Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8991–8994
Tetrahedron Letters

Indium(III) bromide catalyzed one-pot synthesis of trichloromethylated tetrahydropyrimidinones

Marcos A. P. Martins,[a,*] Marcos V. M. Teixeira,[a] Wilson Cunico,[a] Elisandra Scapin,[a] Rodrigo Mayer,[a] Claudio M. P. Pereira,[a] Nilo Zanatta,[a] Helio G. Bonacorso,[a] Clóvis Peppe[b] and Yao-Feng Yuan[c]

[a]*Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Quimica, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS-Brazil*
[b]*Laboratório de Materiais Inorgânicos (LMI), Departamento de Quimica, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS-Brazil*
[c]*Department of Chemistry, State Key Laboratory for Elemento-organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China*

Received 15 September 2004; revised 7 October 2004; accepted 8 October 2004

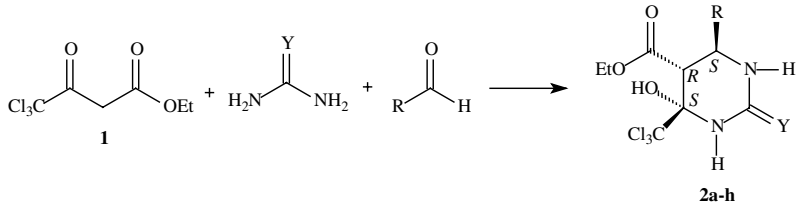
Abstract—One-pot condensation of ethyl trichloroacetoacetate **1** with *p*-substituted aromatic aldehydes (Ph, 4-Me–C_6H_4, 4-Cl–C_6H_4, 4-MeO–C_6H_4) or furfural, and urea or thiourea catalyzed by indium(III) bromide affords eight trichloromethylated tetrahydropyrimidinones, in high yields.

Dihydropyrimidinones have attracted much attention in previous years due to the large range of biological activities such as calcium channel blockers, α-1a-adrenoaceptor-selective antagonists, anti-viral, anti-tumor, and anti-inflammatory drugs.[1] The first, simple and straightforward procedure for the synthesis of dihydropyrimidinones involve one-pot condensation of three components: ethyl acetoacetate, benzaldehyde, and urea, under strong acid conditions.[2] This procedure is known as the Biginelli reaction. The major drawback associated with this protocol is the low yield, particularly for substituted aromatic and aliphatic aldehydes.[2] Yields have been improved compared to the original procedure when Lewis acid catalysts were used, for example, $FeCl_3$ and HCl, $BF_3{\cdot}OEt_2$, $LaCl_3{\cdot}H_2O$, and ytterbium triflate.[3] Reaction of three components in THF containing polyphosphate ester (PPE),[4] and acetonitrile with iodotrimethylsilane (TMSI)[5] also furnished good yield. Recently, indium(III) chloride has emerged as a powerful Lewis catalyst for preparing dihydropyrimidinones in a simple and milder conditions reaction with the ability to tolerate a wide variety of substituents in all of the three components.[6] Indium(III) bromide is also efficient with the advantage that anhydrous conditions are no longer necessary for the reaction and the catalyst can be re-used several times.[7] In our research, we developed a general procedure for preparing trihalomethyl-substituted 1,3-dielectrophilic compounds using halogenated acyl groups CX_3CO.[8] These compounds are of general interest as precursors for a variety of halomethyl-substituted heterocycles, for example, pyrrolidinones,[9] isoxazoles,[10] isoselenazoles,[11] pyrazoles,[12] pyrimidines,[13] thiazolo-pyrimidines,[14] benzoquinones,[15] thiazine 1-oxide,[16] and diazepines.[17] It has also been reported that the trichloromethyl group in ketones such as 1,1,1-trichloroacetone or 1,1,1-trichloroacetophenone can be substituted by amines furnishing acetamides and benzamides, respectively.[18] The trichloromethyl group may also act as a leaving group in heterocyclic synthesis (the classical haloform reaction).[12a,13b,14] The transformation of the trichloromethyl group attached in heterocycles into carboxyl groups[19] and more recently into amide groups[20] was also reported.

