ROKC), implicated in a number of important physiological functions including regulation of smooth muscle contraction, cytoskeleton re-arrangement, cell migration and proliferation and inflammatory responses [5]. In addition, aminoisoquinolines bearing amino functional group may be converted to other interesting and useful structural units in organic synthesis.

Several synthetic routes have been described in the literature to obtain these compounds [6]. However, most of these multi-step procedures have significant drawbacks such as harsh reaction conditions, difficult work-up, and the use of expensive and toxic reagents.

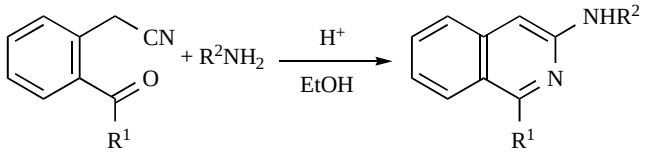
In particular, few synthetic methods can be found in the literature for the preparation of 1-substituted 3-aminoisoquinolines [7].

Tandel and Biehl have reported the preparation of 1-substituted 3-aminoisoquinolines from 2-cyanobenzylcyanide with a variety of lithium amides, alkyllithiums and phenyllithium in good yields, extending this methodology to the preparation of 1,4-disubstituted derivatives [8].

*Address correspondence to this author at the Laboratorio de Estudio de Compuestos Orgánicos, Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, 47 y 115, 1900. La Plata-Argentina; Tel: +54-221-4243104; E-mail: ascanepa@gmail.com

More recently, a synthetic route for the preparation of 1,6 and 1,7-dibromo-3-aminoisoquinolines was devised starting from 4-bromo-2-(cyanomethyl)benzonitrile and HBr in dichloroacetic acid. These products were used as intermediates in the formation of 3-aminoisoquinolines analogs functionalized at C (6) or C (7) [9].

On the other hand, Zdrojewski and Jonczyk described the condensation of 2-cyanomethylbenzaldehydes with amines catalyzed by trifluoroacetic (TFA) acid with good yields of N-substituted 3-aminoisoquinolines [10]. Based on this methodology we have synthesized N-substituted 1-alkyl and 1-aryl 3-aminoisoquinolines **3** via cyclocondensation of 2-acylphenylacetonitriles **1** with amines in good yields, using TFA as catalyst [11] (Scheme **1**).



1 **2** **3**

R^1= CH_2CH_3; *i*-$CH(CH_3)_2$; $CH_2C_6H_5$; C_6H_5; *4*-ClC_6H_4; *4*-$CH_3C_6H_4$
R^2= CH_3; C_6H_5

Scheme 1. Cyclocondensation of 2-acylphenylacetonitriles **1** with amines **2**.

Due to the problem of environmental contamination and corrosion of equipment in various processes, it is prudent to replace the conventional catalysts with a new type of solid acid catalysts which are well-behaved and environmentally friendly.

In the recent years, the use of catalysts and reagents on solid supports has been increased because such reagents not only simplify purification processes but also help to prevent release of reaction residues into the environment.

The leading contenders for environmentally suitable processes are reagents adsorbed on different supports.

1875-6255/13 $58.00+.00

Table 1. Comparative Study for P_2O_5/SiO_2 and $HClO_4/SiO_2$ as Catalyst in the Formation of *N*-methyl-1-phenylisoquinolin-3-amine 3c

Catalyst	Amount (% w/w)	Time (d)	Yield 3c (%)
$HClO_4/SiO_2$	200	3	10
	100	3	38
	30	3	60
	10	7	-
P_2O_5/SiO_2	30	3	20
	20	3	42
	10	3	66

Among them, the use of silica-supported reagents has received considerable importance in organic synthesis. Inside them, P_2O_5 adsorbed on silica gel (P_2O_5/SiO_2) has emerged as valuable catalysts in various organic transformations including nitration of aromatic compounds [12], oxidation of sulfides to sulfoxides [13], condensation of indoles with carbonyl compounds [14], deprotection of 1,1-diacetates [15], tetrahydropyranylation of diols [16], condensation of sulfonamides with aldehydes [17], Fries rearrangement [18], and many others.

