Tetrahedron Vol. 37, pp. 843 to 846
Pergamon Press Ltd., 1981. Printed in Great Britain

0040 4020/81/0215-0843/$02.00/0

ORGANIC REACTIONS IN A SOLID MATRIX—VI†

SILICA-GEL SUPPORTED REAGENTS FOR THE ISOLATION OF ALDEHYDES AND KETONES‡

R. P. SINGH, H. N. SUBBARAO and SUKH DEV*

Malti-Chem Research Centre, Nandesari, Vadodara, India

(*Received in U.K.* 8 *July* 1980)

Abstract—Semicarbazide-on-silica gel and Girard-T-on-silica gel are described and evaluated as convenient reagents for efficient isolation of aldehydes and ketones from mixtures with other usual neutral organic components. Semicarbazide-on-silica gel, which can be readily prepared, can effectively replace the classical Girard reagents, for the isolation of aldehydes and ketones in most cases.

To deal with the problem of isolation of certain carbonyl compounds (aldehydes, ketones) from natural mixtures such as essential oils, plant extracts or mammalian physiological products, in which these compounds may occur only in trace quantities, a number of reagents have been developed,[1] of which the Girard reagents[1] have proved to be outstanding. In connection with our work[2] on the pharmacologically-active constituents of the Ayurvedic crude drug, *Guggulu* (gumexudate from the tree *Commiphora mukul* Engl.), a need arose for the segregation of the neutral fraction into ketonic and non-ketonic cuts. Though, the separation could be effectively achieved[2e] with Girard-P reagent, the acid-labile diterpenoids[2b] in the non-ketonic portion underwent extensive dehydration/isomerization, even under the rather mild conditions[3] involving use of an acid ion-exchange resin. To overcome this handicap[4] attention was directed to the development of a reagent which could be used under neutral or slightly basic conditions,[5] efforts were made to support this reagent in a solid matrix,[6] such that the non-ketonic/non-aldehydic

Table 1. Determination of molar equivalance: reaction[a] of menthone at 70° by various molar equivalents of semicarbazide on different amounts of silica-gel

No.	Silica gel/ semicarbazide ratio	Mole equivalent of semicarbazide per one mole of menthone	Amount of menthone (%, GLC) in the soln. phase
1	9 : 1[b]	1.0	2.9
2	"	1.25	2.7
3	"	1.50	1.9
4	"	1.75	1.4
5	"	2.00	0.7
6	"	2.50	0.0
7	4 : 1[c]	1.00	3.4
8	"	1.50	2.2
9	"	2.00	1.6
10	"	2.50	0.9
11	"	3.00	0.0

[a] Reaction on a one mmole scale (hexane, 70 ± 2°, 12 hr)

[b] 1g of supported reagent ≡ 0.0542g of semicarbazide
≡ 0.723 mmole of semicarbazide

[c] 1g of supported reagent ≡ 0.105g of semicarbazide
≡ 1.40 mmole of semicarbazide

---

†Part V, *Tetrahedron* **35**, 1789 (1979).

‡MRC Communication No. 22.

material would stay in the solution phase, when the condensation is carried out in a non-polar solvent, such as hexane/toluene, in which the semicarbazones are invariably insoluble.[7] We now describe the preparation and use of such a reagent, which permits separation of these carbonyl compounds from other neutral components in an expeditious manner, even on a large scale.[8] We also describe some separations with Girard-T-on-silica gel, which is equally effective, but has no special advantages over the more readily accessible semicarbazide-on-silica gel reagent.

Semicarbazide on silica gel

Using a 10% soln of (–)-menthone in *p*-menthane as test material, preparations of semicarbazide-on-silica gel having silica gel/semicarbazide ratios of either 9:1 or 4:1, and prepared as described under Experimental, were evaluated (Table 1) to determine which ratio was more suitable as well as what was the molar equivalence of the reagent (in terms of active component) for complete removal of the ketone.[9] The reaction was carried out by heating the test material and the reagent in hexane at ~70° for 12 hr. The results have been summarised in Table 1. It is clear from Table 1 that a silica gel/semicarbazide ratio of 9:1 and a molar equivalence of 2.5 is quite suitable for the purpose on hand, and hence all further work was carried out using this preparation and conditions.