In previous works, the synthesis of trihalomethyl-2-pyrimidinones from the reaction of two components 1,1,1-trihalo-4-alcoxy-3-alken-2-ones with urea in acidic

Keywords: Pyrimidinones; Biginelli reaction; Indium(III) bromide.
* Corresponding author. Tel.: +55 55 220 8756; fax: +55 55 220 8031; e-mail: mmartins@base.ufsm.br

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.048



Scheme 1. Reagents and conditions: (i) $InBr_3$ (10% of **1**), THF, reflux, 24 h.

medium, was reported.[13] In this work, we have studied the possibility of obtaining novel trichloromethyl substituted tetrahydropyrimidinones and corresponding pyrimidino thiones using a three component reaction with 1,3-diketone, urea (thiourea), and aromatic aldehydes or furfural using indium(III) bromide as catalyst (Scheme 1). The 4,4,4-trichloro-3-oxo ethyl butanoate **1** was synthesized, in good yields, from the reaction of trichloroacetyl chloride and ethyl ortoacetate in the presence of pyridine using chloroform as the solvent and temperatures ranging from 0 °C to room temperature, for 16 h.[21]

The three component cyclocondensation of 1,3-diketone (**1**) with urea or thiourea and aromatic aldehydes or furfural was carried out in anhydrous THF in the presence of a catalytic amount of indium(III) bromide at 66 °C for 24 h (Scheme 1). The tetrahydropyrimidinones **2a**–**h** were purified by recrystallization from cyclohexane (Table 1).

A summary of the optimization of the reaction yields is provided in Table 2. THF afforded the best yield (entry 4). The catalyst amount was optimized for the synthesis of compound **2c**. The amount of $InBr_3$ (10 mol%) agree with the literature.[7] Larger amounts of catalyst did not improve yields to a great extent (entry 3).

The most relevant feature of this protocol is the formation of just one pair of enantiomers, as revealed by ^1H and ^{13}C NMR data (Table 3). The pair of doublets observed at $\delta = 3.60 \pm 0.17$ ppm and at $\delta = 4.80 \pm 0.14$ ppm with $J_{H-H} = 11.0 \pm 0.02$ Hz are assigned, respectively, to the protons H5 and H6 of the pyrimidine ring. The coupling constants are typical for *trans*-axial protons. A semi-empirical AM1 calculation[23] (Table 4) confirmed this assignment and showed the most stable conformation **I** (4*S*5*R*6*S*/4*R*5*S*6*R*), presented in Scheme 1. This assignment is confirmed by an earlier work, in which the crystal structure of a similar compound was determined by X-ray methods.[22] All compounds **2** were obtained as a single pair of enantiomers.

Therefore, it is reasonable to assume that the compounds obtained in this work have the same relative stereochemistry of the compound previously reported. The mechanism of Biginelli reaction is presumably the usual mechanism proposed using Lewis-acid catalysis.[24]

Table 2. Optimization of the reaction conditions for the synthesis **2c** catalyzed by $InBr_3$

Entry	Solvent	Amount of $InBr_3$[a] (%)	Refluxing time	Yield
1	Ethanol	10	6	26
2	Ethanol	10	24	59
3	Ethanol	20	24	63
4	THF	10	24	84

[a] Molar amounts of **1**, urea, and aldehyde (1.0:1.3:1.0, respectively).

Table 1. Yields and selected physical properties of compounds **2a**–**h**

Product	R	Y	mp[a] (°C)	Yield[b] (%)	Molecular formula (molecular weight)	Analyses (%) Calcd (Found)		
						C	H	N
2a	Ph	O	159–161	70	$C_{14}H_{15}N_2O_4Cl_3$ (381.6)	44.06 (44.13)	3.96 (3.92)	7.34 (7.37)
2b	4-(Me)-C_6H_4	O	160–162	67	$C_{15}H_{17}N_2O_4Cl_3$ (395.6)	45.54 (45.56)	4.33 (4.30)	7.08 (7.11)
2c	4-(Cl)-C_6H_4	O	159–160	84	$C_{14}H_{14}N_2O_4Cl_4$ (416.1)	40.41 (40.40)	3.39 (3.35)	6.73 (6.70)
2d	4-(OMe)-C_6H_4	O	152–154	86	$C_{15}H_{17}N_2O_5Cl_3$ (411.6)	43.77 (43.42)	4.16 (4.12)	6.80 (6.80)
2e	Ph	S	176–177	65	$C_{14}H_{15}N_2O_3Cl_3S$ (397.6)	42.29 (42.55)	3.80 (3.82)	7.04 (7.06)
2f	4-(Me)-C_6H_4	S	174–176	62	$C_{15}H_{17}N_2O_3Cl_3S$ (411.6)	43.77 (44.02)	4.16 (4.18)	6.80 (6.76)
2g	4-(Cl)-C_6H_4	S	173–175	88	$C_{14}H_{14}N_2O_5Cl_4S$ (432.1)	38.92 (38.89)	3.27 (3.22)	6.48 (6.47)
2h	Furyl	O	Oil	71	$C_{12}H_{13}N_2O_5Cl_3$ (371.6)	38.79 (38.74)	3.53 (3.51)	7.53 (7.52)

[a] The melting point is uncorrected.
[b] Yield of isolated compound.

