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New Cellulose-Supported Reagent: A Sustainable Approach to Guanidines

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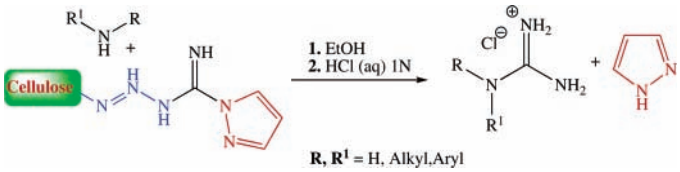
ABSTRACT

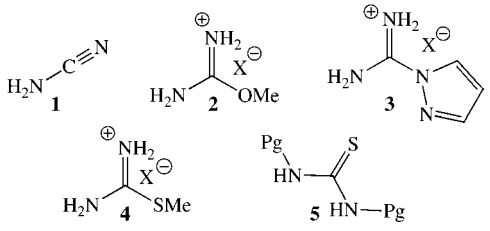


A new cellulose-supported reagent for the synthesis of guanidine in aqueous medium is reported starting from commercially available functionalized cellulose beads. Primary and secondary amines, anilines, and amino acids were transformed to the corresponding guanidines in high yields and under very mild conditions.

The guanidine group is a decisive feature in many biologically active compounds.[1] A growing number of biologically and pharmaceutically relevant compounds incorporate guanidine functionality. Compounds containing the guanidine core have been isolated from many species, such as algae, sponges, and other marine and freshwater microorganisms.[2] Moreover synthetic guanidines have found wide applications in the engineering of advanced synthetic molecular recognition devices, sensors, organic materials, and phase-transfer catalysts.[3]

As a consequence, guanidine synthesis has been intensively investigated using traditional solution-phase chemistry. Typically, the synthesis of guanidine-containing compounds involves treatment of an amine with an electrophilic amidine species. The most commonly used reagents include (Scheme 1) cyanamide[4] (**1**), *O*-methylisourea hydrogen sulfate[5] (**2**),

Scheme 1. Guanidinylating Reagents



derivatives of pyrazole-1-carboxamidine[6] (**3**), *S*-methylisothiouronium salts[7] (**4**), and protected thiourea derivatives (**5**), the last mainly used in conjunction with either mercury salts[8] or the Mukaiyama reagent.[9] Moreover, using reagent

(1) The references cited are only a very few examples of biologically active guanidines. (a) *Guanidines: Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds*; Mori, A., Cohen, B. D., Lowenthal, A., Eds.; Plenum Press: New York, 1985. (b) *Guanidines 2: Further Explorations of the Biological and Clinical Significance of Guanidino Compounds*; Mori, A., Cohen, B. D., Koide, H., Eds.; Plenum Press: New York, 1987. (c) Greenhil, J. V.; Lue. P. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science: New York, 1993; Vol. 30, Chapter 5. For reviews of guanidine natural products, see: (d) Durant, G. J. *Chem. Soc. Rev.* **1985**, *14*, 375−398. (e) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377−409. (f) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339−365. (g) Heys, L.; Moore, C. G.; Murphy, P. J. *Chem. Soc. Rev.* **2000**, *29*, 57−67. (h) Berlink, R. G. S *Nat. Prod. Rep.* **2002**, *19*, 617−649 and references therein.

(2) See refs 1e and 1f and reference therein.

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5, formed *N*-protected guanidines require an additional deprotection step that is associated with workup drawbacks.[10]

A direct synthetic approach should have the advantage of a quick assembly of the guanidines without using protecting groups. However, owing to the polarity of the guanidine group and hence excellent water solubility of organic materials that bear the guanidine moiety, workup and separation from byproducts including those derived from the reagent in Scheme 1 are often cumbersome. Therefore, recent efforts have been focused on solid-phase-based amidination techniques.[11]

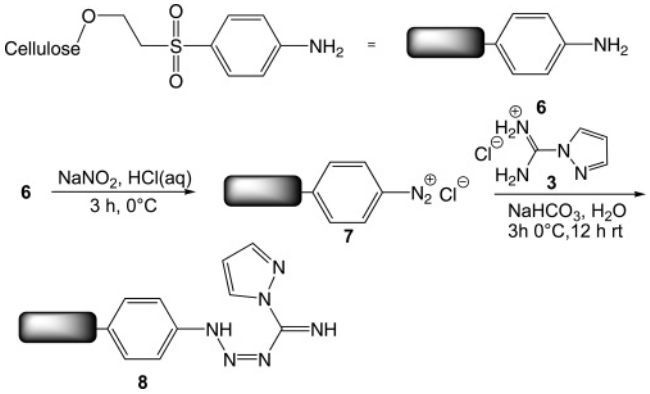
The triazene linker developed by Brase offers an elegant solution to immobilize and modify guanidines on solid support.[12] In fact the synthesis of a small library of guanidines on solid support has been described using this linker.[13] In developing a new strategy for the synthesis of free guanidines, we pointed out the possibility of developing a new supported reagent to generate guanidines in solution. As most of the guanidinylating agents work well in polar media, polystyrene-based supports were considered unsuitable for this pourpose.

Thus, we have examined the applicability of beaded cellulose as the support for this reagent.[14] Cellulose shows good swelling properties both in polar solvents and water and is biodegradable also.[15] Furthermore, the low cost of the cellulose beads may make it possible to carry out a solid-phase synthesis on a macro scale also.

Herein, we wish to report a new example of a cellulose-supported reagent (inspired by compound **3**) for the preparation of an array of guanidines using exclusively EtOH and H_2O as the solvents.

The triazene linker was prepared starting from aniline-functionalized cellulose **6**[16] with aqueous nitrous acid at 0 °C under classical conditions (Scheme 2).[17] Diazotization

Scheme 2. Synthesis of Solid-Supported Reagents **8**



in water with $HCl/NaNO_2$ leads successfully to the polymer-bound diazonium salt **7**, whereas diazotization with with ^{t}-BuONO and boron trifluoride etherate or $NOBF_4$ [18] in organic solvents was less successful and resulted in poor yields of the compound **7**.

The attachment of the guanidinylating agent to the cellulose beads was carried out by shaking at 0 °C a cold aqueous solution of 1*H*-pyrazole-1-carboxamidine hydrochloride **3** with solid-supported diazonium salt **7** in the presence of $NaHCO_3$ (Scheme 2) for 12 h.[19] As observed from elemental analyses,[20] an almost quantitative loading was achieved using a 4-fold excess of guanidinylating reagents **3**.

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(16) The cellulose employed was a modified bead form containing aminoaryl-ethyl sulphone groups in flexible chains obtained from Iontosorb, Czech Republic (Usti nad Labem). The content of amino aryl groups in Iontosorb AV can be regulated according to the customer's demands in the range 0.1−2.8 mmol/g

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(18) (a) Wannagat, U.; Hohlstein, G. *Chem. Ber*. **1955**, *88*, 1839−1846. (b) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572−1574. (c) Brase, S.; Kobberling, J.; Enders, D.; Lazny, R., Wang, M.; Brandtner, S. *Tetrahedron Lett.* **1999**, *40*, 2105−2108.

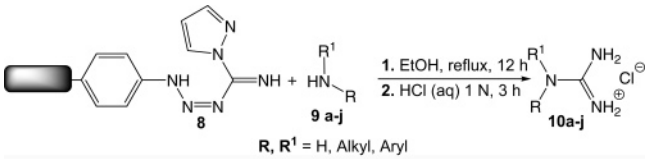
During the development of this protocol, the progress of the reaction was verified by using a colorimetric test. The diazonium group on cellulose was monitored using the β-naphthol test.[21] Thereby, a negative test indicates that the diazonium salt **7** on the solid support was completely converted to **8**. The triazene **8** is stable,[22] and its swelling properties are comparable with those of the starting material. The color of the beads is slightly yellow-orange.

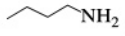
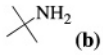
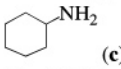
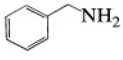
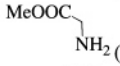
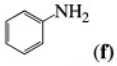
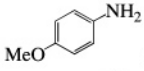
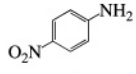
To investigate the scope and limitations of the new solid-supported agent, a series of structurally different amines **9** were reacted with the solid-phase-bound reagent **8** in EtOH[23] at pH = 7−8 to prevent the displacement of pyrazole before reaction or undesired cleavage. Optimal conversions were achieved using 5 equiv of amines in refluxing EtOH for 12 h.[24] Guanidines **10a**−**j** (Scheme 3) were obtained in good to acceptable yields.[20] Most of primary and secondary amines react efficiently with **8** affording compounds **10a**−**j**. Poor nucleophiles such as arylamines (entries 6 and 7) provide the corresponding guanidines in good yields.[25] *p*-Nitroaniline was the only one that did not react (entry 8). Moderate yields were obtained with glycine methyl ester (entry 5), whereas hindered diisopropylamine gave good yields of guanidine **10j**. Typically, the target molecules were prepared from 2 g of cellulose, which correlated to about 1.0 mmol of product.[26]

Finally, chemical identity was established by ^{1}H NMR and HPLC measurements corroborated by comparing their ^{1}H NMR data with the spectra obtained from conventional solution-phase experiments.

In summary, we have described a new solid supported reagent for converting a variety of amines to guanidines using a biodegradable solid support and renewable solvents. The new reagent can be used on a macro scale, giving access, after cleavage, to guanidinium salts without further purifications.

Scheme 3. Synthesis and Cleavage of Cellulose-Attached Guanidines



entry	amine	guanidine	isolated yield (%)
1	 (a)	**10a**	98
2	 (b)	**10b**	91
3	 (c)	**10c**	95
4	 (d)	**10d**	98
5	 (e)	**10e**	65
6	 (f)	**10f**	71
7	 (g)	**10g**	78
8	 (h)	**10h**	n.r.
9	 (i)	**10i**	93
10	 (j)	**10j**	91

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Supporting Information Available: Synthetic procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) **Preparation of Guanidinylating Reagent 8.** Aniline cellulose **6** (2 g, 1 mmol) was added to a chilled solution of $NaNO_2$ (0.21 g, 3.0 mmol) in H_2O (20 mL). The mixture was shaken at 0 °C while 37% aqueous HCl (2.6 mL, 3.1 mol) was added in portions over 10 min. Then the slurry was shaken at 0 °C for a further 3 h, filtered, and washed with chilled water (5 × 20 mL). The resulting cellulose-bound diazonium salt **7** was transferred into water (10 mL) at 0 °C. Then an ice−water solution (15 mL) of 1*H*-pyrazole-1-carboxamidine hydrochloride **3** (0.59 g, 4 mmol) and $NaHCO_3$ (0.42 g 5 mmol) was added in portions at 0 °C over 10 min. The reaction mixture was shaken at 0 °C for 3 h and for 12 h at room temperature. After filtration, the cellulose was washed with H_2O (20 mL) and stirred in EtOH (20 mL) for 1 h, filtered again, and washed with EtOH (20 mL), H_2O (20 mL), and EtOH (20 mL). The cellulose **8** was then swollen in EtOH (15 mL). A few beads of cellulose were dried in high vacum for 1 d to yield pale brown beads of **8**. Functionalization of all cellulose-bound amines was verified by the β-naphthol test. The efficiency of the transformation according to nitrogen elemental analysis proved to be over 99%. IR (KBr): 3228, 3097, 1675 (s), 1600, 1518, 1441, 1379, 1340 (s), 1240, 1153 (s), 828.

(20) The loading was determined by comparison of the amount of N and S determined before and after the reaction with **3**. The contents of N and S in **6** were found to be N 0.75%, S 1.73%. Elementary analysis of S, N content for the cellulose **8** after the loading of pyrazole-1-carboxamide **3** was found be N 4.30%, S 1.59%.

(21) Gaggini, F.; Porcheddu, A.; Reginato, G. Rodriquez, M.; Taddei, M. *J. Comb. Chem.* **2004**, *6*, 805−810.

(22) The triazene **8** can be stored at 0−4 °C for long times.

(23) Water can be used instead, although longer times are required.

(24) After several crossed analyses, we have found that it is possible to quantify the formation of desired supported guanidine by HPLC analysis of the pyrazole released in the reaction.

(25) Reaction time for aromatic amine: 24 h.

(26) **Sample Procedure.** The cellulose **8** previously obtained (1 mmol) was suspended in EtOH (10 mL/g resin), treated with benzylamine (0.53 g, 547 μL, 5 mmol), and heated at reflux for 12 h. The cellulose beads were filtered, then washed sequentially with EtOH, NMP, 2% $NaHSO_4$ (aqueous), H_2O, and EtOH (3 × 15 mL/g of cellulose), and dried in a vacuum. The corresponding guanidine was cleaved from the polymer by treatment with 1 N HCl in H_2O (15 mL) under mechanical agitation for 3 h. Subsequently, the cellulose was filtered and washed with H_2O (2 × 10 mL) and EtOH (15 mL). (In order to increase the recover yields it is better to repeat the cleavage step three times). The cellulose was then washed finally with H_2O (2 × 15 mL), and the combined filtrates were concentrated under vacuum to afford benzylguanidine hydrochloride **10d** (0.182 g, 98%). White crystalline solid, mp 173−174 °C. ^{1}H NMR (DMSO-d_6): δ (ppm) 8.15 (brs, 1H), 6.84−7.62 (m, 9H), 4.35 (brs, 2H). ^{13}C NMR (DMSO-d_6): δ (ppm) 162.8, 141.7, 121.9, 118.0, 114.0, 110.3. (ESI + ve ion): calcd for $C_8H_{12}N_3$ 150.1 [$(M + H)^+$], found. 150.2. HPLC purity 99%. Anal. Calcd for $C_8H_{12}ClN_3$: C, 51.76; H, 6.51; N, 22.63. Found: C, 51.81; H, 6.44; N, 22.66.