Direct and Efficient Synthesis of Dimethylformamidrazones Using Bentriazole Vilsmeier Reagent

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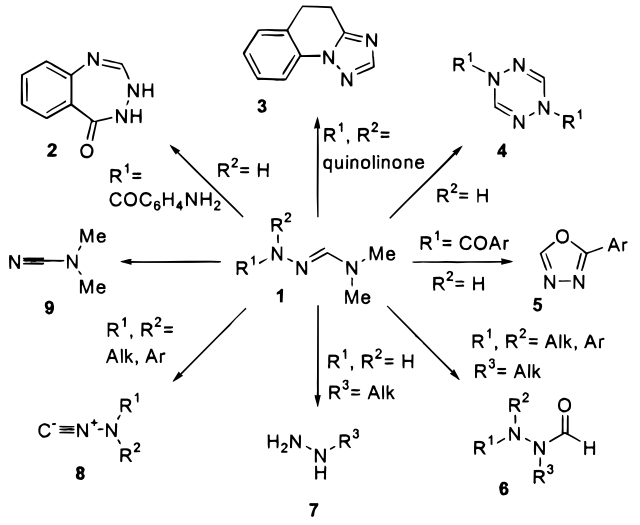
Dimethylformamidrazones **1** are versatile synthetic intermediates and are widely used as $HN^{-}NCH^{+}$ synthons (Scheme 1). Thus, **1** has been used (i) for the construction of various heterocycles including benzotriazepinones **2**,[1a,b] triazoloquinolines **3** and their salts,[2] tetrazines **4**,[3a,b] triazolopyrimidines,[4] triazoles,[5] and oxadiazoles **5**[6] and (ii) for the preparation of formamidrazones **6**,[7] hydrazines **7**,[3b,8] isocyanides **8**,[9] and cyanamides **9**.[9]

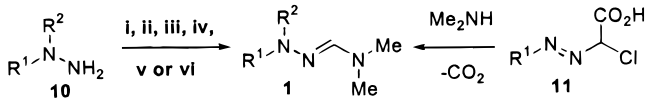
Further uses of **1** include synthesis of nucleosides,[10] precursors for ureas, and other utilities.[11a,b]

Several different preparative methods for dimethylformamidrazones **1** have been used previously (Scheme 2). Among these, the treatment of the corresponding hydrazine **10** with $POCl_3$ and DMF in benzene affords **1** in yields ranging from 63% to 71% and allows both alkyl and aryl substituents R^1 and R^2.[12a,b] Similarly, a mixture of DMF and $(Me)_2NSO_2Cl$ was employed for preparation of **1** with electron-deficient substituents (R^1 = H, R^2 = SO_2Ar, $NO_2C_6H_4$, $(NO_2)_2C_6H_3$, etc.) in yields of 71% to 88%. However, no synthesis of **1** with electron-rich substituents using such methods was reported.[4,13a,b] Other approaches are less straightforward. For example, decarboxylation of arylazochloroacetic acids **11**[14] affords **1** in 41−79% yield but requires a multistep preparation of the precursor that may have its own limitations on the generality of the overall approach. Similar problems arise in other examples such as a reaction of hydrazines

Scheme 1



Scheme 2[a]



[a] Key: (i) DMF, $(Me)_2NSO_2Cl$; (ii) DMF, $POCl_3$; (iii) $Me_2N^{+}CHClCl^{-}$. Bt = benzotriazole; (iv) $(Me)_2N^{+}CHSCH_3Cl^{-}$; (v) $(Me)_2NCH(CN)OCH_3$; (vi) $(Me)_2N^{+}CHBtCl^{-}$.

with *tert*-butylaminal esters[15] or dimethylformamide diethyl acetal[6] with amidrazines, which afford the selected **1** in 64−82% yield. Finally, reaction of hydrazines with dimethylaminoalkoxyacetonitrile[16] produces toxic byproducts.

We now report a direct and general method for the preparation of dimethylformamidrazones **1** starting from corresponding hydrazines **10** (R^1, R^2 = Ar, COAr, Alk, H) in 66−99% yields. For the preparation of **1**, we utilized the novel versatile reagent **12**[17] as a stable Vilsmeier reagent analogue. Previously, **12** was used in the synthesis of quinolines,[18a] pyridines,[18b] and pyrazoles[18c] (Scheme 3).

Typically, to prepare compounds **1** (R^1 = H, Alk, Ar and R^2 = H, Alk, Ar), 4 mmol of hydrazine **10** was reacted with 4 mmol of reagent **12** in 30 mL of THF under reflux to form the product **1** as a white precipitate. The desired product **1** is separated into its pure form by simple filtration. This procedure is applicable to hydrazines with a wide variety of substitutions (Table 1). For example, novel, or not readily available by other procedures,

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Scheme 3

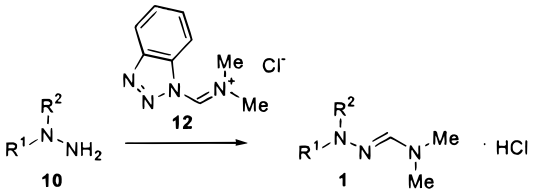
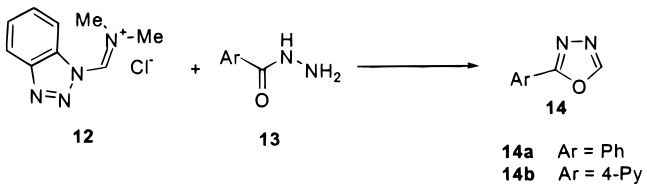


Table 1. Preparation of Dimethylformamidrazone Hydrochlorides 1

entry	R^1	R^2	yield (%)	published yield (%)
1a	C_6H_5	H	99	
1b	4-BrC_6H_4	H	84	
1c	4-$NO_2C_6H_4$	H	98	81[13a]
1d	2,4-$(NO_2)_2C_6H_3$	H	98	71[13a]
1e	4-$CH_3C_6H_4$	H	75	
1f	C_6F_5	H	98	
1g	CH_3	CH_3	88[a]	82[16]
1h	4-(*N*-oxide-pyridinyl)-CO	H	73[b]	
1i	4-$CH_3C_6H_4SO_2$	H	79	not given[19]
1j	H	H	69[a]	not given[20]
1k	H	H	98[c]	80[20]
1l	−CH=N−N=CH−		91	
1m	$C_6H_5SO_2$	H	89	88[e,13b]
1n	$-COC_6H_4CO-$		87	66[e,21]
1o	C_6H_5	CH_3	90	71[e,12b]
1p	$-CH_2CH_2N(CH_3)CH_2CH_2-$		98[d]	
1q	$-CH_2CH_2OCH_2CH_2-$		74	
1r	4-$CH_3OC_6H_4$	H	91	

[a] Extremely hydroscopic, no mp was obtained. [b] 9% of the corresponding oxadiazole was isolated along with the product. [c] Bisadduct was obtained when 2 equiv of **12** was used. [d] Was obtained as the bis hydrochloride salt. [e] The yield for the free amidrazones.

Scheme 4



formamidrazones with both electron-deficient aromatic substituents (entries **1c**, **1d**, and **1f**) and more electron-rich aromatic rings (entries **1a**, **1e**, **1o**, and **1r**) were prepared in 69−98% yields (Table 1). A number of novel heterocyclic formamidrazones (entries **1h**, **1l**, **1p**, and **1q**) are now available in 73−98% yields. In reactions of acyclic 1,1-disubstituted hydrazines, the yields of the corresponding compounds (entries **1g** and **1o**) were 88% and 90%. Similarly, compounds **1j** and **1k** were prepared from unsubstituted hydrazine giving 69% and 98% yields.

When we extended this procedure to hydrazides **13**, 1,3,4-oxadiazoles **14** were obtained as pure compounds in 95−98% yields (Scheme 4).

Conclusion. A simple and efficient procedure of preparation of dimethylformamidrazones was developed. Eighteen examples were prepared in 69−99% yields.

Experimental Section

General Methods. Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluka 51 digital thermometer. NMR spectra were taken in DMSO-d_6, D_2O, and $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted on silica gel 230−400 mesh.

General Procedure for the Preparation of 1a−l. A mixture of 4 mmol (0.85 g) of *N*-(1*H*-1,2,3-benzotriazol-1-ylmethylene)-*N*-methylmethanamium and 4 mmol of the corresponding hydrazine in 30 mL of dry THF was refluxed for 4 h under dry nitrogen. The solution was cooled to room temperature, and the resulting white precipitate was quickly filtrated off and was washed once with 10 mL of dry THF to give **1** as a hydrochloride salt.

***N,N*-Dimethyl-*N′*-phenylhydrazonoformamide hydrochloride (1a):** 98% yield; white solid; mp 185−186 °C; ^1H NMR δ 3.08 (s, 3H), 3.18 (s, 3H), 6.88 (d, 2H, J = 8.0 Hz), 6.97 (t, 1H, J = 7.5 Hz), 7.28 (t, 2H, J = 8.13 Hz), 8.03 (s, 1H); ^{13}C NMR δ 38.3, 44.7, 115.3, 123.7, 131.0, 147.9, 160.4. Anal. Calcd for $C_9H_{14}ClN_3$: C, 54.13; H, 7.07; N, 21.04. Found: C, 53.67; H, 7.22; N, 21.07.

***N′*-(4-Bromophenyl)-*N,N*-dimethylhydrazonoformamide hydrochloride (1b):** 84% yield; pale yellow solid; mp 215−216 °C; ^1H NMR δ 3.19 (br. s, 6H), 6.85 (d, 2H, J = 8.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 8.47 (s, 1H); ^{13}C NMR δ 38.8, 39.9, 114.4, 115.2, 131.2, 146.9, 159.2. Anal. Calcd for $C_9H_{13}BrClN_2$: C, 38.80; H, 4.70; N, 15.08. Found: C, 38.66; H, 4.64; N, 14.83.

***N,N*-Dimethyl-*N′*-4-nitrophenylhydrazonoformamide hydrochloride (1c):** 98% yield; yellow solid; mp 241−242 °C; ^1H NMR δ 3.19 (br.s, 6H), 6.90 (d, 2H, J = 8.0 Hz), 8.04−8.18 (m, 2H), 8.90 (s, 1H); ^{13}C NMR δ 42.0, 43.0, 113.7, 127.6, 142.2, 154.2, 160.8. Anal. Calcd for $C_9H_{13}ClN_4O_2$: C, 44.18; H, 5.36; N, 22.90. Found: C, 43.94; H, 5.61; N, 22.76.

***N,N*-Dimethyl-*N′*-2,4-dinitrophenylhydrazonoformamide hydrochloride (1d):** 98% yield; yellow solid; mp 238−239 °C; ^1H NMR δ 3.22 (br.s, 6H), 7.64 (d, 1H, J = 9.4 Hz), 8.38 (d, 1H, J = 9.3 Hz), 8.53 (s, 1H), 8.9 (s, 1H), 10.96 (s, 1H); ^{13}C NMR δ 23.1, 38.6, 40.3, 116.0, 125.3, 129.8, 136.7, 145.7, 157.7. Anal. Calcd for $C_9H_{12}ClN_5O_4$: C, 37.32; H, 4.18; N, 24.18. Found: C, 37.09; H, 4.26; N, 23.88.

***N′*-(4-Methylphenyl)-*N,N*-dimethylhydrazonoformamide hydrochloride (1e):** 75% yield; white solid; mp 212−213 °C; ^1H NMR δ 2.21 (s, 3H), 3.21 (br. S, 6H), 6.78 (d, 2H, J = 7.2 Hz), 7.04 (d, 2H, J = 7.2 Hz), 8.44 (s, 1H); ^{13}C NMR δ 19.9, 41.9, 113.4, 129.0, 129.1, 145.1, 159.1; HRMS calcd for $C_{10}H_{16}N_3$ (M + 1) 178.1344, found 178.1347.

***N′*-(Pentaflurophenyl)-*N,N*-dimethylhydrazonoformamide hydrochloride (1f):** 98% yield; white solid; mp 202−204 °C; ^1H NMR δ 3.13 (s, 6H), 8.38 (s, 1H); ^{13}C NMR δ 38.7, 40.4, 116.2, 128.1, 137.0, 137.4, 137.6, 139.6, 140.7, 143.0, 160.1. Anal. Calcd for $C_9H_9ClF_5N_3$: C, 37.32; H, 3.13; N, 14.51. Found: C, 36.87; H, 2.97; N, 14.01.

***N,N,N′,N′*-Tetramethylhydrazonoformamide hydrochloride (1g):** 88% yield; colorless solid; mp 144−145 °C; ^1H NMR δ 2.62 (s, 3H). 2.67 (s, 3H), 3.00 (br, 6H), 7.94 (br.s, 1H); ^{13}C NMR δ 38.0, 44.0, 48.5, 157.5. Anal. Calcd for $C_5H_{14}ClN_3$: C, 39.60; H, 9.37; N, 27.71. Found: C, 39.54; H, 9.77; N, 27.44.

***N′*-(4-*N″*-oxideisonicotinoyl)-*N,N*-dimethylhydrazonoformamide hydrochloride (1h):** 73% yield; white solid; mp 155−156 °C; ^1H NMR δ 3.20 (s, 3H), 3.22 (s, 3H), 7.89 (d, 2H, J = 3.9 Hz), 8.27 (s, 1H), 8.77 (s, 2H); ^{13}C NMR δ 42.3, 123.9, 141.8, 150.0, 160.0, 167.1; HRMS calcd for $C_9H_{12}N_4O_2$ 208.0960, found 208.0963. Anal. Calcd for $C_9H_{13}ClN_4O_2$: N, 22.90. Found: N, 22.75.

***N,N*-Dimethyl-*N′*-toluenolsulfonylformamidrazon hydrochloride (1i):** 79% yield; white solid; mp 215−216 °C; ^1H NMR δ 2.32 (s, 3H). 2.90 (s, 3H), 3.17 (s, 3H), 7.37 (d, 2H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.0 Hz), 8.03 (s, 1H); ^{13}C NMR δ 22.5. 38.8, 45.2, 129.6, 131.9, 133.2, 148.1, 160.6. Anal. Calcd for $C_{10}H_{16}ClN_3O_2S$: C, 43.24; H, 5.81; N, 15.13. Found: C, 43.23; H, 5.93; N, 15.15.

***N,N*-Dimethylhydrazonoformamide hydrochloride (1j):** 69% yield; colorless crystals; mp 215−216 °C; ^1H NMR δ 2.57 (s, 6H). 2.60 (s, 3H), 8.38 (s, 1H); ^{13}C NMR δ 35.9, 145.9.

***N,N*-Dimethylhydrazonoformamidine (1k):** 98% yield; colorless oil; ^1H NMR δ 2.64 (s, 3H), 2.66 (s, 3H), 2.71 (s, 3H), 7.83 (s, 1H), 7.86 (s, 1H); ^{13}C NMR δ 36.9, 39.9, 153.7, 163.2.

***N,N*-Dimethyl-*N′*-1,2,4-triazol-4-ylformamidine hydrochloride (1l):** 91% yield; white solid; mp 176−177 °C; ^1H NMR

δ 2.81 (s, 3H), 2.94 (s, 3H), 7.99 (s, 1H), 9.06 (s, 2H); ^{13}C NMR δ 36.3, 42.6, 141.7, 163.1. Anal. Calcd for $C_5H_{10}ClN_5$: N, 39.88. Found: N, 40.07.

***N,N*-Dimethyl-*N′*-(phenylsulfonyl)hydrazonoformide hydrochloride (1m):** 89% yield; white solid; mp 198−200 °C; ^{1}H NMR δ 2.87 (s, 3H), 3.15 (s, 3H), 7.54 (t, 2H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.8 Hz), 7.80 (d, 2H, J = 7.8 Hz), 8.03 (s, 1H); ^{13}C NMR δ 39.1, 45.6, 129.9, 131.8, 136.5, 137.0, 161.0. Anal. Calcd for $C_9H_{14}ClN_3O_2S$: C, 40.99; H, 5.36; N, 15.94. Found: C, 40.87; H, 5.58; N, 15.96.

***N′*-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-*N,N*-dimethyliminoformamide hydrochloride (1n):** 87% yield; white solid; mp 247−248 °C; ^{1}H NMR δ 3.18 (s, 3H), 3.27 (s, 3H), 7.77 (dd, 4H, J = 8.0 Hz, 3.1 Hz), 8.20 (s, 1H); ^{13}C NMR δ 39.0, 45.6, 125.0, 130.3, 137.3, 160.4, 167.1.

***N′*-Methyl-*N′*-phenyl-*N,N*-dimethylhydrazonoformamide hydrochloride (1o):** 90% yield; white solid; mp 223−224 °C; ^{1}H NMR δ 3.04 (s, 3H), 3.10 (s, 3H), 3.19 (s,3H), 6.91−7.02 (m, 3H), 7.29 (t, 2H, J = 6.8 Hz), 8.10 (s, 1H); ^{13}C NMR δ 38.5, 44.4, 44.9, 116.5, 123.7, 131.0, 150.7, 159.8. Anal. Calcd for $C_{10}H_{15}ClN_3$: C, 56.20; H, 7.56; N, 19.67. Found: C, 55.77; H, 8.03; N, 19.70.

***N,N*-Dimethyl-*N′*-(4-methylpiperazino)iminoformamide bishydrochloride (1p):** 87% yield; white solid; mp 250−251 °C; ^{1}H NMR δ 2.79 (s, 3H), 2.93 (s, 3H), 3.13 (s, 3H), 3.22 (t, 4H, J = 7.2 Hz), 3.40 (t, 4H, J = 7.2 Hz), 8.08 (s, 1H); ^{13}C NMR δ 38.4, 44.0, 44.8, 53.7, 54.5, 158.5. Anal. Calcd for $C_8H_{20}Cl_2N_4$: C, 39.51; H, 8.29; N, 23.04. Found: C, 39.12; H, 8.65; N, 22.71.

***N,N*-Dimethyl-*N′*-morpholinoiminoformamide hydrochloride (1q):** 74% yield; white solid; mp 145−146 °C; ^{1}H NMR δ 2.92 (t, 2H, J = 8.0 Hz), 2.96 (s, 3H), 3.17 (s, 3H), 3.72 (s, 3H), 8.07 (s, 1H); ^{13}C NMR δ 38.2, 44.6, 57.1, 67.4, 157.9. Anal. Calcd for $C_7H_{16}ClN_3O$: N, 21.70. Found: N, 21.28.

***N′*-(4-Methoxyphenyl)-*N,N*-dimethylhydrazonoformamide hydrochloride (1r):** 91% yield; white solid; mp 185−186 °C; ^{1}H NMR δ 3.03 (s, 3H), 3.19 (s, 3H), 3.70 (s, 3H), 6.84−6.85 (br. s, 4H), 8.04 (s, 1H); ^{13}C NMR δ 38.3, 44.8, 57.2, 116.5, 117.4, 141.8, 156.0, 160.2. Anal. Calcd for $C_{10}H_{16}ClN_3O$: N, 18.29. Found: N, 18.00.

2-Phenyl-1,3,4-oxadiazole (14a): 89% yield; white solid; mp 34−36 °C; ^{1}H NMR δ 7.75−7.90 (m, 3H), 8.20 (d, 2H, J = 8.4 Hz), 9.57 (s, 1H); ^{13}C NMR δ 123.2, 126.6, 129.3, 131.9, 154.4, 163.6.

2-(4-Pyridinyl)-1,3,4-oxadiazole (14b): 95% yield; white solid; mp 118 °C; ^{1}H NMR δ 7.98 (d, 2H, J = 6.1 Hz), 8.66 (s, 1H), 8.88 (d, 2H, J = 6.1 Hz); ^{13}C NMR δ 120.4, 130.6, 150.9, 153.3, 163.0. Anal. Calcd for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.25; H, 3.44; N, 28.47.

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