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Angeli−Rimini's Reaction on Solid Support: A New Approach to Hydroxamic Acids

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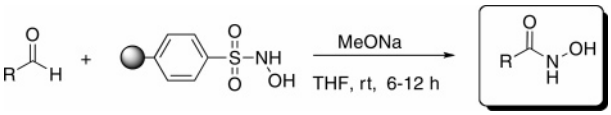

Angeli−Rimini's reaction has been performed for the first time on solid phase. A convenient one-step procedure for the synthesis of hydroxamic acids starting from aldehydes and solid-supported *N*-hydroxybenzenesulfonamide is reported. The hydroxamates are isolated in good to high yields and purities by simple evaporation of the volatile solvents, after treatment of the crude reaction mixture with sequestering agents.

Hydroxamic acids are strong metal ion chelators,[1] they possess a wide spectrum of biological activities, such as antibacterial, antifungal, anti-inflammatory, anti-asthmatic properties, etc.,[2] and are identified as potent inhibitors of matrix metalloproteinases, a family of zinc-dependent enzymes associated with diseases, such as cancer, arthritis, and multiple sclerosis.[3] Moreover, several hydroxamic acids show therapeutic potential as ribonucleoside diphosphate reductase (RDPR) inhibitors,[4] a key enzyme involved in the rate-determining step of DNA biosynthesis, while the hydroxamic acid function is present in several natural products and widespread siderophores.[5] The growing number of published synthetic methods further points to the biological significance of hydroxamic acids.[6]

During these last years, solid-phase organic synthesis (SPOS) has become an important tool for production of combinatorial libraries and represents an important tool for the rapid identification of new lead compounds.[7] Recently, several routes for the preparation of hydroxamic acids on solid phase have been published. These generally involve either the preparation of a special linker to which hydroxylamine is attached through a special *N*- or *O*-linkage or the formation of masked hydroxamic acids on solid support.[8] Hydroxamic acids might also be obtained by direct cleavage of resin-bound esters with hydroxylamine.[9] The development of alternative methods to synthesize this class of compounds is therefore desirable.

The research of unconventional reaction pathways has frequently encouraged the transfer of solution-phase methodologies to the solid phase.[10] In this context, here we wish to report a novel technique that exploits a solid-phase version of the Angeli−Rimini's reaction as an alternative means to achieve hydroxamic acids.

At the end of the last century, in 1896, Angeli and Rimini[11] discovered that *N*-hydroxybenzenesulfonamide **1** formed hydroxamic acids **4** in fair to good yields if treated with aldehydes

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(1) (a) Kurzak, B.; Kozlowski, H.; Farkas, E. *Coord. Chem. Rev.* **1992**, *114*, 169. (b) Boukhris, S.; Souizi, A.; Robert, A. *Tetrahedron Lett.* **1996**, *37*, 179.

(2) (a) Weber, G. *Cancer Res.* **1983**, *43*, 3466. (b) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49. (c) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563.

(3) (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735. (b) Cheng, M.; De, B.; Pikul, S.; Almstead, N. G.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, C. M.; Gu, F.; Dowty, M. E.; Mieling, G. E.; Janusz, M. J.; Wang-Weigand, S. *J. Med. Chem.* **2000**, *43*, 369 and references therein. (c) Brown, P. D.; Davidson, A. H.; Gearing, A.; Whittaker, M. In *Matrix Metalloproteinase Inhibitors In Cancer Chemotherapy*; Clendeninn, N. J., Appelt, K., Eds.; Humana Press: Totowa, NJ, 2001; pp 113−142. (d) Park, J. D.; Kim, D. H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3161. (e) Wu, T. Y. H.; Hassig, C.; Wu, Y.; Ding, S.; Schultz, P. G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 449. (f) Molteni, V.; He, X.; Nabakka, J.; Yang, K.; Kreusch, A.; Gordon, P.; Bursulaya, B.; Warner, I.; Shin, T.; Biorac, T.; Ryder, N. S.; Goldberg, R.; Doughty, J.; He, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1477.

(4) (a) Ashley, G. W.; Stubbe, *J. Pharmacol. Ther.* **1985**, *30*, 301. (b) Reichard, P.; Threnberg, *A. Science* **1983**, *221*, 514−515. (c) Stubbe, J. *J. Biol. Chem.* **1990**, *265*, 5329. (d) Khan, S. I.; Grinstaff, M. W. *Tetrahedron Lett.* **1998**, *39*, 8031.