On the other hand, $HClO_4$ adsorbed on silica gel ($HClO_4/SiO_2$) has been used in various organic processes, including acetylation of phenols, tioles, alcohols and amines [19], Michel addition [20], per-*O*-acetylation of carbohydrates [21], synthesis de coumarins [22] and Ferrier rearrangement [23].

The extensive use of these catalysts is due to their easy preparation and handling in the laboratory. In addition, they can be removed from the reaction mixture by simple filtration.

In continuation of our investigations on the applications of heterogeneous catalyst in organic synthesis [24], and in view of the importance of aminoisoquinolines as future therapeutic agents, herein we decide to study this method for conversion of 2-acylphenylacetonitriles **1** in 3-aminoisoquinolines **3** by reaction with amines using P_2O_5/SiO_2 and $HClO_4/SiO_2$ as catalysts to find the most suitable one.

RESULTS AND DISCUSSION

The substrates **1** were prepared following a procedure previously reported by our group [25]. P_2O_5/SiO_2 and $HClO_4/SiO_2$ were prepared according to the literature procedures [26, 27].

In order to choose the most effective catalyst we selected 2-benzoylphenylacetonitrile **1a** as a model substrate to examine the experimental conditions with methylamine in different amounts of catalysts. The reaction was performed by heating an ethanolic solution of 2-benzoylphenylacetonitrile **1c** (1mmol) and methylamine (2 mmol) at 45 ºC with the catalyst. The mixture was stirred for a certain time and monitored by TLC.

The results, summarized in Table **1**, clearly indicate that both catalysts are efficient for the reaction with similar yields. Nevertheless, is it noteworthy that when P_2O_5/SiO_2 is used the reaction occurred with a minor amount of catalyst (10 %). In addition, the reactions show greater selectivity with lower formation of by-products. For this reason, we have chosen the use of P_2O_5/SiO_2 to perform these reactions.

With the selected catalyst, we expanded the scope of the reaction to various 2-acylphenylacetonitriles **1** and amines **2** in ethanol as solvent at different temperatures according to the properties of amines. The results of the reaction are summarized in Table **2**.

As observed in Table **2**, the reactions proceeded smoothly with various amines in moderate to good yields. Similarly, to process using trifluoroacetic acid as catalyst, extensive reaction times are required to complete the reaction. The workup procedure is simple. The products **3** were isolated by filtration of catalyst followed by evaporation of the solvent and purified by column chromatrography. The products **3e, 3g, 3i** and **3k** are known compounds and were characterized by comparison of their physical and spectroscopic data with those of reported ones. Physical properties of ^1H NMR and ^{13}C NMR spectral data and elemental analysis of new compounds **3a-d, 3f, h, j,** and **3l** are reported in the experimental section.

In conclusion, we have developed an easy and versatile method for the synthesis of N-substituted 1-alkyl and 1-aryl 3-aminoisoquinolines **3** by cyclocondensation of 2-acylphenylacetonitriles **1** with alkyl and aryl amines **2** using P_2O_5/SiO_2 as catalyst. Simplicity of operation and easy work-up are some advantages of this method. In addition, it is in agreement with the green chemistry protocols.

EXPERIMENTAL

Thin layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates and column chromatography was carried out using silica gel (Merck 60, 70-230 mesh). All reagents were of commercial quality or were purified before use. Melting points were determined with a Büchi apparatus. NMR spectra were recorded on a Varian Mercury 200 spectrometer using TMS as the internal standard. P_2O_5/SiO_2 and $HClO_4/SiO_2$ were prepared according to the literature procedures [26, 27].

