An Efficient Synthesis of Substituted Hydrazides

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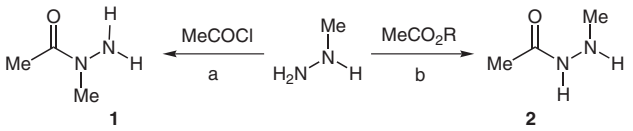
Abstract: Routes for the selective synthesis of 1-, or 2-substituted hydrazides, and 1,2-disubstituted hydrazides are reported. These routes proceed via cyanoborohydride reduction of stable acyl hydrazone intermediates.

Key words: aminations, reductions, hydrazones, condensation, regioselectivity

Substituted hydrazides have recently found use in applications as diverse as: traceless linkers for solid-phase synthesis;[1a] the synthesis of fluorobutenoic acid hydrazide pesticides;[1b] the synthesis of new androstane steroid derivatives;[1c] and as intermediates in the synthesis of antimycobacterials.[1d] The synthesis and applications of di- and tri-substituted hydrazides have been reviewed.[2]

Simple methods for the regioselective synthesis of 1- and 2-mono-substituted hydrazides were first reported in the 1950s and were refined in the 1970s (Scheme 1).[3] More recently, the palladium-catalyzed hydrazinocarbonylation reaction has been shown to be an effective alternative for the synthesis of some 1-methylhydrazides,[1c] whilst a copper-catalyzed coupling of *ortho*-substituted aryl iodides with benzoic acid hydrazides gives rise to moderate yields of the corresponding 2-arylhydrazides.[4a] The Mitsunobu reaction of *N*-acylaminophthalimides may be used to prepare a range of 1-methyl and 1-benzylhydrazides.[4b] Finally, an amination reaction of amides using chloramine has also been shown to produce a limited number of 1-substituted methyl-, phenyl- and benzylhydrazides.[4c]



Scheme 1 *Reagents and conditions*: (a) MeCOCl (0.33 equiv), CH_2Cl_2, 0 °C to r.t.;[3a] (b) $MeCO_2R$ (1 equiv), EtOH (aq), reflux (R = Me,[3b] R = Et[3c]).

The reaction of methylhydrazine with an acyl chloride,[3a] or anhydride,[3b,c] has been reported to give the 1-substituted hydrazide **1** with high selectivity. Conversely, the reaction of methylhydrazine with the corresponding methyl,[3b] or ethyl ester[3c] has been reported to give predominantly the 2-substituted hydrazide **2** (Scheme 1). The regioselectivity of synthesis of 1- or 2-substituted hydrazides from simple hydrazines has been rationalized in terms of a difference in the mechanisms.[3c]

In following these reaction conditions with a range of aroyl chlorides a number of problems were encountered. Rapid reaction of the aroyl chloride even under slow addition at 0 °C meant that a number of side-products was produced, including the related diacyl hydrazines.[3c] Furthermore, the resultant mixtures of 1- and 2-substituted hydrazides proved to be very difficult to separate, and on a larger scale these frequently required careful distillation which drastically lowered the yields of the reaction. Finally, when we attempted to extend the reported preparation of 2-substituted hydrazides[3b] to include the reaction of a wider range of aroyl esters, no reaction was observed even after extended reaction times of up to two weeks. These problems, combined with an additional need for a synthetic route for the preparation of 1,2-dimethylhydrazides avoiding the use of the highly carcinogenic 1,2-dimethylhydrazine, prompted us to investigate further the regioselective synthesis of substituted hydrazides.

In order to control the reaction rate of the acid chloride and prevent the formation of the diacyl hydrazine, the reaction protocol reported by Condon was modified.[3c] Dilution of the acid chloride with the reaction solvent to give a 1.5 M solution in dichloromethane, and inversion of the addition protocol (i.e. adding the acid chloride solution to a solution of methyl hydrazine and not vice versa), whilst increasing the number of equivalents of methyl hydrazine employed, resulted in a significant reduction in by-products. Under these new conditions only the 1-methylhydrazide was observed in the crude material by ^{1}H NMR spectroscopic and HPLC analysis. Analytically pure hydrazides **3** were isolated by pouring the reaction mixture onto a saturated solution of sodium carbonate and extracting the hydrazide into dichloromethane. In this manner, tedious distillation procedures were avoided and the yields of the 1-substituted hydrazides **3** were greatly increased as shown in Table 1.[5]

With a reliable synthesis of the 1-substituted hydrazides **3** in hand, we then attempted to synthesize the 1,2-disubstituted hydrazides **5**. By analogy with the preparation of N-substituted hydrazines,[6a] and simple 1,2-disubstituted acetylhydrazides,[6b] we predicted that this should be readily achieved using a reductive amination protocol (Scheme 2).[7] To this end, we were able to exploit the well-

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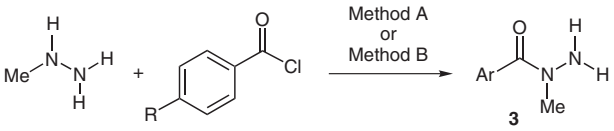
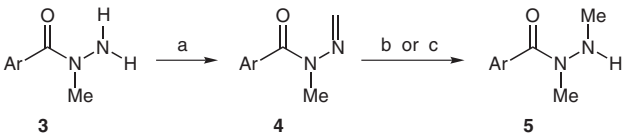
Table 1 Synthesis of 1-Substituted Arylhydrazides **3**



Arylhydrazide **3** (*R*)	Method A[a] (%)[c]	Method B[b] (%)[c]
3a (H)	69	90
3b (OMe)	68	92
3c (Me)	66	93
3d (Cl)	65	92
3e (NO_2)	61	79

[a] Method A: $MeNHNH_2$ (6.5 M in CH_2Cl_2, 3 equiv), ArCOCl (neat, slow addition), 0 °C, 3 h.
[b] Method B: $MeNHNH_2$ (1.5 M in CH_2Cl_2, 10 equiv), ArCOCl (0.15 M in CH_2Cl_2, slow addition), 0 °C, 3 h.
[c] Isolated yields.

known, but unexpected stability of methylene hydrazones. Although few examples of acyl hydrazones such as **4** are known, they were readily produced by condensation of the 1-substituted hydrazides **3** with formaldehyde in toluene under Dean–Stark reflux conditions. The use of paraformaldehyde allowed the accurate introduction of the one equivalent of formaldehyde required for monoalkylation, negating the need for purification of the intermediate acyl hydrazones **4**. ^{1}H NMR spectroscopic analysis of acyl hydrazones **4** in $CDCl_3$ showed two characteristic doublets corresponding to the methylene protons, typically at $\delta = 6.45$ and 6.25 ppm, with a geminal coupling of $^2J_{HH} = 10.6$ Hz.[8] This unusually high coupling constant has been reported in related systems;[6b,9] and this assignment was confirmed by COSY analysis of compound **4b**.



Scheme 2 *Reagents and conditions*: (a) HCHO, $PhCH_3$, reflux, 18 h; (b) $Pd(OH)_2$, H_2 (20 bar), EtOAc, 50 °C, 18 h; (c) $NaCNBH_3$, AcOH, MeOH, r.t., 18 h.

Different reduction conditions were investigated for the conversion of acyl hydrazones **4** to 1,2-disubstituted hydrazides **5**. Literature methods for the catalytic hydrogenation of hydrazones tend not to specify either the hydrogen pressure and/or reaction temperature employed.[10] A high pressure (20 atm) reduction protocol using Pearlman's catalyst [$Pd(OH)_2$/C] in ethyl acetate was shown to reduce acyl hydrazone intermediate **4c** in a moderate yield (53%). However, the effectiveness of this method was by no means universal.

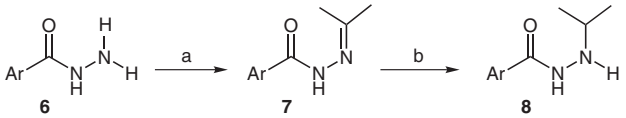
In contrast, the use of $NaCNBH_3$ in the presence of acetic acid was found to be particularly effective (Scheme 2).[7] Using this reductive amination protocol 1,2-disubstituted hydrazides **5**, could be produced in excellent yields (83–97%) as shown in Table 2. This method is applicable to both electron-rich and electron-poor aromatic acyl hydrazones **4** and is particularly attractive as it negates the need for the use of dimethylhydrazine in the synthesis of 1,2-dimethylhydrazides **5**.

Table 2 Synthesis of 1,2-Disubstituted Arylhydrazides **5**

Arylhydrazide **3** (*R*)	Acyl hydrazone **4** (%)[a,b]	Hydrazide **5** (%)[a,c]
3a (H)	**4a** (96)	**5a** (95)
3b (OMe)	**4b** (95)	**5b** (97)
3c (CH_3)	**4c** (96)	**5c** (92)
3d (Cl)	**4d** (93)	**5d** (97)
3e (NO_2)	**4e** (89)	**5e** (83)

[a] Isolated yields.
[b] HCHO, $PhCH_3$, reflux, 18 h.
[c] $NaCNBH_3$, AcOH, MeOH, r.t., 18 h.

It was anticipated that the application of this simple two-step procedure to unsubstituted arylhydrazides would result in the regioselective synthesis of 2-substituted hydrazides (Scheme 3). A range of unsubstituted hydrazides **6** is commercially available, making an attractive starting point for the attempted condensation with formaldehyde. However, in the absence of the methyl group in the 1-position the intermediate unsubstituted acyl hydrazone is not stable to isolation and rapid formation of cyclic dimers and trimers occurs, in agreement with the results of Fox et al. on a related condensation with formaldehyde.[11]



Scheme 3 *Reagents and conditions*: (a) $(CH_3)_2C{=}O$, Na_2SO_4, r.t., 18 h; (b) $NaCNBH_3$, AcOH, MeOH, r.t., 18 h.

In contrast, the same condensation reaction conducted with acetone in place of formaldehyde gives stable acyl hydrazones **7**. These are characterized by two singlets in the ^{1}H NMR spectrum in $CDCl_3$,[6b] typically at $\delta = 2.12$ and 1.93 ppm.[12] Reduction with $NaCNBH_3$/AcOH, gives the isopropyl-substituted hydrazides **8** as shown in Table 3. Again, the efficiency of the cyanoborohydride reduction was independent of the electron-donating/electron-withdrawing nature of the *para* substituent on the acyl hydrazone intermediate **7**.[13]

In conclusion, we have developed an efficient synthesis of 1-methylhydrazides (**3**), 1,2-dimethylhydrazides (**5**), and 2-isopropylhydrazides (**8**). The methodology has been shown to be applicable to hydrazide precursors with a range of electron-donating and electron-withdrawing substituents. The route to the 1,2-dimethylhydrazides is

Table 3 Synthesis of 2-Substituted Arylhydrazides **8**

Unsubstituted hydrazide (*R*)	Acyl hydrazone **7** (%)[a,b]	Hydrazide **8** (%)[a,c]
6a (H)	**7a** (97)	**8a** (93)
6b (OMe)	**7b** (98)	**8b** (89)
6c (CH_3)	**7c** (95)	**8c** (92)
6d (Cl)	**7d** (95)	**8d** (91)
6e (NO_2)	**7e** (91)	**8e** (79)

[a] Isolated yields.
[b] $(CH_3)_2C{=}O$, Na_2SO_4, r.t., 18 h.
[c] $NaCNBH_3$, AcOH, MeOH, r.t., 18 h.

particularly attractive as it avoids the use of 1,2-dimethylhydrazine. The synthesis of 2-isopropylhydrazides opens up a previously uninvestigated class of pharmacophore which will provide an important bridge between 2-methyl- and 2-*tert*-butylhydrazides.[14] Now that a range of unsubstituted hydrazides is readily available through the use of an efficient carbodiimide/HOBt-mediated coupling of carboxylic acids with hydrazine,[15] facile extension of this methodology to a diverse array of 2-substituted hydrazides is envisaged.

Experimental for the Formation of 1-Methylhydrazides 3

To a solution of methylhydrazine (1.5 M in CH_2Cl_2) at 0 °C was added the aroyl chloride (0.15 M in CH_2Cl_2) slowly via syringe pump under an atmosphere of nitrogen. After stirring at 0 °C for 1 h the reaction was warmed to r.t. and stirred for a further 2 h. The reaction mixture was then poured onto sat. aq Na_2CO_3 and extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the pure hydrazide **3**.

Experimental for the Formation of 1,2-Dimethylhydrazides 5

To a stirred solution of 1-substituted hydrazide **3** (0.25 M in toluene) was added paraformaldehyde (1.0 equiv). The reaction mixture was heated under reflux under Dean–Stark conditions for 18 h. The toluene was removed under reduced pressure to yield the acyl hydrazone intermediate **4**. To a solution of hydrazone **4** (0.25 M in MeOH) was added $NaCNBH_3$ (1.1 equiv) and AcOH (1.1 equiv). The reaction mixture was stirred at r.t. for 18 h before being poured cautiously onto sat. aq Na_2CO_3 and extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the pure 1,2-disubstituted hydrazide **5**.

Experimental for Formation of 2-Isopropylhydrazides 8

To a stirred solution of unsubstituted hydrazide **6** (0.25 M in acetone) was added Na_2SO_4 (ca. 100 equiv). The reaction mixture was stirred at r.t. for 18 h, then filtered and concentrated under reduced pressure to yield the acyl hydrazone intermediate **7** as a colorless crystalline solid. To a solution of acyl hydrazone **7** (0.25 M in MeOH) was added $NaCNBH_3$ (1.1 equiv) and AcOH (1.1 equiv). The reaction was stirred at r.t. for 18 h before being poured cautiously onto sat. aq Na_2CO_3 and extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give the pure 2-substituted hydrazide **8**.

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(8) Data for acyl hydrazone **4c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.55 (2 H, d, *J* = 8.0 Hz, Ar*H*), 7.25 (2 H, d, *J* = 8.0 Hz, Ar*H*), 6.45 (1 H, d, *J* = 10.6 Hz, N=CH_aH$_b$), 6.25 (1 H, d, *J* = 10.6 Hz, N=CH$_a$$H_b$), 3.41 [3 H, s, (CO)NC$H_3$], 2.39 (3 H, s, ArC$H_3$). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.29, 140.45, 131.81, 129.34 (2 C), 128.92, 128.07 (2 C), 27.53, 21.31. MS (ESI+): *m/z* = 177 $[M + H]^+$.
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(12) Data for acyl hydrazone **7c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.79 [1 H, br s, C(O)N*H*], 7.65 (2 H, d, *J* = 8.1 Hz, Ar*H*), 7.25 (2 H, d, *J* = 8.1 Hz, Ar*H*), 2.35 (3 H, s, ArCH_3), 2.12 (3 H, s, CCH_3), 1.93 (3 H, s, CCH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.6, 155.6, 142.0, 130.5, 129.0 (2 C), 127.0 (2 C), 25.3, 21.3, 16.4. MS (ESI+): *m/z* = 191 $[M + H]^+$.
(13) Data for 2-isopropyl hydrazides:
Compound **8a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.54 (5 H, m, Ar*H*), 3.26 [1 H, sept, *J* = 6.3 Hz, C*H*$(CH_3)_2$], 1.13 [6 H, d, *J* = 6.3 Hz, CH(CH_3)$_2$]. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.3, 132.8, 131.7, 128.6 (2 C), 126.7 (2 C), 51.2, 20.7 (2 C). MS (ESI+): *m/z* = 179 $[M + H]^+$.
Compound **8b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.74 (2 H, d, *J* = 8.8 Hz, Ar*H*), 6.93 (2 H, d, *J* = 8.8 Hz, Ar*H*), 3.85 (3 H, s, ArOCH_3), 3.20 [1 H, sept, *J* = 6.3 Hz, C*H*$(CH_3)_2$], 1.11 [6 H, d, *J* = 6.3 Hz, CH(CH_3)$_2$]. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.9, 162.3, 128.5 (2 C), 125.0, 113.7 (2 C), 55.3, 51.2, 20.7 (2 C). MS (ESI+): *m/z* = 231 $[M + Na]^+$.

Compound **8c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.63 [1 H, s, C(O)N*H*], 7.65 (2 H, d, *J* = 8.1 Hz, Ar*H*), 7.21 (2 H, d, *J* = 8.1 Hz, Ar*H*), 4.83 (1 H, NHN*H*), 3.23 [1 H, sept, *J* = 6.4 Hz, C*H*(CH_3)$_2$], 2.37 (3 H, s, ArCH_3), 1.08 [6 H, d, *J* = 6.4 Hz, CH(CH_3)$_2$]. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.3, 142.2, 129.9, 129.2 (2 C), 126.7 (2 C), 51.2, 21.3, 20.7 (2 C). MS (ESI+): *m/z* = 193 $[M + H]^+$.

Compound **8d**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.64 (2 H, d, *J* = 8.6 Hz, Ar*H*), 7.36 (2 H, d, *J* = 8.6 Hz, Ar*H*), 3.17 [1 H, sept, *J* = 6.3 Hz, C*H*(CH_3)$_2$], 1.05 [6 H, d, *J* = 6.3 Hz, CH(CH_3)$_2$]. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.3, 137.9, 131.1, 128.8 (2 C), 128.2 (2 C), 51.2, 20.7 (2 C). MS (ESI+): *m/z* = 213 $[^{35}M + H]^+$, 215 $[^{37}M + H]^+$.

Compound **8e**: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.29 (2 H, d, *J* = 8.9 Hz, Ar*H*), 7.95 (2 H, d, *J* = 8.9 Hz, Ar*H*), 3.25 [1 H, sept, *J* = 6.3 Hz, C*H*(CH_3)$_2$], 1.11 [6 H, d, *J* = 6.3 Hz, CH(CH_3)$_2$]. ^{13}C NMR (90 MHz, $CDCl_3$): δ = 165.2, 149.6, 138.3, 128.0 (2 C), 123.8 (2 C), 51.4, 20.7 (2 C). MS (ESI+): *m/z* = 224 $[M + H]^+$.

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