Table 3. Selected ^{1}H and ^{13}C NMR data[a] of compounds **2a–h**

Compound	^{1}H NMR δ, J (Hz); ^{13}C NMR δ, J (Hz)
2a	0.78 (t, 3H, OCH_2CH_3), 3.48 (d, 1H, H6, J = 10.8), 3.74 (m, 2H, OCH_2CH_3), 4.75 (d, 1H, H5, J = 10.8), 6.09 (s, 1H, NH), 6.20 (s, 1H, NH), 7.30 (m, 5H, Ph) 13.1 (OCH_2CH_3), 49.9 (C6), 56.2 (C5), 62.1 (OCH_2CH_3), 88.6 (C4), 104.5 (CCl_3), 127.5, 128.9, 129.4, 136.0 (Ph), 154.8 (C2), 171.7 (C=O)
2b	0.72 (t, 3H, OCH_2CH_3), 2.27 (s, 3H, Me), 3.45 (d, 1H, H6, J = 10.8), 3.78 (m, 2H, OCH_2CH_3), 4.70 (d, 1H, H5, J = 10.8), 5.58 (s, 1H, NH), 6.00 (s, 1H, NH), 7.18 (d, 2H, J = 7.6), 7.24 (d, 2H, J = 7.6)13.2 (OCH_2CH_3), 21.1 (Me), 49.9 (C6), 56.1 (C5), 62.1 (OCH_2CH_3), 88.7 (C4), 104.7 (CCl_3), 127.3, 129.6, 133.0, 139.4 (Ph), 154.5 (C2), 171.9 (C=O)
2c	0.85 (t, 3H, OCH_2CH_3), 3.50 (d, 1H, H6, J = 10.8), 3.84 (q, 2H, OCH_2CH_3), 4.81 (d, 1H, H5, J = 10.8), 6.10 (s, 1H, NH), 6.14 (s, 1H, NH), 7.31 (d, 2H, J = 8.4), 7.37 (d, 2H, J = 8.4), 13.2 (OCH_2CH_3), 49.9 (C6), 55.7 (C5), 62.3 (OCH_2CH_3), 88.6 (C4), 104.4 (CCl_3), 128.9, 129.2, 134.7, 134.7 (Ph), 154.6 (C2), 171.6 (C=O)
2d	0.75 (t, 3H, OCH_2CH_3), 3.43 (d, 1H, H6, J = 10.8), 3.78 (m, 2H, OCH_2CH_3), 3.72 (s, 3H, OMe), 4.69 (d, 1H, H5, J = 11.2), 5.70 (s, 1H, NH), 6.00 (s, 1H, NH), 6.89 (d, 2H, J = 8.8), 7.27 (d, 2H, J = 8.4) 13.2 (OCH_2CH_3), 49.9 (C6), 55.3 (OMe), 55.7 (C5), 62.1 (OCH_2CH_3), 88.6 (C4), 104.6 (CCl_3), 114.3, 127.9, 128.7, 131.9 (Ph), 154.6 (C2), 171.8 (C=O)
2e	0.78 (t, 3H, OCH_2CH_3), 3.60 (d, 1H, H6, J = 11.2), 3.82 (m, 2H, OCH_2CH_3), 4.81 (d, 1H, H5, J = 11.2), 6.30 (s, 1H, NH), 6.92 (s, 1H, NH), 7.14 (m, 5H, Ph) 13.1 (OCH_2CH_3), 48.3 (C6), 57.4 (C5), 62.5 (OCH_2CH_3), 87.9 (C4), 103.8 (CCl_3), 127.7, 129.1, 129.9, 134.4 (Ph), 171.6 (C=O), 178.6 (C2)
2f	0.79 (t, 3H, OCH_2CH_3), 2.36 (s, 3H, Me), 3.57 (d, 1H, H6, J = 11.2), 3.83 (m, 2H, OCH_2CH_3), 4.76 (d, 1H, H5, J = 11.2), 6.37 (s, 1H, NH), 6.99 (s, 1H, NH), 7.21 (m, 5H, Ph) 13.0 (OCH_2CH_3), 21.1 (Me), 48.3 (C6), 57.1 (C5), 62.4 (OCH_2CH_3), 87.8 (C4), 103.8 (CCl_3), 127.5, 129.6, 131.2, 139.8 (Ph), 171.5 (C=O), 178.4 (C2)
2g	0.85 (t, 3H, OCH_2CH_3), 3.56 (d, 1H, H6, J = 11.2), 3.87 (m, 2H, OCH_2CH_3), 4.82 (d, 1H, H5, J = 11.2), 6.20 (br, 1H, NH), 7.31 (d, 2H, J = 8.8), 7.40 (d, 2H, J = 8.8)13.2 (OCH_2CH_3), 48.3 (C6), 56.6 (C5), 62.6 (OCH_2CH_3), 87.8 (C4), 103.6 (CCl_3), 129.2, 129.3, 132.9, 135.9 (Ph), 171.3 (C=O), 178.5 (C2)
2h	1.05 (t, 3H, OCH_2CH_3), 3.77 (d, 1H, H6, J = 10.8), 4.00 (m, 2H, OCH_2CH_3), 4.97 (d, 1H, H5, J = 11.2), 5.79 (s, 1H, NH), 5.99 (s, 1H, NH), 6.36, 6.41, 7,45 (furyl). 13.4 (OCH_2CH_3), 47.5 (C6), 49.9 (C5), 62.4 (OCH_2CH_3), 88.5 (C4), 104.4 (CCl_3), 109.8, 110.5, 143.6, 148.4 (furyl), 154.4 (C2), 171.6 (C=O)