(5) (a) Durette, Ph. L.; Baker, F.; Baker, P. L.; Boger, J.; Bondy, S. S.; Hammond, M. L.; Lanza, T. J.; Pessolano, A. A.; Caldwell, G. C. *Tetrahedron Lett.* **1990**, *31*, 1237. (b) Zhu, J.; Robin, S.; Goasdoué, C.; Loupy, A.; Galons, H. *Synlett* **1995**, 97.

(6) (a) Altenburger, J. M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *33*, 5055. (b) Tamaki, K.; Ogita, T.; Tanzawa, K.; Sugimura, Y. *Tetrahedron Lett.* **1993**, *34*, 683. (c) Staszak, M. A.; Doecke, C. W. *Tetrahedron Lett.* **1994**, *33*, 6021. (d) Bonnette, C.; Salmon, L.; Gaudemer, A. *Tetrahedron Lett.* **1996**, *37*, 1221. (e) Sparks, S. M.; Vargas, J. D.; Shea, K. J. *Org. Lett.* **2000**, *2*, 1473. (f) Liljebris, C.; Larsen, S. D.; Ogg, D.; Palazuk, B. J.; Bleasdale, J. E. *J. Med. Chem.* **2002**, *45*, 1785. (g) Katritzky, A. R.; Kirichenko, N.; Rogovoy, B. V. *Synthesis* **2003**, 2777. (h) Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett.* **2003**, *5*, 2715. (i) Ech-Chada, A.; Minassi, A.; Berton, L.; Appendino, G. *Tetrahedron Lett.* **2005**, *46*, 5113. (j) Gissot, A.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 6925.

(7) (a) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132−143. (b) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. (c) Hermkens, P. H.; Ottenhejim, H. C.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. (d) Hall, S. E. *Mol. Diversity* **1999**, *4*, 131−142.

(8) (a) Floyd, C. D.; Lewis, C. N. PCT Int. Appl. WO 9626223 A1 960829, 1996. (b) Floyd, C. D.; Lewis, C. N.; Patel, S. R.; Whittaker, M. *Tetrahedron Lett.* **1996**, *37*, 8045. (c) Floyd, C. D.; Whittaker, M. PCT Int. Appl. WO 9626918 A1 960906, 1996. (d) Chen, J. J.; Spatola, A. F. *Tetrahedron Lett.* **1997**, *38*, 1511. (e) Richter, L. S.; Desai, M. C. *Tetrahedron Lett.* **1997**, *38*, 321. (f) Ngu, K.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 7088. (g) Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311. (h) Bauer, U.; Ho, W.-B.; Koskinen, A. P. *Tetrahedron Lett.* **1997**, *38*, 7233 (i) Mellor, S. L.; Chan, W. C. *Chem. Commun.* **1997**, *20*, 8045. (j) Khan, S. I.; Grinstaff, M. W. *Tetrahedron Lett.* **1998**, *39*, 8031. (k) Dankwardt, S. M. *Synlett* **1998**, 761. (l) Ede, N. J.; James, I. W.; Krywult, B. M.; Griffiths, R. M.; Eagle, S. N.; Gubbins, B.; Leitch, J. A.; Sampson, W. R.; Bray, A. M. *Lett. Pept. Sci.* **1999**, *6*, 157. (m) Barlaam, B.; Koza, P.; Berriot, J. *Tetrahedron* **1999**, *55*, 7221. (n) Grigg, R.; Major, J. P.; Martin, F. M.; Whittaker, M. *Tetrahedron Lett.* **1999**, *40*, 7709. (o) Dankwardt, S. M.; Billedeau, R. J.; Lawley, L. K.; Abbot, S. C.; Martin, R. L.; Chan, C. S.; Van Wart, H. E.; Walker, K. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2513. (p) Thouin, E.; Lubell, W. D. *Tetrahedron Lett.* **2000**, 457. (q) Sasubilli, R.; Gutheil, W. G. *J. Comb. Chem.* **2004**, *6*, 911. (r) Ho, C. Y.; Strobel, E.; Ralbovsky, J.; Galemmo, R. A., Jr. *J. Org. Chem.* **2005**, *70*, 4873.

(9) Zhang, W.; Zhang, L.; Li, X.; Weigel, J. A.; Hall, S. E.; Mayer, J. P. *J. Comb. Chem.* **2001**, *3*, 151.

(10) Although many useful reactions have been optimized for SPOS, we have observed that the trivial shift of standard solution-phase reactions to the solid-phase can often be problematic.

