Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3919–3923

A new and efficient N-alkylation procedure for semicarbazides/semicarbazones derivatives

Dalci José Brondani,* Diogo Rodrigo de Magalhães Moreira, Maria Patrícia A. de Farias, Flávio Ricardo da S. Souza, Fábio Fernandes Barbosa and Ana Cristina Lima Leite

LabSINFA—Laboratory for the Planning, Synthesis and Evaluation of Pharmaceutical Products, Department of Pharmaceutical Science, Centre for Health Science, Federal University of Pernambuco, 50740-520 Recife, PE, Brazil

Received 10 November 2006; revised 7 March 2007; accepted 8 March 2007
Available online 13 March 2007

Abstract—An easy to perform and regioselective synthesis of *N*-alkyl hydrazones/hydrazides is described, which uses an aprotic medium with kinetic control. This procedure produced the desired monoalkylated or dialkylated amines with excellent yields and selectivities.

Semicarbazones and semicarbazides are important pharmacophores in the search for new drugs.[1] Their biological activity and diversity of medical applications are exemplified by a range of therapeutic properties, acting against *Trypanossoma cruzi*, tumors, and bacteria.[2] They can also be used as important intermediaries in organic synthesis, mainly for obtaining heterocycle rings, such as thiazolidones, oxadiazoles, pyrazolidones, and thiadiazoles.[3] The semicarbazone derivatives are polar profile compounds and this poses a crucial problem for the planning of bioactive agents. Generally, an improvement in the lipophilic character of bioactive compounds may produce attractive physicochemical advantages for drug design.[4]

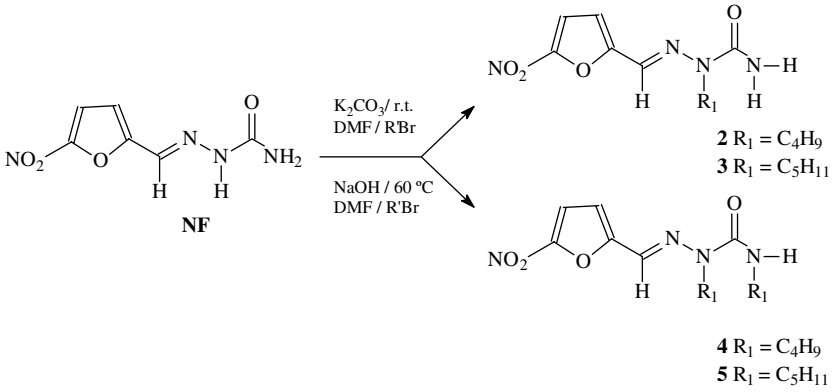
A large number of N-alkylation methods have been reported in recent years.[5] The literature describes the synthesis of tertiary from secondary amines as well as selective N-alkylation of primary to secondary amines,[6] although there is no mention of chemoselective N-alkylation of the hydrazides/hydrazones moieties. Transition-metal-mediated N-arylations and N-allylations have been developed as a mild and regioselective method for preparing substituted hydrazines and hydrazones.[7] Traditional methods employed for N-alkylation of hydrazide/hydrazone derivatives typically use a protic medium, but this procedure is only regioselective for the NH_2 of the amide.[8] Thus, new methods to yield N-alkylated compounds derived from semicarbazones/semicarbazides using chemoselectivity are of general interest.

Clearly, the occurrence of overalkylation, giving rise to a mixture of primary, secondary, and tertiary amines, as well as quaternary ammonium salts, is well known for the 'Hofmann alkylation'. Recently, Jung and co-workers provided an alternative solution to this chronic problem, by employing cesium hydroxide, and N-alkylation was efficiently carried out producing various secondary amines. A cesium base was found not only to give rise to mono-N-alkylation, but also to suppress overalkylations, favoring secondary amine formation over tertiary amines in the presence of activated 4 Å molecular sieves.[9]

The use of aprotic solvents in a reaction medium has received considerable attention because of the interesting level of chemoselectivity and environmental compatibility of these as well as the simplicity of the procedure.[10] For example, Srivastava and co-workers have observed that N-alkylation with primary alkyl halides in DMSO using K_2CO_3 as the base provided a simple method for obtaining either dialkyl- or trialkylamines selectively, by varying the nature of the electrophile used in these reactions.[11]

Keywords: N-Alkylation; Aprotic medium; Hydrazides; Hydrazones.
* Corresponding author. Tel./fax: +55 81 2126 8511; e-mail: dalci@ufpe.br

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.03.057



Scheme 1. Strategy for N-alkylations of hydrazones.

