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The High-Pressure S_NAr Reaction of N-p-Fluorobenzyl-2-chlorobenzimidazole With Amines; An Approach to Norastemizole and Analogues

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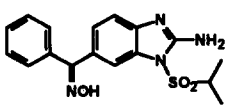
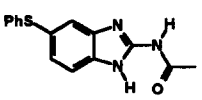
Abstract: N-*p*-fluorobenzyl-2-chlorobenzimidazole was treated under hyperbaric conditions with a variety of primary and secondary amines. The resulting S_NAr reaction proceeded smoothly to produce excellent yields of adducts in most cases. This methodology provides rapid access to astemizole, norastemizole and related analogues.

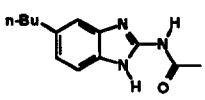
2-Aminobenzimidazoles are of significant medicinal interest owing to their wide ranging biological activity. Several examples, among the many which are known, are shown below. Astemizole for example is a



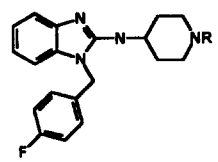
Zinviroxime (Z-isomer)
Enviroxime (E-isomer)
antiviral



Panacur
antithelmintic



Verminium
antinematode



Norastemizole :R = H
Astemizole :R = 
antiallergic, antihistaminc

potent antihistamine introduced for the treatment of allergic diseases. Its metabolite, norastemizole is currently in clinical trials.[1] A common preparation of these compounds often involves the nucleophilic aromatic substitution (S_NAr) reaction of an amino nucleophile with a 2-chlorobenzimidazole. Typical conditions for such reactions usually involve bringing the mixture of the nucleophile and electrophile to elevated temperatures in the presence of an acid scavenger (usually a 3° amine or pyridine derivative) for extended periods of time.[1] Such harsh conditions would be intolerant of many functional groups and may preclude the preparation of many new and potentially interesting compounds.

A palladium-catalyzed amination of 2-chlorobenzimidazoles based on Buchwald chemistry[3] has been recently reported[1]. Conditions were relatively mild, employing temperatures of 85°C and yields were moderate to good for a variety of piperidine nucleophiles. We wish to report our work in this area, specifically, the formation of 2-aminobenzimidazoles via an ultra high-pressure S_NAr reaction between a variety of primary and secondary amines and N-*p*-fluorobenzyl-2-chlorobenzimidazole (see table 1).

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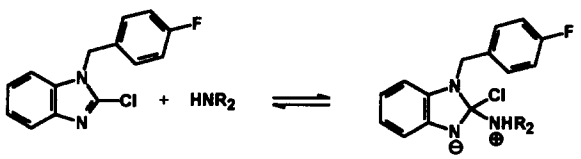
Equation 1 shows the rate-determining step for the amination of 2-chlorobenzimidazoles. The intermediate Meisenheimer complex in an S_NAr reaction is lower in volume than the overall molar volume of the starting materials and, therefore, has a negative volume of activation (ΔV_{act}). The ΔV_{act} for S_NAr reactions is both negative in sign and significant in magnitude, a typical value being about –30 to –40 cm^3/mol.[4] Such reactions are ideal candidates for ultra high-pressure techniques. Table 1 summarizes the results of our study involving the reaction at high pressures of a series of amines with N-*p*-fluorobenzyl-2-chlorobenzimidazole.[5,6]

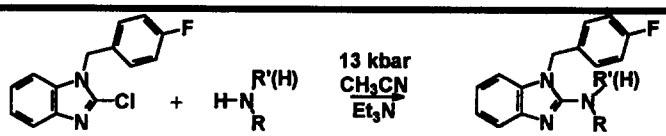


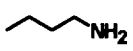
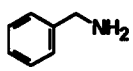
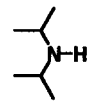
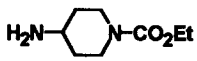
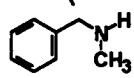
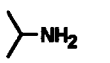
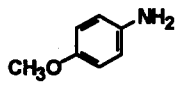
$\Delta V^{\neq}$ = -30 to -40 cm^3/mol (1)

1 2

It is not surprising that anilines (even relatively nucleophilic ones such as *p*-anisidine) fail to react under these conditions.[7] Also note that, while secondary amines such as diethylamine, N-methylbenzylamine, and morpholine give excellent yields of adduct, branching (as in the case of diisopropylamine) suppresses the desired reaction. *t*-Butylamine also failed to react under these conditions. None of the reactions proceeded to any appreciable extent at atmospheric pressure and temperature. The addition of catalytic fluoride ion (in the hopes of generating an intermediate fluoroaromatic compound[7,8]) failed to affect the reaction course.