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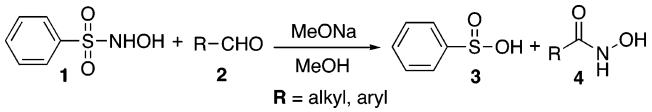
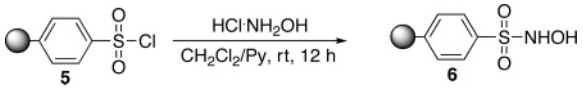
SCHEME 1. Angeli−Rimini's Reaction



SCHEME 2. Polymer-Bound *N*-Hydroxybenzenesulfonamide 6 Synthesis



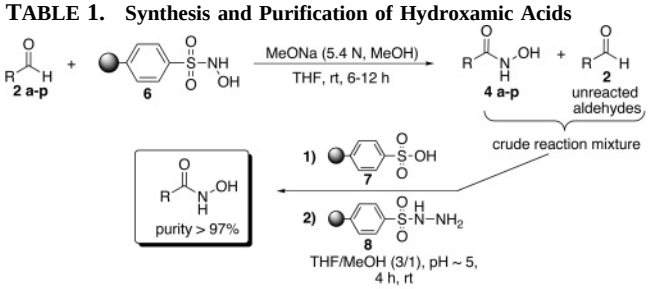
2 in the presence of a strong base in MeOH (Scheme 1).[12] Unfortunately, the acidic workup afforded the desired hydroxamic **4** together with the benzensulfinic acid **3** as a byproduct. Because this impurity is not easily removed from the desired product, the Angeli−Rimini's reaction has been seldom used in organic synthesis.

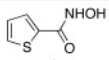
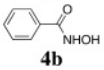
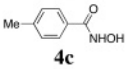
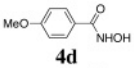
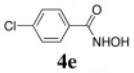
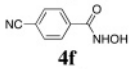
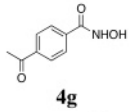
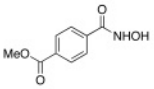
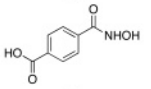
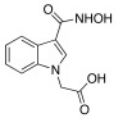
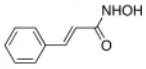
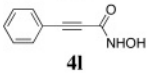
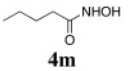
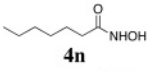
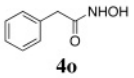
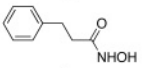
Intrigued by this old procedure, we envisaged that a solid-supported *N*-hydroxybenzenesulfonamide reagent would solve this problem and make easier the preparation and the final purification of the hydroxamic acids. This new supported reagent **6** was so prepared by shaking at room temperature a pyridine solution of $HCl·NH_2OH$ with polystyrene sulfonyl chloride[13] (Ps−TsCl) **5** in CH_2Cl_2 for 12 h, as outlined in Scheme 2.

Colorimetric and spectroscopic techniques often offer simple, practical tools to qualitatively and/or quantitatively monitor solid-phase reactions.[14] Thus, the formation of *N*-hydroxybenzenesulfonamide on the resin was monitored using a simple bead-staining test[15] to check if the reaction was complete (Scheme 3). When the final color of the beads is white or off-white, the reaction is ended.

This rather sensitive assay enables the detection of even small amounts of free chlorosulfonyl groups on the resin, and thereby a negative test indicates that the hydroxylamine is quantitatively anchored on the solid support. The presence on the resin of hydroxamic acid groups can be easily detected using an iron-(III) test, too, that gives an intensely colored complex (rust-brown) with this functional group.[15] As observed from the colorimetric analyses, a quantitative loading was achieved using a 5-fold excess of hydroxylamine hydrochloride. The outcomes of the colorimetric tests were further confirmed by elemental analyses.

TABLE 1. Synthesis and Purification of Hydroxamic Acids



entry	aldehyde	hydroxamic acid	time (h)	% yield (purity)
1	**2a**	 **4a**	7	95 (99)
2	**2b**	 **4b**	7	97 (99)
3	**2c**	 **4c**	7	99 (98)
4	**2d**	 **4d**	7	95 (98)
5	**2e**	 **4e**	6	98 (99)
6	**2f**	 **4f**	7	95 (97)
7	**2g**	 **4g**	7	63 (99)
8	**2h**	 **4h**	6	98 (99)
9	**2i**	 **4i**	7	95 (98)
10	**2j**	 **4j**	7	88 (98)
11	**2k**	 **4k**	6	91 (98)[a]
12	**2l**	 **4l**	8	93 (98)
13	**2m**	 **4m**	12	40 (97)
14	**2n**	 **4n**	12	55 (97)
15	**2o**	 **4o**	10	80 (97)
16	**2p**	 **4p**	12	71 (97)

[a] Only the trans isomer was isolated.

(11) (a) Angeli, A. *Gazz. Chim. Ital.* **1896**, *26*, 17. (b) Rimini, E. *Gazz. Chim. Ital.* **1901**, *31*, 84. (c) Angeli, A.; Angelico, E. *Gazz. Chim. Ital.* **1904**, *34*, 50. (d) Yale, H. L. *Chem. Rev.* **1943**, *33*, 228. (e) Vlasov, B. M.; Zaharova, O. V. *J. Org. Him.* **1974**, *10*, 66. (f) Lwowsky, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 897.

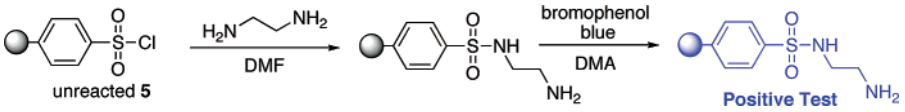
(12) A possible reaction mechanism was described in the literature, even if not definite in all details: Hassnerr, A.; Wiederkehr, E.; Kascheres, A. J. *J. Org. Chem.* **1970**, *35*, 1962.

(13) (a) The polystyrene sulfonyl chloride employed was obtained from Argonaut Technologies Inc. (Biotage AB, loading 2.70 mmol/g). (b) For a reviews on the use of Ps−TsCl, see: Huang, W.; He, B. *Chin. J. React. Polym. (Engl.)* **1992**, *1*, 61. (c) For additional product information, see the specifications (pdf file) available free of charge via the Internet at http://www.biotage.com/Download.aspx?id=1785.

(14) Different colorimetric methods to monitor functional groups on resin are collected in: Gaggini, F.; Porcheddu, A.; Reginato, G.; Rodriquez, M.; Taddei, M. *J. Comb. Chem.* **2004**, *6*, 805.

(15) A few beads of the resin from the mixture reaction were treated with ethylenediamine to convert unreacted sulfonyl chloride functions into sulfonamide-linked primary amines. The free amine groups on polymer were monitored using the bromophenol blue test (or Kaiser test). In the presence of free amine (it means unreacted sulfonyl chloride moiety), resin beads immediately take on blue appearances. Alternatively, beads in which the starting chlorosulfonyl groups have reacted completely retain their original color.

SCHEME 3. Bromophenol Blue Test



The formation of *N*-hydroxybenzenesulfonamide on the resins was also characterized by FTIR, monitoring the infrared absorption band at 1365 cm^{-1} (−S−O stretch of $-SO_2Cl$), which shifts to 1320 cm^{-1} ($-SO_2-NH-$) as well as by the appearance of a typical OH absorption at 3430 cm^{-1}.

To check the eventual limits of the applicability of Ps−Ts−NHOH **6** in the Angeli−Rimini reaction, a series of structurally different aldehydes **2a**−**p** were reacted in parallel with this solid-phase-bound reagent. Owing to the poor swelling ability of polystyrene/1% divinylbenzene resin in conventional MeOH, all the reactions were performed in THF.

The resin **6**, suspended in THF, was treated with a solution of NaOMe in MeOH and then reacted with several aliphatic and aromatic aldehydes. After the reaction was complete, the resin was filtered off and dry MeOH was added to the starting solvent.[16] The solution containing the crude reaction mixture was then treated with acid ion-exchange resin Dowex **7** that quenches excess MeONa by reducing the pH to ∼5[17] (Table 4). The unreacted aldehyde was then sequestered by polystyrene sulfonyl hydrazide **8** (Ps−Ts−$NHNH_2$), leaving behind a solution containing the desired product, free of starting components (HPLC or TLC analysis). Finally, the mixture was filtered through a small plug of silica gel to remove traces of water and salts, and the resulting solution was concentrated to give the desired *N*-hydroxyamide. To optimize the yield, the reaction was initially conducted with 1 equiv of Ps−Ts−NHOH **6** relative to the aldehydes **2a**−**p**. In this case, the conversion from aldehyde to hydroxamic acid was incomplete, and significant amounts of aldehydes were recovered (20−30%). Two equivalents of **6** was, however, sufficient to achieve a high conversion of aldehydes **2a**−**p** into the *N*-hydroxyamides **4a**−**p** (Table 1).

The progress of the reaction was monitored by HPLC, and this procedure affords the desired hydroxamic acids **4a**−**p** in good yields and excellent purity. All the runs were conducted at least in duplicate or in multiple batches to ensure the reproducibility of the methodology. The results are summarized in Table 1.