We report here a simple and efficient method for regioselective N-alkylation for semicarbazone/semicarbazide derivatives. In order to effect the regioselective procedure, an aprotic medium under kinetic control was employed (Scheme 1).

The N^2-alkyl derivatives were obtained with good selectivity after addition of the equivalent of 2.0 of the alkyl halide and then stirred for 36 h at room temperature, producing a 75% yield of N^2-alkylated product. The di-N^2,N^4-alkylated compounds were subsequently easily prepared when the reaction procedures were carried out at a temperature of 60 °C and with 2.2 of alkyl bromide with an excess of base, producing a good yield of the dialkylated products.

As shown in Table 1, the reaction of nitrofurazone (**NF**) as a model compound for the N-alkylation procedures was examined under various reaction conditions. NOE-*diff* NMR spectroscopic studies showed the structure of compound **3** prepared under these reaction conditions to be the *Z*-isomer. Among the bases examined, potassium carbonate generally produced the highest yields and selectivities, although sodium hydroxide also worked well, mainly for synthesis of the dialkylated compounds (entry 18). When various non-hydrogen bonding donor solvents were examined, DMF was found to be the most effective solvent, as can be seen in Table 1. The use of *N*-methyl-pyrrolidin-2-one (NMP, entry 11) also afforded a good yield with an acceptable reaction time, but this solvent generated more problems at the treatment or extraction stage than DMF or DMSO, owing to their higher solubility in organic media. Interestingly, for additional 2.0 stoichiometric amounts of alkyl bromide in 1.4 in an alkali base (K_2CO_3) at room temperature yielded 75 of the N^2-alkylated compounds for only 36 h of the reaction time, and, after 72 h of reaction time, a ratio of 65% and 15% of the desirable mono- and undesirable di-alkylated compounds was obtained, respectively (entries 3 and 5). As for the reaction selectivities, an excess of alkyl halides resulted in satisfactory yields but it was preferred

Table 1. N-Alkylation of nitrofurazone (**NF**) under different reaction conditions

Entry	Solvent	RBr (s.a.)[a]	Base (s.a.)[a]	Time (h)/*T* (°C)	Yield (%) **2/4**
1	DMF	1.0	K_2CO_3 (1.2)	48/rt	50/None
2	DMF	1.2	K_2CO_3 (2.0)	72/rt	60/None
3	DMF	2.0	K_2CO_3 (1.4)	36/rt	75/None
4	DMF	2.0	K_2CO_3 (2.5)	72/rt	67/3.0
5	DMF	2.5	K_2CO_3 (1.4)	72/rt	65/15[b]
6	DMF	1.2	NaOH (2.2)	24/rt	40/60[b]
7	DMF/MeCN	2.0	K_2CO_3 (1.4)	48/rt	60/None
8	DMSO	1.1	NaOH (2.0)	72/rt	60/None
9	DMSO	2.2	K_2CO_3 (2.5)	48/rt	60/10[b]
10	DMSO	2.0	NaOH (2.0)	36/rt	50/35[b]
11	NMP	2.0	K_2CO_3 (1.5)	36/rt	65/None[b]
12	CH_2Cl_2	1.2	Et_3N (1.2)	48/rt	30/10[c]
13	CH_3CN	2.0	K_2CO_3 (1.4)	72/rt	45/None[d]
14	DMF	1.2	K_2CO_3 (2.5)	1/60	50/20 [d]
15	DMF	2.2	K_2CO_3 (2.5)	18/60	20/78
16	DMF	2.2	K_2CO_3 (2.5)	24/60	None/99
17	DMF	2.2	NaOH (2.5)	2/60	None/99

[a] s.a. is stoichiometric amounts.
[b] Isolated through a short pad of silica gel (60–230 mesh).
[c] The reaction was sluggish and the s.m. was recovered predominantly.
[d] 30% of starting material (s.m.).

to carry out the reaction with a small excess of alkali base (1.4 equiv), in order to preserve the selectivity of the procedure (entry 4).