Table 1: The high-pressure amination of N-*p*-fluorobenzyl-2-chlorobenzimidazole



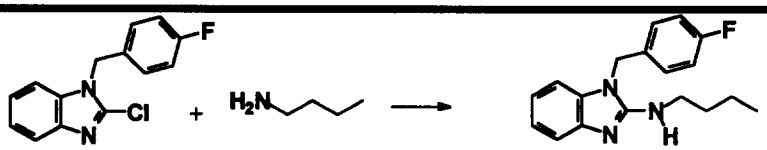
amine	time(d)	yield(%)	amine	time(d)	yield(%)
	2	91		7	80
	5	83		8	no reaction
	7	57		4	87
	3	66		3	90
	7	no reaction		5	no reaction

Three amines were subjected to typical[2] thermal reaction conditions. n-Butylamine, morpholine, and isopropylamine were heated with chlorobenzimidazole **1** in refluxing n-butanol containing triethylamine as an acid scavenger. After 8 h the morpholine adduct was formed in 90% yield (identical to hyperbaric conditions), however, the n-butyl adduct was formed in 52% yield with 39% of the starting material recovered after 4 days of reflux (compared with 91% yield after 2 days at 13 kbar). The most striking difference in performance thermally was observed in the case of isopropyl amine. After 5 days in refluxing n-butanol, no formation of the adduct was

observed (compared with 66% after 3 days at high pressure). Hyperbaric conditions appear to complement existing methodology by facilitating the formation of thermally inaccessible adducts as well as offering improved yields in other cases.

The conditions used in Table 1 represent optimum conditions as determined from a separate set of experiments, which examined the reaction of the well-behaved *n*-butylamine with the chlorobenzimidazole under a variety of reaction conditions. The variables were solvent, reaction time, the acid scavenger and the use of the free base vs. the hydrochloride salt of the 2-chlorobenzimidazole. The results of this study are shown in Table 2. Several points are worthy of note. The use of the hydrochloride salt of the 2-chlorobenzimidazole produces the product in almost identical yield to the free base. Although 2,6-lutidine is often used as an acid scavenger for the thermal variant of these reactions (due to its high boiling point), we found triethyl amine to be equally suitable. The variation of the solvent produced some interesting results. The use of THF or 2-methoxyethanol resulted in a diminished yield of product. The choice of 2-methoxyethanol was made as a mimic of *n*-butanol (which is used under typical thermal conditions) which would be less likely to freeze under hyperbaric conditions.[9] Nitromethane reacted violently on more than one occasion,[10] driving the pressurizing piston of the reactor down with enough force to blow a safety seal. The reaction mixture, which was recovered, was completely carbonized. Entry 9 represents our optimum conditions.

Table 2: Optimization of reaction conditions for the amination of N-*p*-fluorobenzyl-2-chlorobenzimidazole



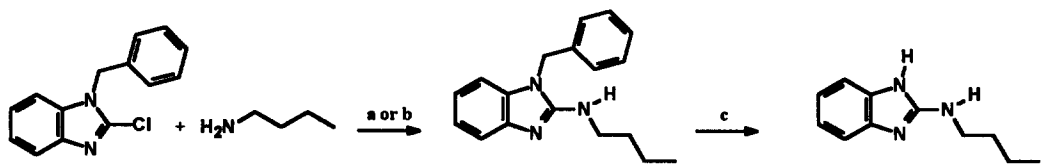
entry	benzimidazole	solvent	acid scavenger	time(h)	yield(%)
1	free base	CH_3CN	Et_3N	23	74
2	HCl salt	CH_3CN	Et_3N	23	74
3	free base	CH_3CN	2,6-lutidine	23	75
4	free base	THF	Et_3N	23	35
5	free base	$CH_3OCH_2CH_2OH$	Et_3N	23	40
6	free base	CH_3OH	Et_3N	23	0
7	free base	CH_3NO_2	Et_3N	23	0*
8	free base	CH_2Cl_2	Et_3N	23	0
9	**free base**	**CH_3CN**	**Et_3N**	**48**	**91**
10	free base	CH_3CN	Et_3N	72	91
11	free base	CH_3CN	Et_3N	96	91

