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A new reagent and its polymer-supported variant for the amidination of amines

Gerald Dräger,[a] Wladimir Solodenko,[a] Josef Messinger,[b] Uwe Schön[b] and Andreas Kirschning[a,*]

[a]*Institut für Organische Chemie der Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany*
[b]*Solvay Pharmaceuticals GmbH, Hans-Böckler-Allee 20, D-30173 Hannover, Germany*

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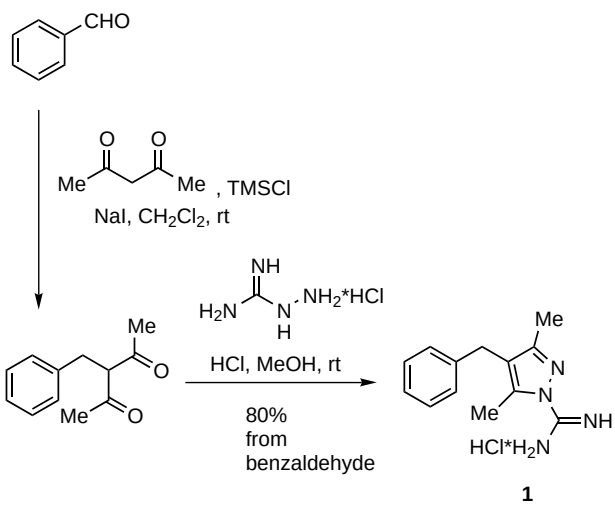
Abstract—New reagents for the high yielding amidination of primary and secondary amines are described. By attaching a benzyl substituent to the 3,5-dimethyl-1*H*-pyrazole-1-carboxamidine ring, a reagent **1** is obtained which allows easy work-up after amidination because of solubility of byproducts in organic solvents. In addition, the polystyrene-bound analogue **2** was prepared which allows amidination of various amines with high purity.

The guanidine moiety is present in many biologically active compounds and plays a key role in the biochemical recognition and catalysis.[1] Synthetic guanidines are widely used in the design of drugs covering a variety of therapeutic areas.[2] As a consequence, guanidine synthesis has been intensively investigated using traditional solution-phase chemistry.

However, due to the polarity of the guanidine group and hence excellent water solubility of organic materials that bear the guanidine moiety, work-up and separation from by-products including those derived from the reagent are often cumbersome. Therefore, recent efforts have been focussed on solid phase based amidination techniques. These latter methods either result in resin-bound guanidines which must be cleaved from the polymer support in the last step[3–5] or use resin-bound isothiourea intermediates which liberate the guanidines after treatment with amines.[6,7] In these cases, *N*-BOC-protected guanidines are generated requiring an additional deprotection step which is associated with work-up problems. In the context of solution phase methodologies it is well established that pyrazole-1-carboxamidines are well suited to convert primary and secondary amines to the corresponding guanidines.[8,9] In this report, we describe the preparation of new 4-benzyl-3,5-dimethyl-1*H*-pyrazole-1-carboxamidine hydrochloride **1** which is a very versatile amidinating reagent for primary and secondary amines. In comparison to the known analogous unsubstituted reagent work-up of the reaction mixture is substantially simplified because the byproduct from the amidination, the dimethylated benzylpyrazole, can easily be removed due to its solubility in organic solvents. Reagent **1** was prepared in two steps in 80% yield by employing literature procedures described for analogous transformations.[10,11] Here, benzaldehyde and acetylacetone served as starting materials (Scheme 1).[12]

In a similar way, we prepared polymer-bound 3,5-dimethyl-1*H*-pyrazole-1-carboxamidine **2** which to our knowledge is the first polymer-bound amidinating agent which directly transfers the unprotected amidate moiety onto primary and secondary amines (Scheme 2).[13]



Scheme 1.

* Corresponding author.

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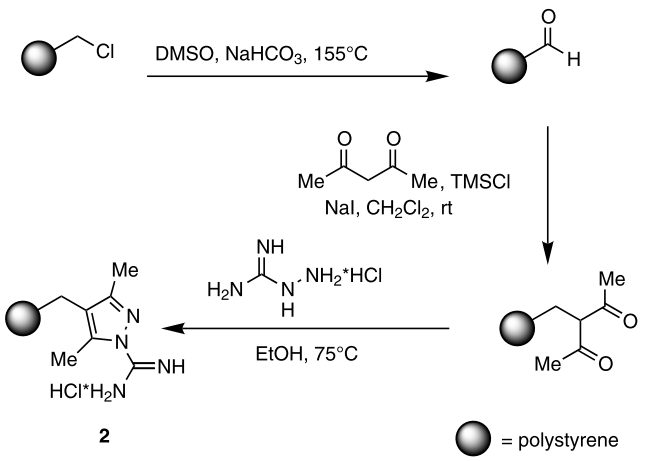

Scheme 2.