[a] NMR spectra were recorded on a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz) in $CDCl_3$/TMS.

Table 4. The estimated differences of energy for possible enantiomer pairs of **2a** obtained from the semi-empirical AM1 calculations

	Pair of enantiomers	ΔE[a]	%[b]
I	4*S*5*R*6*S*[c]/4*R*5*S*6*R*	0.0	99.0
II	4*R*5*S*6*S*/4*S*5*R*6*R*	2.8	0.9
III	4*S*5*S*6*R*/4*R*5*R*6*S*	4.2	0.1
IV	4*R*5*R*6*R*/4*S*5*S*6*S*	15.2	0.0

[a] kcal mol^{-1}.
[b] Percentage for enantiomer pairs estimated from ΔE.
[c] Presented in the Scheme 1.

The product **2** was formed instead of usual Biginelli product (dihydropyrimidinone) due to the great stability of the trihalomethyl semi-acetal moiety as observed in the literature.[8,10,13,14]

In conclusion, we presented the synthesis of a novel series of trichloromethylsubstituted tetrahydropyrimidinones by the Bignelli-type three-component cyclocondensation reaction of chlorinated 1,3-dicarbonyl compound with (thio)urea and aromatic aldehydes using $InBr_3$ as the catalyst, in good yields. Also, $InBr_3$ demonstrated to be an efficient catalyst for the Biginelli reaction furnishing tetrahydropyrimidinones in good yields and anhydrous reaction condition is not necessary. The biological properties of these compounds are currently under investigation.

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz), 298 K, digital resolution of ±0.01 ppm, 0.5 M in $CDCl_3$ containing TMS as in internal standard.

All spectra were acquired in a 5 mm tube, at natural abundance. The calculations were carried out by the Austin Model 1 (AM1) semi-empirical method, implemented in the HyperChem 6.03 package (1999).[25] Convergence to a local minimum is achieved when the energy gradient is <0.01 kcal mol^{-1}.

General procedure for the preparation of tetrahydropyrimidinones **2a–h**: A solution of ethyl trichloroacetoacetate **1** (1 mmol), substituted benzaldehydes or heterocyclic aldehyde (1 mmol), urea (thiourea) (1.3 mmol), $InBr_3$ (0.1 mmol), in dry THF (10 mL) was heated under reflux for 24 h. The product was extracted with $CHCl_3$ (2 × 20 mL) and dried ($MgSO_4$). The solution was filtered, the solvent evaporated and the product was recrystallized from cyclohexane or purified by silica column chromatography using hexane as the eluent (**2e**,**f**). Yields, physical data are shown in Table 1, and spectroscopic data are reported in Table 3.

Acknowledgements

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), PADCT-III/CNPq 62.0228/97-0-QEQ, and Fundação de Apoio a Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support. Fellowships from CAPES (W.C.), (M.V.M.T.) and (C.M.P.P.) are also acknowledged.

