7.93 (4 H), 7.60 (2 H), and 7.56 (2 H) (all d's, $J = 9$, aromatic H's); D/CI-MS (NH_3) m/z 526, 528, 530 ($[M + NH_4]^+$), 482, 484, 486 ($[M - 44]^+$).

Acknowledgment. We are grateful to Dr. Y. Kawamatsu, Takeda Chemical Industries, for discussions. The studies were supported by NIH Grant CA 11572.

Vacuum Dry Column Chromatography

Eric Jan Leopold

Chemistry Department, Stanford University, Stanford, California 94305

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Today's organic chemist is faced with a dry column of techniques for purifying mixtures on a large or small scale. Unfortunately, the recent advances in separation science often involve expensive equipment.

Reported here is the development of vacuum dry column chromatography (VDCC). This method involves no expensive or exotic equipment. VDCC has been used successfully in our laboratories in separating large and small samples with a significant saving of time. The use of dry-column chromatography (DCC) was first detailed by Loev and Snader.[1]

In the process of dry-column chromatography, a nylon tube is sealed at one end and packed with dry adsorbent. The compound to be purified is placed at the top of the column and a small puncture hole is made at the column base. The eluting solvent is added at the top of the column and is allowed to flow by gravity to the bottom. The various impurities are separated from the desired compound(s) in the fully developed column. Although elution for a small column by using DCC can be carried out in 30 min, with larger columns much longer elution times are required.

The technique described here makes use of a vacuum during the process of dry-column chromatography. Thus, the vacuum is applied to the base of the dry column and the eluting solvent is pulled by the vaccum down the column, the advantage being that the time for elution is greatly reduced. The rapid elution has no effect on the resolving power of the adsorbent.

Another advantage of VDCC is that compounds that are unstable to silica gel or other adsorbents are in contact with the adsorbent for a minimum length of time. Further, if an inert gas is used during the preparation of the column as described below, the elution can be carried out in the absence of air in the case of air-sensitive compounds. In this method, 160-gauge nylon tubing, of various circumferences (2, 3, 4, 5, or 6 in.)[2] is used to contain the adsorbent such as silica gel or alumina, but in no way is the process limited to these two substances.

For mixtures of average separation, VDCC has been used successfully to purify 22 g of material in a 28 × 2 in. (circumference) nylon column by using 700 g of silica gel. The impurities were located at TLC R_f values of 0.25 and 0.7 while the desired material had an R_f of 0.4. On a smaller scale, 120 mg of an impure compound was chromatographed by VDCC on 50 g of silica gel in a 20 × 2 in. (circumference) nylon column. In this case, the desired compound had a TLC R_f of 0.4 while the impurities had values R_f of 0.04 and 0.5. For difficult separations, see the Experimental Section.

The use of vacuum[3] and pressure[4,5] in chromatography processes using glass columns to contain the adsorbent has been described. In the vacuum process, a vacuum pump and coolent traps are required. In the pressure processes, a source of compressed air for medium and large columns is necessary. These processes are similar to conventional liquid chromatography in that fractions of eluant are collected and analyzed. With VDCC, fraction collection is unnecessary and a water aspirator vacuum is sufficient.

VDCC uses deactivated adsorbent, since such adsorbent has greater resolving power than undeactivated adsorbent.[1] Relative flow or R_f data from thin-layer chromatography (TLC) plates is transferable to a vacuum dry column. In this way, the approximate location of the desired compound(s) can be anticipated.

The VDCC process makes use of single solvent systems for elution. If the best separation calls for the use of a mixed solvent system, then it is necessary to pretreat the water-deactivated adsorbent with 10% v/w of solvent mixture (see Adsorbents).

In general, if the TLC R_f of a compound is greater than 0.6, then the compound elutes at a higher R_f on the column than on a TLC plate. Conversely, if the R_f of a compound is less than 0.25, then the compound elutes at a lower R_f on the column than on a TLC plate. When the R_f is in the range of 0.2–0.6, the TLC data and the position on the column are closely comparable. If a difficult separation is to be carried out, then more than a 50:1 ratio of adsorbent to substrate is used, and tubing with a high ratio of length to diameter is selected.