The efficiency of reagents **1** and **2** as a amidinating agents was established in the direct amidination of a set of primary and secondary amines (Table 1).[14] Amidination of various amines including a proline derivative and a β-amino acid as well as aminodeoxyhexoses using reagent **1** proceeded with excellent yields. The byproducts are soluble in organic solvents while the target guanidines stay in the aqueous phase. Likewise, polymer-bound reagent **2** was also found to convert various primary and secondary amines to the corresponding guanidines in good yields (Table 1). The functionalized polymer was used in excess and reacted with amines in THF at 60°C in the presence of Et_3N. After the transformation was completed (TLC) the guanidines were isolated from the solution phase by treatment with anion-exchange resin followed by lyophilization.[15]

Both protocols allow the preparation of unprotected guanidines with a purity exceeding 90–95% (Table 1). The amidination is compatible with a wide variety of functional groups, but amines with low solubility in organic solvents (glycine, phenylglycine) or with enhanced thermolability (*tert*-butyl amine, glycine methyl ester, sarcosine methyl ester) gave unsatisfactory results.

In summary, we have developed new reagents for the one-step transformation of various primary and secondary amines into the corresponding guanidines. Both the soluble as well as the insoluble reagents can easily be prepared from readily available starting materials. They are stable and the polymer-supported variant can be used in excess to allow quantitative conversion, simple purification and isolation of the final products.

Acknowledgements

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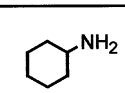
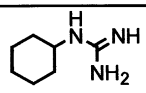
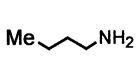
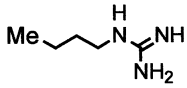
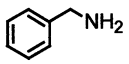
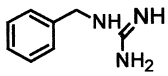
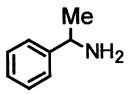
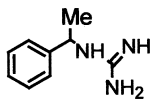
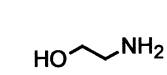
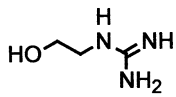
Table 1. Amidinations of selected amines with reagents **1** and **2**[a]

Amine	Reagent	Guanidine	Yield (%)[b]
	**1**		96
	2		69
	**1**		95
	2		82
	**1**		98
	2		90
	**1**		>99
	**1**		>99
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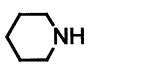
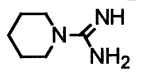
	**1**		92
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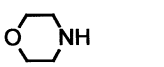
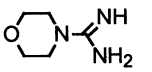
	**1**		>99
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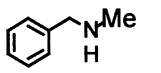
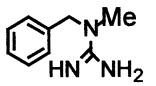
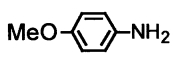
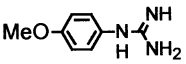
	**1**		88
	**1**		97
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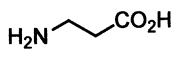
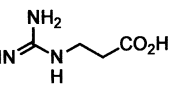
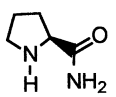
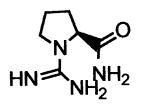
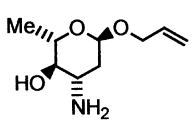
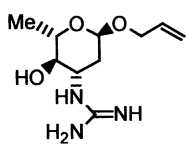
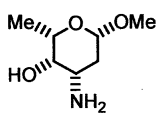
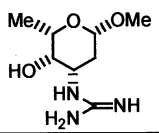
	**1**		47
	2		50
	**2**		87
	**2**		>99
	**2**		94

[a]For details refer to references and notes. [b]Yields refer to isolated pure products. The purity of all compounds was >95%.