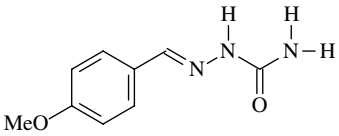
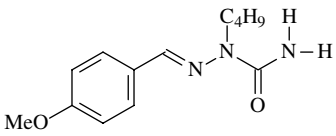
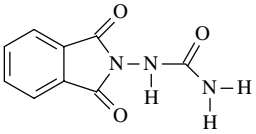
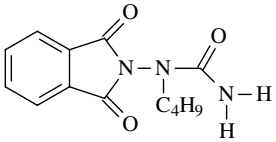
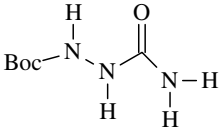
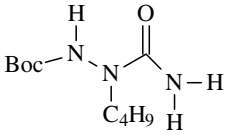
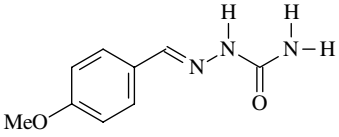
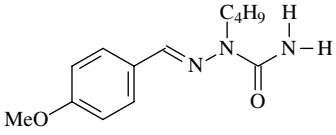
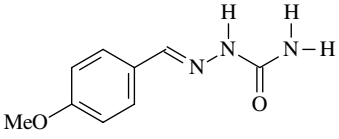
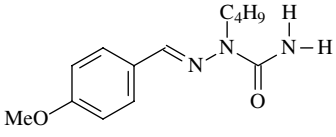
In fact, the reason for the chemoselective N^2-alkylation observed is that the imine proton should be sufficiently acidic to be abstracted by bases at room temperature compared to amide protons that are only available when heated or maximized by a protic medium. As predicted, the heating affords access first to the iminic proton and thereafter, to the abstracted amide protons. This phenomenon probably occurs as a result of some kind of solvation complex that preferentially occurs between the free electrons of the imine (which are more acid and protected from the semicarbazone protons). A nucleophilic attack on this free pair under aprotic medium is thereby brought about.

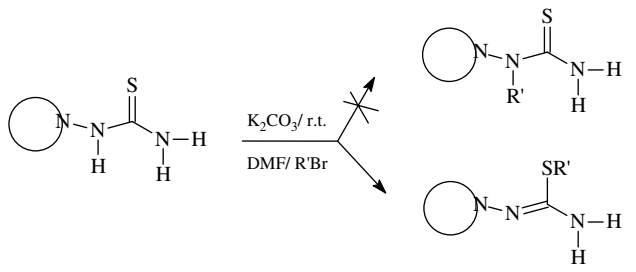
One crucial feature of this reaction procedure was the absence of overalkylation, while other known simple methods are inefficient in terms of chemoselective N-alkylation or require extremely long reaction times under difficult conditions, with the exception of the techniques described by Srivastava and co-workers.[11] It is worth noting that O-alkylation of phenol under these reaction conditions was not successful. No side pathway reactions were observed when phenol was added intentionally (entry 22). Similar trends were noted when propylamine was also intentionally added during the reaction procedure as described in entry 23, without production of the by-product (Table 2).

The hydrolysis of ester to carboxylic acid and alcohol and transformation of alkyl bromides to hydroxides or carbonates may also occur in an alkaline reaction medium, and although theoretically feasible,[12] side reactions were not observed in the reactions described in entries 3 and 5 (GC analysis). However, when a larger excess of base was used, a small quantity of by-product was observed (>5%) related to the decomposition of the *n*-bromobutane to monoalkylcarbonates and *n*-butanol, for entries 9 and 10 (GCMS), respectively.

Furthermore, the same hydrazones/hydrazides were subjected to N^2-alkylation under the standard conditions to evaluate their efficiency and chemoselectivity in general. As expected, this reaction procedure also led to the exclusive formation of N^2-alkylated from other semicarbazide/semicarbazone derivatives (entries 18–22).

Table 2. Efficient N-alkylation of semicarbazides/semicarbazones

Entry	Hydazide/hydrazone	Product (yield/time)
18		 (60/12 h)
19		 (75/5 h)
20		 (72/6 h)
21	 + $C_3H_5NH_2$	 (60/14 h)
22	 + PhOH	 (60/12 h)



Scheme 2. Alkylation of thiosemicarbazones afforded the S-alkylated products.