References and notes

1. (a) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043; (b) Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000**, *56*, 1859.
2. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
3. (a) Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454; (b) Lu, J.; Ma, H. *Synlett* **2000**, 63; (c) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075; (d) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
4. Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.
5. Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Synlett* **2003**, *6*, 858.
6. Ranu, B. C.; Hara, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
7. Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801.
8. (a) Martins, M. A. P.; Colla, A.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483; (b) Martins, M. A. P.; Bastos, G. P.; Bonacorso, H. G.; Zanatta, N.; Flores, A. F. C.; Siqueira, G. M. *Tetrahedron Lett.* **1999**, *40*, 4309; (c) Flores, A. F. C.; Brondani, S.; Zanatta, N.; Rosa, A.; Martins, M. A. P. *Tetrahedron Lett.* **2002**, *43*, 8701.
9. (a) Zanatta, N.; Rosa, L. S.; Cortelini, M. F. M.; Beux, S.; Santos, A. P. D.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2002**, *16*, 2404; (b) Martins, M. A. P.; Pereira, C. M. P.; Zimmermann, N. E. K.; Moura, S.; Sinhorin, A. P.; Cunico, W.; Zanatta, N.; Flores, A. F. C.; Bonacorso, H. G. *J. Fluorine Chem.* **2003**, *123*, 261.
10. (a) Martins, M. A. P.; Beck, P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Blanco, R. F.; Peres, R.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2002**, *43*, 7005; (b) Martins, M. A. P.; Sinhorin, A. P.; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P. *Synthesis* **2002**, *13*, 1959.
11. Martins, M. A. P.; Bastos, G. P.; Sinhorin, A. P.; Zimmermann, N. E. K.; Bonacorso, H. G.; Zanatta, N. *Synthesis* **2002**, *15*, 2220.
12. (a) Flores, A. F. C.; Zanatta, N.; Rosa, A.; Brondani, S.; Martins, M. A. P. *Tetrahedron Lett.* **2002**, *43*, 5005; (b) Martins, M. A. P.; Pereira, C. M. P.; Sinhorin, A. P.; Bastos, G. P.; Zimmermann, N. E. K.; Rosa, A.; Bonacorso, H. G.; Zanatta, N. *Synth. Commun.* **2002**, *32*(3), 419; (c) Zanatta, N.; Flores, D. C.; Madruga, C. C.; Faoro, D.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2003**, *6*, 894.
13. (a) Zanatta, N.; Pacholski, I. L.; Blanco, I.; Martins, M. A. P. *J. Braz. Chem. Soc.* **1993**, *2*(3), 118; (b) Zanatta, N.; Lopes, E. C. S.; Fantinel, L.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2002**, *39*, 943; (c) Bonacorso, H. G.; Lopes, I. S.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P. *J. Fluorine Chem.* **2003**, *120*, 29.
14. Bonacorso, H. G.; Lourega, R. V.; Wastowski, A. D.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2002**, *43*, 9315.
15. Bonacorso, H. G.; Duarte, S. H. G.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2002**, *8*, 1037.
16. Bonacorso, H. G.; Bittencourt, S. R. T.; Lourega, R. V.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2000**, *10*, 1431.
17. Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **1999**, *36*, 45.
18. Zucco, C.; Nome, F.; Rezende, M. C.; Rebelo, R. A. *Synth. Commun.* **1987**, *32*, 1585.
19. (a) Martins, M. A. P.; Freitag, R.; Flores, A. F. C.; Zanatta, N. *Synthesis* **1995**, 1491; (b) Martins, M. A. P.; Freitag, R.; Rosa, A.; Flores, A. F. C.; Zanatta, N.; Bonacorso, H. G. *J. Heterocycl. Chem.* **1999**, *36*, 217; (c) Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A. P.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293.
20. Martins, M. A. P.; Emmerich, D.; Beck, P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Brondani, S.; Peres, R.; Teixeira, M. V.; Zanatta, N.; Bonacorso, H. G. *Synth. Commun.* **2004**, *34*, 1915.
21. Martins, M. A. P.; Pereira, C. M. P.; Zimmermann, N. E. K.; Moura, S.; Sinhorin, A. P.; Cunico, W.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C. *Synthesis* **2003**, *15*, 2353.
22. (a) Kappe, C. O.; Falsone, S. F.; Fabian, W. M. F.; Bela, J. F. *Heterocycles* **1999**, *51*, 77; (b) Saloutin, V. I.; Burgat, Y. V.; Kuzueva, O. G.; Kappe, C. O.; Chupakhin, O. N. *J. Fluorine Chem.* **2000**, *103*, 17.
23. Dewar, M. J. S.; Zoebish, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1990**, *107*, 3902.
24. Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.
25. *HyperChem* 6.03 Hypercube: Gainesville, Fl, **1999**.