The original article by Loev[1] describes the procedure for location of separated compounds by scanning with short wavelength ultraviolet light. This method is limited to the use of ultraviolet light transparent solvents and to compounds capable of "blanking out" the fluorescence of indicators. The exact location of separated compounds in VDCC is determined by using a small syringe having a stainless-steel needle to puncture the nylon wall and remove 1–10-μL samples for analysis.[6]

Experimental Section

Adsorbents. In the VDCC method, the adsorbent is deactivated by the addition of 5–15% v/w of water and is allowed to stand for more than 12 h or is rotated in a flask on a rotary evaporator without the application of vacuum for 3 h. If a mixed solvent is to be used, the adsorbent is treated with a 10% v/w solvent mixture along with the water for deactivation. The treated adsorbent is allowed to stand for more than 12 h or is rotated in a flask by using a rotary evaporator without a vacuum for 3 h.[1]

Column Apparatus. The nylon tubing is attached at one end to the exterior of an appropriately sized Büchner funnel by means of rubber bands (adhesive tape may also be used). A clamp is used to make the junction secure. The Büchner funnel is modified and has a three-way vacuum stopcock on the stem (Figure 1). Other methods of attaching the nylon tubing may be used, including attaching the nylon tubing to an appropriately sized glass bushing adapter and securing it with rubber bands, tape, and/or

(1) Loev, B.; Snader, K. M. *Chem. Ind. (London)* **1965**, 15. See also: Loev, B.; Goodman, M. *Ibid.* **1967**, 2026. Perry, A.; Oss, A. Eds. "Progess in Separation and Purification"; Interscience: New York, 1970; Vol. III, p 73.

(2) Nylon tubing is available as Copol 8(YK) 160-gauge nylon tubing from Walter Coles and Co., Ltd., Plastics Works, 47/49 Tanner Street, London, SE 1, England.

(3) Targett, N. M.; Kilcoyne, J. P.; Green, B. *J. Org. Chem.* **1979**, *44*, 4962.

(4) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(5) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

(6) Hadd, H. E.; Caspi, E. *J. Chromatogr.* **1972**, *71*, 353. These authors describe puncturing the nylon wall with glass pipettes. The use of a syringe is the suggestion of John Thomas Welch.

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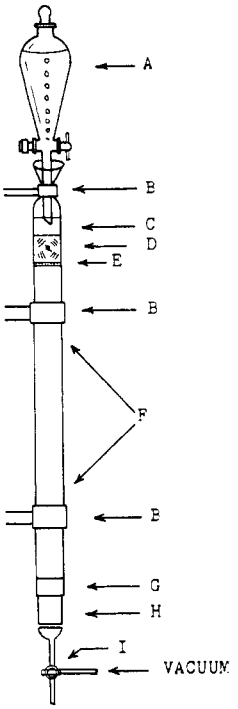

Figure 1. VDCC apparatus and some specifications: A, stoppered separatory funnel, 0.5–1 L; B, clamp; C, solvent head, 2–5 cm; D, compound/Celite deposit; E, sand; F, nylon tubing containing adsorbent; G, adhesive tape or rubber bands (clamp optional); H, modified Büchner funnel with medium sintered frit; I, three-way vacuum stopcock.

a clamp. A glass adapter having a stopcock is inserted into the bushing adapter, and the vacuum line is attached to the adapter. A small plug of cotton or glass wool is inserted into the bushing adapter to retain the adsorbent in the nylon tube during the application of the vacuum.

A third method uses a three-way stopcock having tubing of ca. 5 mm i.d. The nylon tubing, having a plug of cotton in the end, is fastened to the exterior of the tubing by means of rubber bands in the case of small-diameter tubing or rubber bands and a clamp in the case of large-diameter tubing. The three-way stopcock allows regulation of the vacuum and can be used to admit an inert gas in the case of air-sensitive compounds.

Column Preparation. A length of nylon tubing is chosen to contain the volume of the adsorbent and the compound deposited on Celite (see Sample Application). Four to five inches of excess nylon tubing is left unpacked. The nylon tubing affixed as above is charged to one-fourth its length with adsorbent. The column is vibrated with a vibrator or gently tapped by hand. Another charge of adsorbent is added, and the column is again vibrated. This process is repeated until the column packing is firm. A small amount of sand is added to the top of the adsorbent–packed nylon column, and the compound–Celite mixture is added. The sand provides a visual demarcation between the Celite and the adsorbent.

In the case of air-sensitive compounds, the air of the packed column can be replaced by an inert gas by successive evacuations and refillings with an inert gas. The chromatography can then be run in an inert atmosphere.

Sample Application. The sample to be purified is dissolved in ether or methylene chloride, and a quantity of Celite is added (4–5 times the weight of the sample). The solvent is then removed on a rotary evaporator at low bath temperature (30–40 °C). The compound is thus eluted from the Celite onto to the adsorbent in an even manner.

Elution Solvents. Pure or mixed solvents may be used for elution in VDCC. If a mixed solvent is used, the boiling points should be similar. Mixed solvents of dissimilar boiling points may give results different from those observed in TLC.

Elution. The column is positioned vertically and is clamped securely. The excess nylon tubing is fastened by means of a clamp, etc., around the stem of the separatory funnel containing the eluting solvent. The solvent flow is started, and when the liquid has reached the top of the adsorbent, vacuum is applied at the base of the column. This ensures an even solvent front and no channeling. Application of the vacuum before the eluant has reached the adsorbent may result in channeling. The rate of solvent application from the separatory funnel is adjusted to provide a constant head of solvent above the column. This is done by keeping the separatory funnel stoppered with the tip below the surface of the liquid and the valve open. In some cases, an uneven solvent front may be observed, but this in no way affects the separation. A vacuum of 100 mmHg is sufficient to produce a rapid flow of eluant. For large or very long (>84 in.) columns a higher vacuum may be necessary for rapid eluant flow. A water aspirator vacuum is usually sufficient. If the R_f of the desired compound is high (>0.7), then the end of the Büchner funnel may be attached to a vacuum filter flask to prevent loss of compound. In a typical experiment, the time for solvent elution in a silica gel (150 g) column 21 in. long by 3 in. in circumference with methylene chloride was 15 min.

When the solvent front reaches the bottom of the column, the vacuum is broken, and air is admitted to the bottom of the column (with air-sensitive compounds, an inert gas may be used). The flow of eluant is stopped, and a small amount of solvent is allowed to remain at the top of the column. If the adsorbent is not packed firmly, the entrance of air or inert gas in place of the applied vacuum may cause some separation in the column packing. When the column has reached atmospheric pressure, the stopcock is closed. The separatory funnel is removed, and the top of the nylon tubing is twisted or folded over several times so as to force the remaining solvent into the column, thus removing any separation in the column packing that may have occurred (N.B., the tendency for adsorbent separation is eliminated by packing the column by using a vibrator). The twisted nylon tubing is clamped to saturate the column with solvent and also to prevent loss of solvent by evaporation.

Location of Compounds. The developed column is then placed in a horizontal position alongside a ruler. At intervals near the R_f of the desired compound, as determined from TLC data, a small syringe of 50–100-μL capacity is used to penetrate the nylon column wall and withdraw samples for analysis. Thus, for example, 5 μL can be removed and spotted on a TLC plate, or 1 μL can be removed by means of a 10-μL syringe for vapor-phase chromatographic analysis and/or mass spectral analysis. If the particle size of the adsorbent is fine, it may be necessary to bend the tip of the syringe needle 0.5–1.0 mm so as to produce a barrier to prevent the adsorbent particles from entering the syringe needle. Alternatively, such syringe needles are commercially available (Unimetric Corp., Anaheim, CA).

In the event that the column in a horizontal position has gone semidry and it becomes difficult to withdraw samples via a syringe, an additional 5–10 mL of eluting solvent may be added to the top of the column. The excess nylon tubing is then folded over several times so as to force the solvent into the column and resaturate the support. A similar treatment can be carried out at the bottom of the column by using air pressure to force the eluting solvent onto the support if necessary. Only a small amount of solvent is needed, and the operations are conveniently carried out with the column in a horizontal position. If the middle of the column becomes semidry, a small amount of eluting solvent may be injected into the column by using a syringe. This saturates the column so as to facilitate the removal of a sample for analysis, but does not change the position of the compounds. This type of sampling difficulty may also be encountered when using low-boiling solvents such as ether if the room temperature is high. If access to an air-conditioned room is not possible, then substituting an ethyl acetate–hexane mixture for the low-boiling solvent may be necessary. If the R_f of the desired compound is low, then the bottom portion of the column may be packed with used adsorbent. In this way, the amount of adsorbent used is kept to a minimum.

Difficult Separations. In the situation where the R_f of the desired compound and that of the impurity are very close or the same, separations are possible by using VDCC. An elution solvent is chosen to provide a low R_f (<0.15) of the desired compound. The adapter end of the column is connected to a vacuum filter flask. Elution is carried out by collecting several column volumes

of eluant in the filter flask. The process is analogous to continuous or extended elution TLC. The column in a horizontal position is sampled as above with a syringe.

Example. A 0.75-g mixture of steroids consisting of equal parts of 3β-hydroxy-5α-androstan-17-one, testosterone propionate, and pregnenolone acetate deposited on 4 g of Celite was added to a 100-g column of silica gel (E. Merck, 0.063–0.200 mm) that had been deactivated by the addition of 5% v/w of water and further equilibrated with 10% v/w of a solvent mixture of 30% ethyl acetate in hexane. The silica gel was contained in a nylon tube with a total length of 45 in. and a 2-in. circumference. The length of the silica gel column after packing with the aid of a vibrator was 39 in. The column was eluted with 125 mL of 30% ethyl acetate in hexane by using a vacuum of 100 mmHg in a period 12 min. A 100-μL syringe was used to puncture the nylon column, withdraw 5-μL samples, and spot them on a 10 × 20 cm TLC plate. Upon development with 30% ethyl acetate–hexene, the 3β-hydroxy-5α-androstan-17-one was found in the 2–6-in. region, the testosterone propionate was found in the 9–15-in. region, and the pregnenolone acetate was found in the 16–22-in. region. The 2–6-in. section gave 0.233 g of 3β-hydroxy-5α-androstan-17-one, mp 175–178 °C (lit.[7] mp 177–179 °C), the 9–15-in. section gave 0.238 g of testosterone propionate, mp 119–124 °C (lit.[8] mp 118–122 °C), and the 16–22 in. section gave 0.230 g of pregnenolone acetate, mp 148–149 °C (lit.[8] mp 149–151 °C).