Unexpectedly, when thiosemicarbazone/thiosemicarbazide derivatives were reacted using this method, the desired N-alkylated compounds were not produced; instead of these, S-alkylated products were isolated, as proposed in Scheme 2. This illustrates a powerful preference of the thiocarbonyl carbon for being less basic but more susceptible to nucleophilic attack than an iminic proton in thiosemicarbazone/thiosemicarbazide groups,[13] and thus, these groups react in such a way as to favor the production of S-alkylated product under these reaction conditions.

Although it appears that this new synthetic protocol is only applicable to semicarbazones/semicarbazides of generic structure, the N^2-alkylated semicarbazones/semicarbazides may be easily converted into the corresponding N^2-alkylated thiosemicarbazones/thiosemicarbazides by way of the thiocarboxylation reaction, using Lawesson's reagent.[14] Further studies of this thiocarboxylation reaction will be reported in due course.

In conclusion, we have described a novel one-pot procedure for selective N^2-alkylation of hydrazone/hydrazide compounds.[15,16] This procedure offers several practical advantages, averting common side reactions under basic conditions and using techniques for the reaction and isolation of the products that are simple and inexpensive.

Acknowledgments

We would like to thank the CNPq (Grants # 471834/2006-8 and 475355/2006-7) and FACEPE for financial support. D.R.M.M. is a recipient of CAPES fellowship. Our thanks are also due to the Department of Chemistry at the Federal University of Pernambuco (UFPE), for recording the ^1H and ^{13}C NMR, IR spectra and elemental analyses of all compounds, to Ms. Célio R. M. Nascimento for the help in technical works (CNPq #500361/2004-5) and to Professor Dr. Ulf Ragnarsson (Sweden) to provide some references.