Table 2. Synthesis of 1, *N*-substituted 3-isoquinolin 3-amines using P_2O_5/SiO_2 as catalyst

Entry	R^1	R^2	Temperature (ºC)	Time (d)	Yield (%) 3	Mp (ºC) Found/Lit. [11]
3a	Methyl	Methyl	45	1.5	83	80-81
3b	Methyl	*n*-Butyl	80	2	80	123-124.5
3c	Methyl	Phenyl	80	4	59	63-64
3d	Methyl	p-Tolyl	80	5	58	88-89
3e	Ethyl	Methyl	45	2	63	97-98/97-98
3f	Ethyl	p-Tolyl	80	5	53	42-43
3g	Phenyl	Methyl	45	5	67	142-143/142-144
3h	Phenyl	*n*-Butyl	80	5	60	164-166
3i	Phenyl	Phenyl	80	5	48	88-90/89-90
3j	Phenyl	p-Cl-phenyl	80	5	38	192-193
3k	Benzyl	Methyl	45	5	63	117-118/115-117
3l	Benzyl	p-Cl-phenyl	80	5	30	152-155

The starting 2-acylphenylacetonitriles **1** we have obtained via reaction of 2-cyanomethylbenzoylchloride with Grignard reagents in the presence of cuprous iodide at –5 ºC [25].

General procedure for the preparation of *N*,1-substituted isoquinolin-3-amines: The reaction was performed by heating an ethanolic solution of **1** (1mmol), the amine **2** (2 mmol) and the catalyst. Different reaction temperatures were necessary depending on the amine employed. The progress of reaction was monitored by TLC and carried out for several days (up to 5 days).

The products of these reactions were isolated by filtration of catalyst followed by evaporation of the solvent and purified by column chromatrography on silica gel (70-230 mesh) using hexane/ethyl acetate.

***N*,1-Dimethylisoquinolin-3-amine (3a).** Green solid, mp: 80-81 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.81 (s, 3H, $NHCH_3$), 2.91 (s, 3H, CH_3), 6.27 (s, 1H, H-4), 7.11 (ddd, 1H, *J*= 8.2, 6.9, 1.5 Hz, H-7), 7.32-7.42 (m, 1H, H-6), 7.47 (d, 1H, *J*= 8.1 Hz, H-5), 7.82 (d, 1H, *J*= 8.2 Hz, H-8); ^{13}C NMR (62.9 MHz): δ 21.79(CH_3), 29.68 ($NHCH_3$), 93.48 (C-4), 122.25, 122.45, 125.80, 123.08, 130.19, 139.60, 155.61, 158.38. Anal. calcd. for $C_{11}H_{12}N_2$: C,76.71; H, 7.02; N, 16.27; Found: C, 76.39; H, 7.43; N, 16.15.

***N*-(*n*-Butyl)-1-methylisoquinolin-3-amine (3b).** Greenish yellow solid, mp: 123-124.5 ºC; ^{1}H NMR (200 MHz, $CDCl_3$):δ 0.91 (t, 3H, *J* = 7.2 Hz ,$CH_2CH_2CH_2C\underline{H}_3$), 1.32-1.49 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 1.53-1.70 (dt, 2H, *J* = 13.0, 7.8, Hz , $CH_2C\underline{H}_2CH_2CH_3$), 3.01 (s, 3H, CH_3), 3.12 (t, 2H, *J* = 8.4 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 4.49 ($N\underline{H}CH_3$), 6.26 (s, 1H, H-4), 7.13-7.04 (m, 1H, H-7), 7.29-7.40 (m, 1H, H-6), 7.45 (d, 1H, *J*= 8.1 Hz, H-5) 7.84 (dd, *J* = 8.4, 0.8 Hz, 1H, H-8), ^{13}C NMR (62.9 MHz): δ 12.85 ($CH_2CH_2CH_2\underline{C}H_3$), 19.30 ($CH_2CH_2\underline{C}H_2CH_3$), 28.41 ($CH_2\underline{C}H_2CH_2CH_3$), 31.61 ($NHCH_3$), 41.71($\underline{C}H_2CH_2CH_2CH_3$), 92.91, 121.43, 122.78, 124.87, 125.46, 129.30, 139.46, 154.79, 162.66. Anal. calcd. for $C_{14}H_{18}N_2$: C,78.46; H, 8.47; N, 13.07; Found: C, 78.35; H, 8.52; N, 13.11.