Acknowledgment. Financial support by National Institutes of Health Grant GM 10421 is greatly acknowledged. Special thanks are due Dennis Faler.

Registry No. 3β-Hydroxy-5α-androstan-17-one, 481-29-8; testosterone propionate, 57-85-2; pregnenolone acetate, 1778-02-5.

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Facile Conversion of Primary Thioamides into Nitriles with Butyltin Oxides[1]

Mu-Ill Lim, Wu-Yun Ren, and Robert S. Klein*

Laboratory of Organic Chemistry, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

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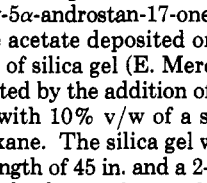
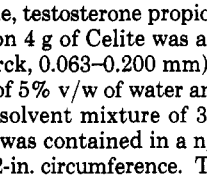
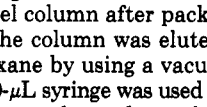
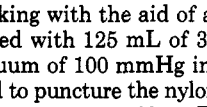
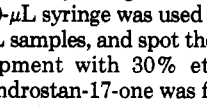
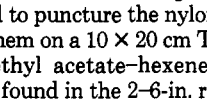
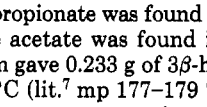
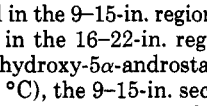
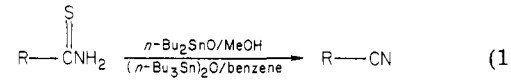
Butyltin oxides have recently received much attention for their utility as stereoselective nucleophile activators[2] and for mediating macrolide formation via template-driven processes.[3] During an investigation of the potential utilization of stannylation to enhance the nucleophilicity of heteroatoms bound to C-nucleosides, we observed that 3-amino-4-(2′,3′-di-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-2-thiocarboxamido-1*H*-pyrrole (1, Table I) was readily converted into the corresponding 2-cyanopyrrole[4] in the presence of dibutyltin oxide or bis(tri-*n*-butyltin) oxide under mild conditions in excellent yields (eq 1).

Table I

Entry No.	Thioamide	Product	Yield (%) by Method A	Yield (%) by Method B
1			98[a]	95[a]
2			100[a]	98[b]
3			91[a]	93[b]
4			62[a]	92[a]
5	C_6H_5-C(=S)-NH_2	C_6H_5CN	80[a]	88[c]
6	p-$O_2NC_6H_4CH_2$-C(=S)-NH_2	p-$O_2NC_6H_4CH_2CN$	55[a]	94[b]
7	$CH_3(CH_2)_{10}$-C(=S)-NH_2	$CH_3(CH_2)_{10}CN$	46[c]	77[c]
8	C_6H_5NH-C(=S)-NHC_6H_5	C_6H_5NH-C(=O)-NHC_6H_5	-	80[d]

[a] Isolated by preparative TLC. [b] The products were obtained by crystallization after addition of petroleum ether (bp 30–60 °C) to the residue. [c] Isolated by distillation. [d] Reaction time was 2 h. The product was isolated by direct crystallization from the reaction mixture.

Because of its general applicability, the procedure conveniently complements other methods presently available for such conversions.



$$R\text{—}C(=S)NH_2 \xrightarrow[(n\text{-}Bu_3Sn)_2O/\text{benzene}]{n\text{-}Bu_2SnO/MeOH} R\text{—}CN \qquad (1)$$

Dehydrosulfurization of thio amides and dehydration of amides into nitriles have been carried out with $Ph_3P/CCl_4/Et_3N$;[5] dichlorocarbene generated in a phase-transfer system containing $CHCl_3/NaOH/PhCH_2N^+Et_3Cl^-$;[6] $P(NEt_2)_3$ in boiling THF[7]; and, finally, with P_2O_5.[8] Several recently reported procedures that have been applied specifically to the conversion of thio amides into nitriles include metal ion promoted dehydrosulfurization;[9] treatment with PhC≡CC=NPh(NHPh);[10] EtOOCN=NCOOEt/Ph_3P/THF;[11] α-halogenated ketones, esters, or nitriles in DMF/NaOEt;[12] and Ph_3SnN=C=$NSnPh_3$.[13]

Our original observation (1, Table I) which utilized a slight molar excess of dibutyltin oxide in boiling methanol was found to be readily applicable to the conversion of

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