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12. *Preparation of reagent **1***: To a solution of benzaldehyde (2.04 mL, 400 mmol) and acetylacetone (4.1 mL, 40 mmol) in dry dichloromethane (100 mL) under nitrogen were added sodium iodide (30 g, 200 mmol) and dropwise trimethylchlorosilane (25.6 mL, 200 mmol). After stirring for 6 h the mixture was hydrolyzed with an aqueous solution of sodium thiosulfate and extracted with dichloromethane (3×20 mL). The combined organic extracts were dried, and the solvent was removed in vacuo. The remaining diketone was dissolved in a solution of methanol (100 mL), aminoguanidine hydrochloride (4.2 g, 38 mmol) and conc. HCl (7.5 mL), and the mixture was stirred overnight at rt. The solvent was evaporated in vacuo, the solid residue was treated with refluxing ethyl acetate (2×20 mL), filtered and dried in high vacuum, affording the title compound **1** (8.4 g, 31.7 mmol; 80%): mp 186–188°C (MeOH, ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ: 2.10 (s, 3H), 3.45 (s, 3H), 3.79 (s, 2H), 7.15–7.35 (m, 5H), 9.37 (br s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.1, 12.1, 28.1, 121.7, 126.2, 128.1, 128.5, 139.4, 139.9, 153.2, 153.7. MS: 228 (M^+ as free base). Anal. calcd for $C_{13}H_{16}N_4 \cdot HCl$: C, 58.98; H, 6.47; N, 21.16. Found: C, 58.60; H, 6.44; N, 21.09.
13. *Preparation of reagent **2***: Merrifield resin (2.5 g, 4.3 mmol chloride/g, 2% DVB, 200–400 mesh) and sodium bicarbonate (9.24 g, 110 mmol) were stirred in dry DMSO (25 mL) at 155°C under nitrogen for 20 h. After cooling water (50 mL) was added, the resin was filtered, washed successively with water, methanol, dichloromethane, methanol, and dried in high vacuum at 30°C over P_2O_5. The dried resin (ca. 2.2 g) was suspended in dry dichloromethane (30 mL), sodium iodide (8.24 g, 55 mmol) was added, and with stirring under nitrogen trimethylchlorosilane (6.98 mL, 55 mmol) and acetylacetone (1.65 mL, 16 mmol) were added separately during 6 h (syringe pump). The mixture was stirred overnight at rt and then treated with water (50 mL). After 10 min the resin was filtered and washed with water, methanol, acetone, dichloromethane, and dried in high vacuum. The resin obtained (ca. 3 g) and aminoguanidine hydrochloride (1.16 g, 10.5 mmol) were stirred in abs. ethanol (30 mL) at 75°C for 20 h. The resin was filtered and washed with methanol, water, methanol, acetone, dichloromethane, methanol, and dried in high vacuum at 40°C over P_2O_5. The reagent **2** (ca. 3.5 g) was obtained as a brown resin. The loading with active groups was determined to be ca. 1.7 mmol/g based on the weight increase. Combustion analysis: N 10.3 (corresponds to the loading ca. 1.8 mmol/g); IR: $\nu_{C=N}$ 1675 cm^{-1} (strong).
14. *Typical amidination using reagent **1***. Cyclohexylamine-*N*-carboxamidine (first example in Table 1): A solution of reagent **1** (265 mg, 1 mmol), cyclohexylamine (50 mg, 0.5 mmol) and triethylamine (139 μL, 1 mmol) in dry acetonitrile (1.25 mL) was heated at 60°C for 24 h. The solvent was removed in vacuo and the residue was treated with water (5 mL), sonicated for 2 min, and separated by centrifugation. The supernatant was separated by decantation, and the solid precipitate was treated with water (2×) in a similar way as described above. The combined supernatants were washed with ethyl acetate (2×5 mL), and flushed through a column loaded with Amberlite IRA-400 (hydroxide-form, 10 mL) by eluting with water. The eluate was cooled to −30°C and lyophilized furnishing cyclohexylamine-*N*-carboxamidine as a light-green gummy solid (67.8 mg, 0.48 mmol; 96%). ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ: 1.18, 1.28, 1.53, 1.67, 1.79 (5m, 5×2H), 3.35 (m, 1H), 4.5–6.0 (br s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.9, 24.8, 32.2, 49.1, 156.0; MS: 141 (M^+).
15. *Typical amidination using reagent **2***. Piperidine-*N*-carboxamidine (11th example in Table 1): Reagent **2** (870 mg), piperidine (29.7 μL, 0.3 mmol), and Et_3N (208 μL, 1.5 mmol) in dry THF (4 mL) were stirred at 60°C for 24 h. After completion of the reaction (TLC monitoring) the mixture was filtered, the resin on the filter was washed with THF (2×2 mL) and methanol (3×4 mL), and the combined filtrates were evaporated in vacuo. The residue was taken up in water (5 mL) and passed through a column of Amberlite IRA-400 (hydroxide-form, 10 mL), eluting with water. The eluate was cooled to −30°C and lyophilized affording piperidine-*N*-carboxamidine (31 mg, 0.245 mmol; 82%) as a light green adhesive solid. ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ: 1.37–1.54 (m, 6H), 3.31 (t, J=5.25 Hz, 4H), 4.3–5.2 (br s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.0, 25.1, 45.9, 158.8; MS: 127 (M^+).