1-Methyl-*N*-phenylisoquinolin-3-amine (3c). Yellow solid, mp: 63-64 ºC; ^{1}H NMR (200 MHz , $CDCl_3$):δ 2.86 (s, 3H, $NHCH_3$), 6.63(s, 1H), 6.98 (brs, 1H, NH), 7.07 (s, 1H, H-4), 7.22-7.40 (m, 5H), 7.44-7.57 (m, 2H), 7.94 (dd, 1H, *J*=8.4, 0.9 Hz, H-8). ^{13}C NMR (62.9 MHz): δ 22.29, 97.75, 119.98, 122.58, 123.51, 123.62, 125.97, 126.17, 129.63, 130.40, 139.03, 141.36, 150.71, 158.89. Anal. calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96; Found: C, 82.15; H, 6.09; N, 11.77.

1-Methyl-*N*-(4-methylphenyl)isoquinolin-3-amine (3d). Yellow solid, mp: 88-89 ºC; ^{1}H NMR (200 MHz , $CDCl_3$):δ 2.34 (s, 3H, $C_6H_4CH_3$) 2.85, (s, 3H, $NHC\underline{H}_3$), 6.56 (s, 1H, NH), 6.97 (s, 1H, H-4), 7.11-7.29 (m, 5H), 7.41-7.53 (m, 2H), 7.92 (dd, 1H, *J*=8.4, 0.8 Hz, H-8). ^{13}C NMR (62.9 MHz): δ 20.98, 22.06, 97.00, 120.71, 123.11, 126.00, 130.24, 130.39, 132.41,139.46, 138.56, 151.41, 158.82. Anal. calcd. for $C_{16}H_{14}N_2$: C, 82.22; H, 6.49; N, 11.28; Found: C, 82.22; H, 6.36; N, 11.61.

1-Ethyl-*N*-(4-methylphenyl)isoquinolin-3-amine (3f). Red solid, mp: 42-43 ºC; ^{1}H NMR (200 MHz , $CDCl_3$): δ 1.35 (t, 3H, *J* = 7.6 Hz, $C\underline{H}_3CH_2$), 2.27 (s, 3 H, $C_6H_4CH_3$), 3.15 (q, 2H, *J* = 7.6 Hz, $CH_3C\underline{H}_2$), 6.49 (s, 1H, NH), 6.90 (s, 1H, H-4), 7.04 – 7.22 (m, 5H), 7.29 – 7.49 (m, 2H), 7.90 (dd, 1H, *J* = 8.4, 0.9 Hz, H-8). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.86, 21,05, 28.33, 97.11, 120.77, 122.41, 123.34, 125.57, 126.27, 130.13, 130.20, 132.43, 138.65, 139.49, 151.40, 163.35. Anal. calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68; Found: C, 82.36; H, 6.97; N, 10.65.

***N*-(*n*-Butyl)-1-phenylisoquinolin-3-amine (3h).** Orange solid, mp: 80-81 ºC; ^{1}H NMR (200 MHz , $CDCl_3$):δ 0.95 (t, 3H, *J* = 7.3 Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.36-146 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 1.58-65 (m, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 2.99

(s, 3H, CH_3), 3.01 (t, 2H, J = 7.1 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 6.15 (s, 1H, H-4), 6.78 (1H, NH), 7.24 (td, 1H, J = 7.3 Hz, 7.2, 0.9, H-7), 7.39-7.48 (m, 3H, H-6, Ph), 7.51-7.72 (m, 4H), 7.78 (d, 1H, J = 7.1 Hz, H-8). .^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.01 ($CH_2CH_2CH_2\underline{C}H_3$), 19.89 ($CH_2CH_2\underline{C}H_2CH_3$), 28.47 ($CH_2\underline{C}H_2CH_2CH_3$), 32.11 ($NHCH_3$), 41.54 ($\underline{C}H_2CH_2CH_2CH_3$), 92.91, 120.99, 122.40, 123.38, 126.01, 126.78, 129.13, 130.27, 132.88, 139.49, 154.30, 161.57. Anal. calcd. For $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14; Found: C, 82.57; H, 7.29; N, 10.14.

***N*-(4-Chlorophenyl)-1-phenylisoquinolin-3-amine (3j).** Brownish yellow solid, mp: 192-193 ºC; ^{1}H NMR (200 MHz , $CDCl_3$):δ 6.88 (s, 1H, H-4), 7.11 (ddd, 1H, J = 7.1, 8.2, 0.9 Hz, H-7), 7.15-7.25 (m, 4H), 7.30-7.48 (m, 4H), 7.57-7.70 (m, 3H), 7.81 (dd, 1H, J = 8.2, 0.9 Hz, H-8) .^{13}C NMR (62.9 MHz, $CDCl_3$): δ 97.6, 119.8, 123.0, 123.5, 123.8, 124.22, 127.15, 128.32, 129.36, 129.87, 130.77, 130.80, 131.99, 138.16, 140.11, 151.22, 160.99. Anal. calcd. For $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47; Found: C, 76.54; H, 4.50; Cl, 10.54 N, 8.32.

1-Benzyl-*N*-(4-chlorophenyl)isoquinolin-3-amine (3l). Yellow solid, mp: 152-155 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.48 (s, 2H, $CH_2C_6H_5$)), 6.61 (s, 1H, H-4), 6.91 (s, 1H, NH), 6.95-7.04 (m, 2H), 7.07-7.25 (m, 6H), 7.30-7.52 (m, 3H), 7.84 (dd, 1H, J = 7.6, 1.1 Hz), 7.92 (d, 1H, J= 8.2 Hz, H-8).^{13}C NMR (62.9 MHz, $CDCl_3$): δ 41.52, 99.14, 116.45, 120.78, 121.05, 121.73, 124.18, 126.05, 128.47, 129.06, 129.33, 130.46, 130.83, 132.09, 139.93, 139.60, 150.34, 160.17 . Anal. calcd. For $C_{22}H_{17}ClN_2$: C,76.63; H, 4.97; Cl, 10.28; N, 8.12; Found: C, 76.64; H, 4.93; Cl, 10.09 N, 8.32.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

The authors thank UNLP for financial support. L.J.M is a holder of a CONICET fellowship.

REFERENCES

[1] Neumeyer, J. L.; Weinhardt, K. K. 3-Amino- and 3-fluoroisoquinoline derivatives as potential antimalarials. *J. Med. Chem.*, **1970**, *13*, 613-616.

[2] Yapi, A. D.; Mustofa, M.; Valentin, A; Chavignon, O.; Telaude, J-C.; Mallie, M.; Chapat, J-C.; Blache, Y. New Potential Antimalarial Agents: Synthesis and Biological Activities of Original Diaza-analogs of Phenanthrene. *Chem. Pharm. Bull*., **2000**, *48*, 1886-1889.

[3] (a) Neumeyer, J. L.; Weinhardt, K. K.; Carrano, R. A.; McCurdy, D. H. 3-Aminoisoquinoline derivatives with central nervous system depressant activity. *J. Med. Chem.*, 1973, *16*, 808-813. (b) Filer, C. N.; Granchelli, F. E.; Soloway, A. H.; Neumeyer, J. L. Potential central nervous system antitumor agents. Nitrogen mustards of 3-amino-4-(p-aminophenyl)isoquinoline. *J. Med. Chem.*, **1977**, *20*, 1504-1508.