To evaluate the efficacy of the reagent, four more test mixtures (Table 2, entries 2–5) were subjected to separation by this method. In each case, the solution phase was analysed by glc for the carbonyl component and the solid phase treated for the regeneration of the carbonyl compound. Though, a number of methods are available[10] for the regeneration of the carbonyl compound from its semicarbaze, we find stirring and refluxing of the solid phase with toluene/heptane and ~6% oxalic acid aq.[10b,11] most convenient and effective. It is clear from the data presented in Table 2, that the reagent is quite effective for the isolation of both aldehydes and ketones.

Next, the reagent was evaluated for the isolation of aldehydes/ketones from natural mixtures. The essential oils of *Cedrus deodara* Loud. (wood),[12] *Cyperus rotundus* Linn. (tubers),[13] and *Eucalyptus citriodora* Hook. (leaves and terminal branchlets)[14] have been well-investigated for their ketones/aldehydes and these compounds have been well-characterised.[15] Table 2 summarises the results obtained with these materials and as is evident, the reagent has given gratifying results. The gum-resin of *Commiphora mukul* Engl. contains a number of

Table 2. Isolation of aldehydes/ketones from test mixtures by reaction[a] with semicarbazide-on-silica gel

No.	Test Mixture (Aldehyde/ketone content, %)[b]	Material Recovery[c]			
		Carbonyl part		Non-carbonyl part	
		Wt(%)	Aldehyde/ketone content,%[b]	Wt(%)	Aldehyde/ketone content,%[b]
1	(–)-Menthone in p-menthane (10%)	94	100	92	0.0
2	Benzaldehyde in p-menthane (10%)	65[d]	100	90	0.0
3	Cinnamaldehyde in p-menthane (10%)	78[d]	98	91	0.0
4	(+)-Carvone in p-menthane (10%)	93	98	93	0.2
5	β-Ionone in p-menthane (10%)	93	96	97	0.0
6	Essential oil: *Cyperus rotundus* (~30%)	97	90	97	1.2
7	Essential oil: *Cedrus deodara* (~40%)	96	90	93	0.5
8	Essential oil: *Eucalyptus citriodora* (~63%)	74[d]	90	88	0.0
9	Neutral EtOAc extract of *Commiphora mukul* gum-resin (~13%)	94	100	97	-

[a] Reaction on one mmole scale of aldehyde/ketone present in the mixture using 2.5 molar equivalents of reagent; solvent hexane except for entry 9, where toluene was used; temp., 70 ± 2°; time, 12 hr, except for entry 9, where reaction was carried out for 18 hr.

[b] For natural mixtures, the % is based on GLC (for essential oils), since the aldehyde/ketone components of these oils are well-known (see Text); for entry 9, the ketone content is based on isolation with Girard-P reagent.[2a]

[c] Represents isolated products, after distillation.

[d] Low recoveries are due to formation of the corresponding acid during the regeneration step; no special precautions were taken to avoid oxidation.

steroidal ketones, which have been earlier isolated by column chromatography.[2a] The neutral EtOAc extract of this material on treatment with Girard-P reagent, in the usual manner,[3] gave the ketone fraction in a yield of 13% (w/w);[2e] the application of semicarbazide-on-silica gel for the isolation of these ketones gave a product of comparable purity (tlc; solvent: 25% EtOAc in C_6H_6) in almost the same yield (Table 2).

Girard-T on silica gel

One disadvantage of Girard-T (trimethylammonium acetylhydrazide chloride) is its extremely hygroscopic nature.

Girard-T-on-silica gel was next used for the isolation of ketones from test mixtures 4, 6, 7, 9 (entries in Table 2) and, in general, the recoveries were of the order of 90–98% with carbonyl compound purity of 92–98%.

In view of the above results, both semicarbazide-on-silica gel and Girard-T-on-silica gel, and especially the former, are recommended for the separation of aldehydes and ketones from other usual neutral constituents. Chief advantages are: condensation is carried out in a convenient simple manner under essentially neutral conditions, and the exceptional ease of work-up.

EXPERIMENTAL

The following instruments were used for spectral/analytical data: Perkin–Elmer Infracord model 267; Perkin–Elmer model R32 (90 MHz) NMR spectrometer; Hewlett–Packard 5712A and 7624A gas chromatographs (Al columns, 360 × 0.6 cm; support, 60–80 mesh Chromosorb W; stationary phase, 10% Carbowax 20M; carrier gas, H_2).

All compounds described in this communication are known and after recovery from mixtures were distilled and the product recognized by IR, PMR and purity established by glc (tlc).

Silica gel as supplied by Beechems, Kanpur, was sieved and the fraction −80, +200 mesh (bulk density, 0.71 g/ml) employed as the support. Girard-T was prepared according to a standard procedure.[16] Semicarbazide hydrochloride, oxalic acid, NaOH and HCl were all reagent grade. Hexane, heptane were purified,[17] before use. All other solvents were distilled before use. All essential oils were available from our collection.

Preparation of reagents

(i) *Semicarbazide-on-silica gel.* Semicarbazide hydrochloride (5.0 g; 0.045 mole) was added to a soln of NaOH (2.0 g; 0.05 mole) in water–MeOH (1:1; 60 ml) and to the resulting clear soln, silica gel (45 g) was introduced with stirring. The whole mixture was mechanically shaken (1 hr) at room temp. (30–35°) and water–MeOH removed on a rotary evaporator (~90°/80–90 mm; 30–45 min) to get a white free-flowing powder. This material should weigh 60–63 g. The product is stored in a brown bottle at room temp. A two year-old product had undergone no deterioration.

(ii) *Girard-T-on-silica gel.* To a soln of Girard-T (5.0 g; 0.0299 mole) in t-BuOH and water (1:1; 60 ml), silica gel (45 g) was added and the mixture mechanically shaken for 1 hr at room temp (30–35°). Most of t-BuOH/water were removed on a rotary evaporator (~90°/80–90 mm/; ~1 hr) to get a white free-flowing powder, which should weigh 52–55 g. This material can be stored in a dark bottle at room temp, without any deterioration (1 yr). When the yield of the reagent is 52.5 g, 1.0 g of it is equivalent to 0.0952 g of Girard-T (≡0.5685 mmole).

General procedure for condensation

(i) *With semicarbazide-on-silica gel.* An amount of material containing ~1 mmole of the ketone/aldehyde is dissolved in hexane or toluene (7 ml), and to the resulting soln 3.5 g of reagent (1.0 g ≡ 0.0542 g of semicarbazide; 2.5 mmole semicarbazide) is added. The mixture is heated (70 ± 2°) and stirred for 12–18 hr and the absence of the carbonyl compound in the soln phase ensured by tlc (spray: 10% 2,4-dinitrophenylhydrazine in HCl aq). The mixture is cooled, filtered and the solid washed with the same solvent (5 ml × 4; at 15–20°). The filtrate and washings are combined and processed in the usual manner for the non-carbonyl portion, while the solid part is treated for the regeneration of the aldehyde/ketone (see below).

(ii) *With Girard-T-on-silica gel.* The procedure as detailed above is followed except that Girard-T-on-silica gel (2.0 molar equiv.) is used instead of the semicarbazide reagent.

General procedure for regeneration

(i) *From semicarbazones.* The solid phase containing the semi-carbazone (~1 mmole) is added to a soln of oxalic acid (0.9 g; 10 mmole) in water (16 ml), covered with a layer of heptane or toluene (10 ml) and the mixture, stirred and refluxed for 4–5 hr. After cooling, the solvent and aqueous part are removed by decantation and the silica gel washed with heptane/toluene (5 ml × 2). The combined solvent layer is separated, the aqueous part extracted with the same solvent (10 ml × 2) and the extracts mixed with the main extract. The total solvent soln is washed with water (10 ml × 2), brine (5 ml), dried (Na_2SO_4) and the solvent removed at ~80/200 mm through a short Vigreux column to get the regenerated carbonyl compound, which is appropriately processed further.

(ii) *From Girard hydrazones.* The solid phase containing the hydrazone (~1 mmole) is added to hydrochloric acid aq (10% v/v; 15 ml), covered with ether (15 ml), well-swirled and the whole allowed to stand overnight (~12 hr) at room temp. (~25°). The regenerated aldehyde/ketone was isolated exactly as detailed under (i) above.

REFERENCES

[1] See e.g.: [a]O. H. Wheeler, *Chem. Rev.* **62**, 205 (1962); [b]O. H. Wheeler, *J. Chem. Educ.* **45**, 435 (1968).

[2a] V. D. Patil, U. R. Nayak and Sukh Dev, *Tetrahedron* **28**, 23541 (1972); [b]V. D. Patil, U. R. Nayak and Sikh Dev, *Ibid.* **29**, 341 (1973); [c]V. D. Patil, U. R. Nayak and Sukh Dev, *Ibid.* **29**, 1595 (1973); [d]R. S. Prasad and Sukh Dev, *Ibid.* **32**, 1437 (1976); [e]A. G. Bajaj, Ph.D. Thesis, M.S. University, Baroda (1980).

[3] C. L. Teitelbaum, *J. Org. Chem.* **23**, 646 (1958).

[4] Dehydration/isomerization of certain hydroxy- and olefinic-ketones have been noted both at the condensation stage and at the stage of hydrolysis of the Girard hydrazones.[2]

[5] See e.g.: P. Anziani, *Bull. Soc. Chim. Fr.* **6**, 954 (1944); D. E. Pearson, K. N. Carter and C. M. Greer, *J. Am. Chem. Soc.* **75**, 5906 (1953).

[6] See: R. P. Singh, H. N. Subbarao and Sukh Dev, *Tetrahedron* **35**, 1789 (1979).

[7] This limits the application of the reagent to ketone/aldehyde-containing materials that are soluble in non-polar solvents such as hexane, toluene, etc.

[8] The semicarbazide-on-silica gel has been used to get 90 g of ketones from 725 g of the *guggulu* extract per batch.[2e]

[9] This investigation was necessary, as conceivably some amount of the semicarbazide may not be available for semicarbazone formation, because of location at sites, in the silica gel matrix, which may be inaccessible to the aldehyde/ketone.

[10] See e.g.: [a] L. Ruzicka, M. W. Goldbery and H. Brungger, *Helv. Chim. Acta* **17**, 1389 (1934); [b] L. Ruzicka, M. W. Goldberg, J. Meyer, H. Brungger and E. Eichenberger, *Ibid.* **17**, 1395 (1934); [c] E. B. Hershberg, *J. Org. Chem.* **13**, 542 (1048); [d] St. Goldschmidt and W. L. C. Veer, *Rec. Trav. Chim.* **65**, 796 (1946); [e] V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.* **70**, 882 (1948); [f] D. H. R. Barton, D. J. Lester and S. V. Ley, *Chem. Comm.* 445 (1977).

[11] Sukh Dev, *J. Indian Chem. Soc.* **34**, 176 (1957).

[12] [a] G. S. Krishna Rao, Sukh Dev and P. C. Guha, *J. Indian Chem. Soc.* **29**, 721 (1952); [b] B. S. Pande, S. Krishnappa, S. C. Bisarya and Sukh Dev, *Tetrahedron* **27**, 841 (1971).

[13] [a] A. E. Bradfield, B. H. Hegde, B. S. Rao, J. L. Simonsen and A. E. Gillam, *J. Chem. Soc.* 667 (1936); [b] V. H. Kapadia, V. G. Naik, M. S. Wadia and Sukh Dev, *Tetrahedron Letters* 4661 (1967).

[14] P. S. Rao and K. Bhatia, *Indian Forester* **84**, 162–63 (1958).

[15] Authentic samples of atlantone (*Cedrus deodara*),[12b] α-cyperone (*Cyperus rotundus*)[13b] and citronellal (citronella oil),[14] which constitute the major carbonyl components of the respective oils, were available.

[16] A. Girard, *Organic Synthesis* Coll. vol. II, p. 85 (1969).

[17] N. A. Sorensen, *Chemist-Analyst* **44**, 24 (1955).