Aromatic or conjugated aldehydes (**2a**−**l**) react in excellent yields, whereas the reaction with aliphatic aldehydes (compare **2m**−**p** with **2a**−**l**) requires longer times and leads to *N*-hydroxyamides **4m**−**p** in lower, although satisfactory, yield.[18]

As it is known,[19] ketones do not react under these conditions,[20] and therefore, when both aldehyde and ketone groups are present on the same substrate (**2g**), only the aldehyde moiety is selectively transformed into the corresponding *N*-hydroxyamide function. Noteworthy also is that the Ps−Ts−NHOH **6** reacts with aldehyde **2h**, affording the desired hydroxamic acid **4h**, not affecting the methyl ester.

As seen from the data referring to the compounds **4i** and **4j** (Table 1), this synthetic approach indicates even an interesting solution for the preparation of monohydroxamic acids, in a single step, from substrates containing carboxylic acid functions, too, without implementing protection/deprotection strategies. Within the limits of the Angeli−Rimini's procedure, due mainly to the basic conditions,[21] this method is easy to use for many synthetic purposes as it neither produces byproducts nor requires tedious purifications of the product obtained. In conclusion, we report a convenient preparation of a polymer-supported *N*-hydroxybenzenesulfonamide that was successfully used to convert aldehydes into hydroxamic acids, adapting a seldom-used procedure in order to facilitate access to the hydroxamic acid functionality. The procedure is selective and tolerates the presence of other functional groups on the substrates. Work is underway to explore if the resin-bound *N*-hydroxybenzenesulfonamide **6** could also be used as an interesting source for producing HNO in biochemistry studies.[22]

Experimental Section

Polymer-Bound *N*-Hydroxybenzenesulfonamide (6) Synthesis. Polystyrene sulfonyl chloride **5** (222 mg, 0.6 mmol) suspended in anhydrous THF (5 mL) was treated with a pyridine solution (5 mL) of hydroxylamine hydrochloride (208.5 mg, 3.00 mmol) at room temperature for 12 h. The reaction progress was monitored by the colorimetric "*bromophenol blue test*" (negative) and "*iron(III) test*" (positive). The polymer was filtered, washed several times with THF, and then a mixture of THF and H_2O (1:1), H_2O, and anhydrous THF, and, finally, dried under high vacuum to give off-white resin beads. IR (KBr): 3430 (br), 1446, 1320 (s), 1162 (s).

Sample Procedure. The resin **6** previously obtained (0.6 mmol) was swelled in 5 mL of THF, treated with a 5.4 N solution of NaOMe (1.2 mmol) in MeOH (0.22 mL), shaken at room temperature for 10 min and then reacted with *p*-chlorobenzaldehyde **2e** (42.2 mg, 0.3 mmol). After 6 h, the resin was filtered off and alternatively rinsed with THF (4 × 1 mL) and MeOH (3 × 1 mL). The combined extract (THF:MeOH 3:1) was transferred to another tube, and Dowex 50WX2-400 ion-exchange resin **7** (150 mg) was portionwise added to adjust the pH to ∼5. The ion-exchange resin was collected by filtration, the solution treated with Ps−Ts−$NHNH_2$ **8** (200 mg, 0.6 mmol), and the suspension shaken at room temperature for additional 4 h. The resin was filtered out and washed with THF (2×), MeOH (2×), DCM (2×), and MeOH (2×). The filtrate was concentrated in vacuo, diluted with DCM (2 mL), and filtered through a small plug (1.00 cm) of silica gel with hexane/AcOEt (1:1). Finally, the solution, after evaporation of the solvent, gave the desired *N*-hydroxyamide **4e** (50.4 mg, 98% respect to **2e**) as the sole product. The product gives a red color with $FeCl_3$, too.

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

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(16) Using 1 mL of MeOH for each 3 mL of THF.

(17) The pH was adjusted as required by adding the acid ion-exchange resin Dowex **7** and confirmed by a pH meter.

(18) The reaction did not reach completion even after 2 days.

(19) Panizzi, L.; diMaio, G.; Tardella, P. A.; D'Abbiers, L. *Ric. Sci., Parte 8, Sez. A* **1961**, *31*, 312.

(20) Under this reaction condition, acetophenone or hexan-2-one did not react even after 1 week at room temperature or 12 h at refluxing temperature.

(21) In particular, the use of MeONa in the reaction could not allow the use of optically active amino acids that are known to racemize easily under these conditions.

(22) Wilson, E. K. *Chem. Eng. News* **2004**, *82*, 39.