References and notes

1. Beraldo, H.; Gambino, D. *Mini-Rev. Med. Chem.* **2004**, *4*, 31.
2. (a) Leite, A. C. L.; Lima, R. S.; Moreira, D. R. de M.; Cardoso, M. V. de O.; Brito, A. C. G. de; Santos, L. M. F.; Hernandes, M. Z.; Kiperstok, A. C.; de Lima, R. S.; Soares, M. B. P. *Bioorg. Med. Chem.* **2006**, *14*, 3749; (b) Patole, J.; Padhye, S.; Padhye, S.; Newton, C. J.; Anson, C.; Powell, A. K. *Indian J. Chem., Sect. A* **2004**, *43*, 1654; (c) Du, X. H.; Guo, C.; Hansell, E.; Doyle, P. S.; Caffrey, C. R.; Holler, T. P.; McKerrow, J. H.; Cohen, F. E. *J. Med. Chem.* **2002**, *45*, 2695.
3. (a) Leite, A. C. L.; Santos, L. M. F.; Barbosa, F. F.; Cardoso, M. V. de O.; Moreira, D. R. de M.; Souza, I. A. *Biomed. Pharmacother.* **2006**, *60*, 121; (b) Du, C. X.; Guo, C.; Hansell, E.; Doyle, P. S.; Caffrey, C. R.; Holler, T. P.; McKerrow, J. H.; Cohen, F. E. *J. Med. Chem.* **2004**, *47*, 3212; (c) Kucukguzel, G.; Kocatepe, A.; De Clercq, E.; Sahin, F.; Gulluce, M. *Eur. J. Med. Chem.* **2006**, *41*, 353; (d) Wujec, M.; Pitucha, M.; Kosikowska, U.; Malm, A. *Acta Pharm.* **2004**, *54*, 251.
4. Clark, D. E. *Ann. Rep. Comp. Chem.* **2005**, *1*, 133.
5. Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785.
6. (a) Kurosu, M.; Dey, S. S.; Crick, D. C. *Tetrahedron Lett.* **2006**, *47*, 4871; (b) Bar-Haim, G.; Kol, M. *Org. Lett.* **2004**, *6*, 3549; (c) Maeda, H.; Kikui, T.; Nakatsuji, Y.; Okahara, M. *J. Org. Chem.* **1982**, *47*, 5167.
7. (a) Tsubrik, O.; Mäeorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **2002**, *43*, 6213; (b) Matunas, R.; Lai, A. J.; Lee, C. *Tetrahedron Lett.* **2005**, *61*, 6298.
8. (a) Cerecetto, H.; DiMaio, R.; Ibarruri, G.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Paulino, M. *Il Farmaco* **1998**, *53*, 89; (b) Chung, M. C.; Guido, R. V. C.; Martinelli, T. F.; Gonçalves, M. F.; Polli, M. C.; Botelho, K. C. A.; Varanda, E. A.; Colli, W.; Miranda, M. T. M.; Ferreira, E. I. *Bioorg. Med. Chem.* **2003**, *11*, 4779; (c) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205.
9. Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. *Org. Lett.* **1999**, *12*, 1893.
10. (a) Browman, W. R.; Coghlan, D. R. *Tetrahedron Lett.* **1997**, *53*, 15787; (b) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 9705; (c) Penso, M.; Albanese, D.; Landini, D.; Lupi, V.; Scaletti, D. *Synlett* **2006**, *5*, 741.
11. Srivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P. *Synth. Commun.* **1999**, *29*, 2085.
12. (a) Verdecchia, M.; Feroci, M.; Palombi, L.; Rossi, L. *J. Org. Chem.* **2002**, *67*, 8287; (b) Cella, J. A.; Bacon, S. W. *J. Org. Chem.* **1984**, *49*, 1122.
13. Langenhan, J. M.; Thorson, J. S. *Curr. Org. Synth.* **2005**, *2*, 59.
14. de Souza, M. V. N.; Ferreira, S. B.; Mendonça, J. S.; Costa, M.; Rebello, F. R. *Quim. Nova* **2005**, *28*, 77.
15. The representative procedure for the reaction of N^2-alkylation was as follows: The hydrazone **NF** (0.39 g, 2 mmol) was dissolved in anhydrous DMF (10 mL), then K_2CO_3 powder (0.40 g, 2.8 mmol, 1.4 equiv) was added to the solution at ambient temperature. Shortly afterwards (20 min), *n*-bromobutane (0.51 g, 4.0 mmol) was added in portions to the dark suspension. The reaction proceeded at ambient temperature for 36 h or for the length of time needed for the initial hydrazone **NF** to be consumed (controlled using TLC, *n*-hexane/AcOEt; 4/6). The inorganic salt was filtered and rinsed twice with dichloromethane. The solution was poured into water and extracted using dichloromethane (2×30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo resulting in N^2-alkylated hydrazone **2** (0.38 g, 75%) in the form of an orange solid. If the initial hydrazone has not been fully extracted by water, the resulting product can be diluted with ethyl ether, frozen overnight, and the unreacted hydrazone filtered. ^1H NMR $CDCl_3$ (300 MHz,

ppm) δ: 7.42 (s, 1H, CH=N); 7.37 (d, 1H, $J = 3.89$ Hz, Het-H), 6.80 (d, 1H, $J = 3.89$ Hz, Het-H); 6.63 (s, 2H, NH_2), 3.93 (t, 2H, $J = 7.19$ Hz, CH_2N), 1.60–1.47 (m, 2H, CH_2), 1.45–1.31 (m, 2H, CH_2), 0.95 (t, 3H, $J = 7.19$ Hz, CH_3). ^{13}C NMR $CDCl_3$ (75.5 MHz, ppm) δ: 156.08 (C=O), 152.68 (C1), 151.78 (C4), 123.73 (C5), 113.52 (C2), 110.76 (C3), 40.77 (C7), 27.16 (C8), 20.03 (C9), 13.71 (C10). Anal. Calcd for $C_{10}H_{14}O_4N_4$: C, 47.24; H, 5.55; N, 22.03. Found: C, 47.25; H, 5.88; N, 22.17. IR (KBr, cm^{-1}): 3272 and 3221 (N–H); 2950–2886 (aliphatic CH); 1707 (C=O); 1580 (C=N); 1484 (C=C); 1350 (NO_2).

16. The N^2,N^4-dialkylated compounds were diluted with ethyl ether and frozen overnight, filtered in vacuo and washed with water, a dilute solution of $KHSO_4$, and brine, dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil.