Hydrazides and Hydrazones from Carbazates

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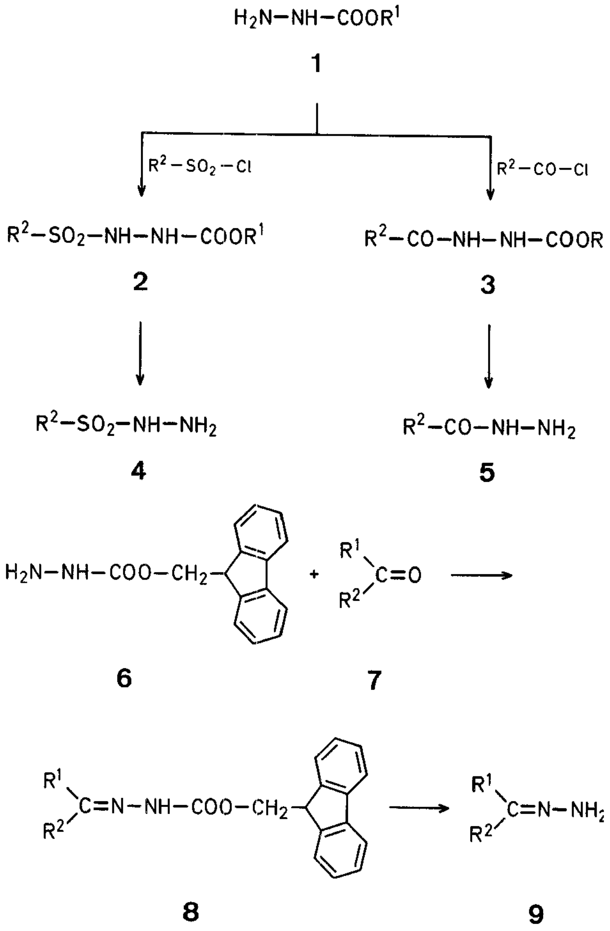
The preparation of sulfonic and carboxylic acid hydrazides by reaction of sulfonyl or acyl chlorides with hydrazine is often complicated by the production of considerable amounts of 1,2-disulfonyl- or 1,2-diacylhydrazines[1]. The synthesis of hydrazones by reaction of an aldehyde or ketone with hydrazine is often accompanied by the formation of quantities of azine[2]. Yet another frequently occurring problem arises when a desired hydrazide or hydrazone were to contain some other functional group which is capable of reacting with either: (1) a second equivalent of hydrazine to produce bis-hydrazides or hydrazones[3], or (2) with the primary amino function of the hydrazide or hydrazone to produce cyclized products[4].

We have developed procedures employing protected hydrazines which allow preparation of hydrazides and hydrazones without concomitant formation of undesirable side products. We have used either *t*-butyl carbazate (**1**, $R^1 = t\text{-}C_4H_9$, Method A) or benzyl carbazate (**1**, $R^1 = CH_2C_6H_5$, Method B) in the preparation of hydrazides **4** and **5** and 9-fluorenylmethyl carbazate (**6**) in the preparation of hydrazones **9** as outlined below.



Method B is preferred for the preparation of water soluble hydrazides since the procedure does not involve an aqueous work-up. The use of 9-fluorenylmethyl carbazate (**6**) in the preparation of hydrazones **9** was required due to the fact that the 9-fluorenylmethoxycarbonyl protecting group can be removed under mildly basic conditions (e.g. morpholine) which are compatible with the highly sensitive hydrazone function. *t*-Butyl carbazate or benzyl carbazate cannot be used to prepare hydrazones in this fashion since the acidic conditions necessary for removal of the *t*-butyloxycarbonyl group convert hydrazones to azines, and the hydrogenolysis conditions necessary for removal of the benzyloxycarbonyl group reduce hydrazones to hydrazines.

Hydrazides 4 and 5, General Procedures:

Method A: *t*-Butyl carbazate (0.05 mol) is dissolved in anhydrous ether (200 ml) containing pyridine (0.055 mol). The sulfonyl or acyl chloride (0.05 mol) dissolved in ether (50 ml) is added dropwise with stirring at 10 °C. The mixture is stirred for 1 h in ice and for 1 h at room temperature following addition. Water (200 ml) is added. The ether layer is removed and washed with 5% aqueous hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and dried with magnesium sulfate. The ether is removed in vacuo yielding the intermediate **2** or **3** ($R^1 = t\text{-}C_4H_9$). Trifluoroacetic acid (35 ml) is added to the residue at 10 °C and the mixture is left to warm to room temperature for 1 h. The trifluoroacetic acid is removed in vacuo, and the residue triturated with 10% aqueous sodium hydrogen carbonate. The hydrazide **4** or **5** (Table 1) is isolated by vacuum filtration and washed with water.

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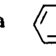
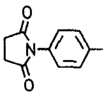
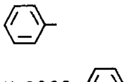
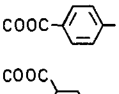
Method B: The procedure for preparing the intermediates **2** or **3** (R = $CH_2C_6H_5$) is identical to that described in Method A except that benzyl carbazate is substituted for *t*-butyl carbazate. The intermediate is then dissolved in methanol (50-100 ml) and a 10% Pd/C catalyst (0.5 g) is added. The mixture is subjected to 3.3–4 atm (50–60 p.s.i.) of hydrogen gas pressure until hydrogen uptake is complete (1-8 h). The catalyst is removed by filtration and the solvent evaporated in vacuo to recover the hydrazide **4** or **5** (Table 1).

Table 1. Hydrazides **4** and **5**

Product No.	R^2	Method	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]
4a		A	70	200 (dec.)	$C_{10}H_{11}N_3O_4S$ (269.3)
4b[d]		A	78	100–102	104–106[8]
5a		B	85	105–108	113–117[7]
5b		A	92	200–201	205[6]
5c[c]		B	88	107–110	$C_9H_{10}N_2O_3$ (194.2)

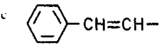
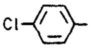
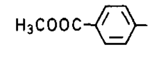
[a] Overall yield based on acid chloride.

[b] Satisfactory microanalyses obtained (C ±0.33, H ±0.09, N ±0.12, S +0.14).

[c] See Ref. [6] for an unsuccessful attempt to prepare this compound.

[d] See Ref. [3] for an unsuccessful attempt to prepare this compound.

Table 2. Hydrazones **9**

Product No.	R^1	R^2	Yield [%][a]	m.p. [°C]	Molecular formula[b]
9a[c]		H	45	oil	---
9b[d]		H	75	55–57	–
9c[e]	$-(CH_2)_5-$		50	oil	
9d		H	74	163–164[f]	$C_{12}H_9N_3O_3$ (243.2)[f]
9e		H	60	96–97	$C_9H_{10}N_2O_2$ (178.2)

[a] Overall yield based on carbonyl compound **7**.

[b] Satisfactory microanalyses obtained (C ±0.36, H ±0.04, N ±0.21).

[c] See Ref. [4] for preparation of this compound contaminated with 5-phenyl-Δ^2-pyrazoline.

[d] Compound's I.R. and N.M.R. spectra identical to those of hydrazone prepared by method of Newkome and Fishel[9].

[e] See Ref. [2] for preparation of this compound contaminated with cyclohexanone azine.

[f] *p*-Nitrobenzylidene derivative.

Hydrazones 9; General Procedure:

9-Fluorenylmethyl carbazate[5] (**6**; 0.01 mol) is dissolved in ethanol (200 ml) and the aldehyde or ketone **7** (0.011 mol) is added in one portion. The solution is heated under reflux until T.L.C. examination shows the absence of unreacted **6** (usually 1-3 h). A few drops of boron trifluoride etherate can be added to the solution to reduce required reflux time. One-half of the solvent is removed in vacuo and the precipitate of **8** collected by vacuum filtration. The intermediate **8** is stirred with morpholine (75 ml) at room temperature for 45 min and then the mixture is poured into ice/water (350 ml). The aqueous mixture is left in an ice bath for 30 min, filtered, and the precipitate of *N*-(9-fluorenylmethyl)-morpholine discarded. The filtrate is extracted with three 100 ml portions of ether. The combined ether extracts are dried with magnesium sulfate and evaporated to yield the hydrazone **9** (Table 2).

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