One pot synthesis of azole carboximidamides and guanidinylation of amines

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Introduction

Amidino (carboximidamide) group transfer reagents LG-C(NR)NR_1R_2 are useful tools for the preparation of guanidines from amines both in solution and on the solid phase. Derivatives of pyrazole **1** (Fig. 1) are selective inhibitors of inducible nitric oxide synthase. The benzene ring in benzotriazole causes **2** to be more reactive than **1**[1-4]. The rate of guanidinylation of poorly nucleophilic amines with **2**:Y=H, Cl or NO_2; R=R_1=Boc; R_2=H is significantly superior [3] to those with **1**: R=R_1=Boc; R_2=H or even the more reactive reagent, where LG=CF_3SO_2NH-.

1,2 have been prepared by prolonged heating of benzotriazole/pyrazole with acids and cyanamides in organic solvents, from azoles and carbodiimide, from β-diketones or pyrimidines and aminoguanidine, and by reaction of Bt-C(=NH)-Bt [5] or benzotriazole-1-carboximidoyl chlorides with amines.

Results and Discussion

For the preparation of **1** and **2** (Scheme 1) we apply solvent-free classical heating (*Method A*) or microwave irradiation (*Method B*) of pyrazole or benzotriazole salts with organic or inorganic acids (pK_a from –2 to –13) and 5-30% excess of wide variety of cyanamides. Other azoles: 3,5-Dimethyl-1*H*-pyrazole, 1*H*-Indazole, 1*H*-[1,2,3]Triazole, 1*H*-[1,2,4]Triazole; 5-Nitro-1*H*-benzotriazole, 5-Chloro-1*H*-benzotriazole, 1*H*-Benzotriazole-5-carboxylic acid 5,6-Dichloro-1*H*-benzotriazole reacts likewise with cyanamides under solvent-free conditions. The reaction yields of **1**, **2** are >90% and the reaction times are exceedingly short. **1**, **2** can be prepared advantageously using *Method B*, where the reaction is speeded-up by several 10-fold. The optimal temperature for azole salts with Tos-OH, H_2SO_4 and HCl was ~ 60 - 80 °C, for TFMSA-salts < 40 °C. The reaction has high conversion rate even at room temperature. All cyanamides, with an exception of those sterically hindered, afford almost quantitatively expected products **1**,**2**.

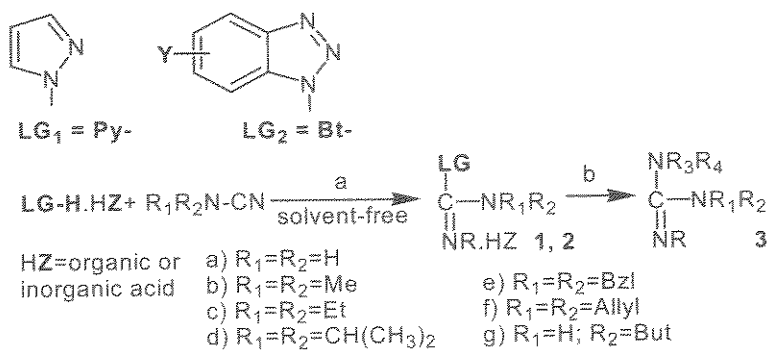

Fig. 1. Reagents and conditions: a. Δ (-20 - +80 °C), 5 - 360 min (Method A) or MW irradiation, 0.5 - 12 min (Method B); b. 2 (1 - 5M in MeCN) / NEt_3 / HNR_3R_4 =2/2/1, 60 °C, 2 - 6 hrs.

*Table 1: Guanidinylation of selected amines with reagents **2a** and **2b**: series **3a**, R=H; series **3b**, R=Me*

Amine	Guanidine[a] **3a(3b)**	Yield (%)
Z-Orn-OH [b]	Z-Orn[C(NH)NR_2]-OH	97(95)
Boc-NHNH_2	Boc-NHNHC(NH)NR_2	97(98)
$C_6H_5CH_2NH_2$	$C_6H_5CH_2$NHC(NH)NR_2	99(99)
$C_6H_5CH_2ONH_2$	$C_6H_5CH_2$ONHC(NH)NR_2	99(99)
$C_6H_5CH_2NHCH_3$	$C_6H_5CH_2$N[C(NH)NR_2]CH_3	94(87)
$C_6H_5NH_2$	C_6H_5NHC(NH)NR_2	98(95)
2,4-$(MeO)_2C_6H_3NH_2$	2,4-$(MeO)_2C_6H_3$NH C(NH)NR_2	95(95)
4-$NH_2C_6H_4NH_2$	4-$NH_2C_6H_4$NH C(NH)NR_2	98 (95)[c]

*[a] – purity 92-98% (LC-MS or ^1H NMR); [b] – 0.2 M in MeCN/H_2O=5/1, 2.5 h at 60 °C. The half time for guanidinylation of Z-Orn-OH with **2a/2b** was <1 min.; [c] – only $NH_2C_6H_4NHC(NH)NH_2$, respectively $NH_2C_6H_4NHC(=NH)N(CH_3)_2$ were detected by LCMS;*

Both methods are superior to previously reported ones in terms of high yields, facile work-up, short reaction times and easy scale-up. The use/cost of the solvents have been minimized. The purity of resulting crude **2** was sufficiently high to be used in a simple one-pot procedure for guanidinylation of amines (*Table 1*). In addition, both **2** and a benzotriazole, present in crude **2** or as result of N-amidination, are well soluble in organic solvents, which allows the reaction procedure to be accomplished with easy work-up [4] for isolation of the corresponding guanidines (up to tetra-substituted), without any need of activating agents or protecting group manipulations. A resin bound ornitine-containing peptide Boc-Orn-Phe-Ala-O-2ClTrt-resin react separately with 4 equivalents **2a, 2b** or **2c**, containing 4 equivalents DIEA in THF (0.3M) overnight at room temperature and after cleavage/deprotection forms H-Orn[C(NH)N(R_2)]-Phe-Ala-OH, where R=H, Me or Et, with yield >95%. The crystal structure of **2b**, a reagent for the preparation of N^{ω},N^{ω}-dimethylarginine in solution and on solid support, has been determined.

In conclusion, in this study we have presented two simple eco-friendly methods for preparation of azole-carboximidamides 1 and 2, valuable synthons for guanidinylation of amines both in solution and on the solid supports.

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