* The reaction underwent a violent exothermic process

This methodology is also an efficient process for the formation of 2-aminobenzothiazoles. The application of high pressures to the reaction of *n*-butylamine with 2-chlorobenzothiazole reduced the reaction time from several days to 3 hours. The reaction of amines with 2-chlorobenzoxazoles is very fast under ambient conditions and the use of high pressures was not explored.

Although the methods described here were designed with norastemizole analogues in mind, they are quite general and may be used to prepare a variety of 2-amino benzimidazoles. The reaction of n-butylamine, for example, with N-benzyl-2-chlorobenzimidazole **3** (Scheme 1) produced the expected product **4** in 74% yield under our optimized hyperbaric conditions (compared with 24% yield after 6 days in refluxing n-butanol). The benzyl group could be hydrogenolytically removed to produce the parent compound **5** in 89% yield.

Scheme 1



a) 13 kbar/CH_3CN/3 d (74%) b) n-butanol/reflux/6 d (24%) c) ammonium formate/MeOH/5% Pd on C (89%)

In summary we have shown that the use of high pressures can greatly accelerate nucleophilic aromatic substitution reactions involving 2-chlorobenzimidazoles and amines. This method provides access to a variety of norastemizole analogues under low temperature and neutral reaction conditions. We are currently exploring the application of this methodology to the synthesis of other amino-substituted heterocycles.

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References and Notes

1. For leading references concerning norastemizole, and the nucleophilic substitution of 2-chlorobenzimidazoles see: Hong, Y.; Tanoury, G.J.; Wilkinson, S.; Bakale, R.P.; Wald, S.A.; Senanayake, C.H. *Tetrahedron Lett.* **1997**, 38, 5607-5610.
2. Janssens, F.E.; Hens, J.F.; Torremans, J.L.G.; Heykants, J.J.P. *European Patent* No. 0 232 937 B1, **1992**.
3. a) Wolfe, J.P.; Buchwald, S.L. *J. Am Chem. Soc.* **1997**, 119, 6054-6058. b) Wolfe, J.P.; Buchwald, S.L. *Tetrahedron Lett.* **1997**, 38, 6359-6362. c) Ahman, J.; Buchwald, S.L. *Tetrahedron Lett.* **1997**, 38, 6363-6366. d) Wolfe, J.P.; Buchwald S.L. *J. Org. Chem.* **1997**, 62, 6066-6068.
4. Isaacs, N.S., Chemical Transformations. In: Holzapfel, W.P.; Isaacs, N.S., editors. High-Pressure Techniques in Chemistry and Physics. Oxford University Press. **1997**, p 308.
5. All compounds showed satisfactory ^1H NMR, ^{13} NMR, ms, and infrared spectra.
6. Typical reaction procedure: To a solution of 1 (188 mg, 0.72 mmol) in 1.5 mL dry CH_3CN was added *n*-butylamine (143 μL, 1.44 mmol) and triethylamine (201 μL, 1.44 mmol). The solution was transferred to a length of heat-shrinkable Teflon™ tubing, clamped at one end with a brass clamp. Air was squeezed from the tube and it was sealed with a second brass clamp. The vessel placed in a LECO Tempres™ high pressure chemical reactor at 13 kbar for 48 hours. Upon depressurizing the reactor, the mixture was diluted with dichloromethane and washed with saturated $NaHCO_3$, brine and was dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel (eluted with 50% EtOAc/hexanes). The yield was 194 mg (91%), as a white solid.
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8. Finger, G.C.; Starr, L.D.; Dickerson, D.R.; Gutowsky, H.S.; Hamer, J. *J. Org. Chem.* **1963**, 28, 1666-1668.
9. See ref. 3 p 314.
10. See ref. 3 p 325.