[4] Ray, P.; Wright, J.; Adam, J.; Bennet, J.; Boucharens, S.; Black, D.; Cook, A; Sherry, L.; van Straten, N.; Westwood, P.; Zaman, G. Z. R. Fragment-based discovery of 6-substituted isoquinolin-1-amine based ROCK-I inhibitors *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 97-101.

[5] Smith, A. L.; DeMorin, F. F.; Paras, N. A.; Huang, Q.; Petkus, J. K.; Doherty, E. M.; Nixey, T.; Kim, J. L.; Whittington, D. A.; Epstein, L. F.; Lee, M. R.; Rose, M. J.; Babij, C.; Manory F.; Hess, K.; Le, O.; Beltran, P.; Carnahanz, J. Selective inhibitors of the mutant B-raf pathway: discovery of a potent and orally bioavailable aminoisoquinoline. *J. Med. Chem.*, **2009**, *52*, 6189-6192.

[6] For a review of isoquinoline chemistry: Álvarez, M.; Joule, J. A., *Isoquinolines* in *Science of Synthesis;* Black, D., Ed.; Thieme: Germany, **2005**, *15*, 661-838.

[7] Suzuki, H.; Abe, H. A simple cyclization route to some 4-substituted 3-aminoisoquinolines. *Synthesis*, **1995**, *49*, 763-765.

[8] (a) Wang, A.; Zhang, H.; Biehl, E. R. Convenient synthesis of 1-substituted derivatives of 4-([E]-1-propenyl)- and 4-allyl-3-aminoisoquinolines. *Heterocycles*, **2000**, *53*, 291. (b) Tandel, S.; Biehl, E., *Heterocycles*, **2000**, *53*, 1183-1191. (c) Rao, U. N.; Biehl, E. R. Convenient synthesis of 3*H*-pyrrolo[2,3-c]isoquinolines and 3*H*-pyrrolo[2,3-c][1,7]-, 3,4-benzo[c][1,7]-, and dihydropyrido [4,3-c][1,8] naphthyridines via palladium-assisted nucleophilic amination. *Heterocycles*, **2002**, *56*, 443-455.

[9] Choi-Sledeski, Y. M.; Becker, M. R.; Green, D. M.; Davis, R.; Ewing, W. R.; Mason, H. J.; Ly, C.; Spada, H. J.; Liang, A. G.; Cheney, D.; Barton, J. Chu, V.; Brown, K.; Colussi, D.; Bentley, R.; Leadley, R.; Dunwiddie, C.; Pauls, H. W. Aminoisoquinolines: Design and synthesis of an orally active benzamidine isostere for the inhibition of factor Xa. *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 2539-2544.

[10] Zdrojewski, T; Jonczyk, A. A general approach to 3-aminoisoquinoline, its N-mono- and N,N-disubstituted derivatives. *Tetrahedron*, **1995**, *51*, 12439-12444.

[11] Cánepa, A. S.; Bravo, R. D. Convenient synthesis of *N*-substituted 1-alkyl and 1-aryl-3-aminoisoquinolines. *J. Heterocyclic Chem.*, **2006**, *43*, 235-238.

[12] Hajipour, A. R.; Kooshki, R. B.; Ruoho, A. E. Nitric acid in the presence of supported P_2O_5 on silica ge: an efficient and novel reagent for oxidation of sulfides to the corresponding sulfoxides. *Tetrahedron Lett.*, **2005**, *46*, 5503-5506.

[13] Hajipour; A. R.; Ruoho, A. E. Nitric acid in the presence of P_2O_5 supported on silica gel a useful reagent for nitration of aromatic compounds under solvent-free conditions. *Tetrahedron Lett.*, **2005**, *46*, 8307-8310.

[14] Hasaninejad, A.; Zare, A.; Sharghi, H.; Niknam, K.; Shekouhy, M. P_2O_5/SiO_2 as an efficient, mild, and heterogeneous catalytic system for the condensation of indoles with carbonyl compounds under solvent-free conditions. *Arkivoc*, **2007**, *XIV*, 39-50.

[15] Eshghi, H.; Shafieyoon, P. P_2O_5/SiO_2 as an Efficient reagent for selective deprotection of 1,1-diacetates under solvent-free conditions. *J. Chin. Chem. Soc*., **2005**, *52*, 155-157.

[16] Eshghi, H.; Rahimizadeh, M.; Saberi, S. Selective monotetrahydropyranylation of symmetrical diols using P_2O_5/SiO_2 under solvent-free conditions and their depyranylation. *Chin. Chem. Lett.*, **2008**, *19*, 1063-1067.

[17] Hasaninejad, A.; Zare, A.; Sharghi, H.; Shekouhy, M. P_2O_5 /SiO_2 an Efficient, green and heterogeneous catalytic system for the solvent-free synthesis of *N*-sulfonyl imines. *Arkivoc*, **2008**, *XI*, 64-74.

[18] Eshghi, H.; Rafie, M.; Gordi, Z.; Bohloli, M. Improvement of selectivity in the Fries rearrangement and direct acylation reactions by means of P_2O_5 /SiO_2 under microwave irradiation in solvent-free media *J. Chem. Res*., **2003**, *12*, 763-764.

[19] Chakraborti, A.K.,Gulhane, R. Perchloric acid adsorbed on silica gel as a new, highly efficient, and versatile catalyst for acetylation of phenols, thiols, alcohols, and amines *Chem. Commun*., **2003**, *9*, 1896-1897.

[20] Khan, A.T.; Ghosh, S.; Choudhury, L.H. Perchloric acid impregnated on silica gel ($HClO_4/SiO_2$): A versatile catalyst for Michael addition of thiols to the electron-deficient alkenes. *Eur. J. Org. Chem*., **2006**, 2226-2231.

[21] Misra, A. K.; Tiwari, P.; Madhusudan, S.K. $HClO_4$-SiO_2 catalyzed per-*O*-acetylation of carbohydrates, *Carbohydr. Res.*, **2005**, *2*, 325.

[22] Maheswara, M.; Siddaiah, V.; Lakishmi, G.; Damu, V.; Rao, Y. K.; Rao, C.V. *J. Mol Catal*. A: 2006, *1*, 49-52.

[23] Agarwal, A.; Vankar, Y. D. *Carbohydr. Res*., **2005**, *340*, 1661-1667.

[24] (a) Sasiambarrena, L. D.; Méndez, L. J.; Cánepa, A. C.; Ocsachoque, M. C.; González, M. G.; Bravo, R. D. Sulfated Zirconia as an efficient catalyst for sulfonylamidomethylation of benzylsulfonamides and 2-phenylethanesulfonamides: Effect of catalyst thermal

treatment. *Cat. Lett.*, **2010**, *138*, 180-186. and references cited therein. (b) Sasiambarrena, L. D.; Cánepa A. S.; Bravo, R. D. Synthesis of 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxides using Amberlyst-15. *Synth. Commun.*, **2011**, *41*, 200-205. (c) Mendez, L. J; Cánepa, A. S.; González, M. G.; Bravo, R. D. A convenient one-pot synthesis of 1-aryl-substituted 2*H*-isoquinolin-3-ones. *Tetrahedron Lett.*, **2012**, *53*, 688-690.

[25] Cánepa, A. S.; Bravo, R. D. A convenient synthesis of 2-acylphenylacetonitriles. *Synth. Commun.*, **2004**, *34*, 579-588.

[26] Hajipour, A. R.; Zarei, A.; Khazdooz, L.; Zahmatkesh, S.; Ruoho, A. E. A mild and chemoselective catalyst for thioacetalization under solvent free conditions. *Phosphorus, Sulfur, Silicon*, **2006**, *181*, 387-395.

[27] Chakraborthi, A. K.; Gulhane, R. Perchloric acid adsorbed on silica gel as a new, highly efficient, and versatile catalyst for acetylation of phenols, thiols, alcohols, and amines *Chem. Commun.*, **2003**, 1896-1897.