Preparation, properties, and reductive alkylation of arylhydrazides

Giancarlo Verardo, Nicoletta Toniutti, and Angelo G. Giumanini

Abstract: 1-Acyl-2-arylhydrazines (**1**), readily obtained in high yield from the condensation of arylhydrazines and the appropriate liquid carboxylic acid (**2**), underwent reductive alkylation with the same or different liquid carboxylic acids (**2**) and $NaBH_4$ to give 1-acyl-2-alkyl-2-arylhydrazines (**3**) in good to moderate yields. The carboxylic acid has both the role of supplying the entering alkyl group and of acting as solvent. Most likely, it also modifies the BH_4^- anion to an active reducing agent under those conditions. The ^1H NMR criteria for identifying the location of acylation of hydrazines and *E* and *Z* isomers are given. The MS spectra of the prepared hydrazides were analyzed in order to identify relevant structural features leading to specific fragmentations.

Key words: 1-acyl-2-arylhydrazine, 1-acyl-2-alkyl-2-arylhydrazine, reductive alkylation, sodium tetrahydroborate, carboxylic acid.

Résumé : La condensation d'arylhydrazines et d'acides carboxyliques liquides appropriés (**2**) conduit facilement aux 1-acyl-2-arylhydrazines (**1**) avec d'excellents rendements; celles-ci, par alkylation réductrice avec les mêmes (ou d'autres) acides carboxyliques (**2**) liquides et du $NaBH_4$, conduisent aux 1-acyl-2-alkyl-2-arylhydrazines (**3**) avec des rendements qui vont de bons à moyens. L'acide carboxylique joue à la fois le rôle de source du groupe méthyle qui entre et de solvant. Il est probable qu'il modifie aussi l'anion BH_4^- afin qu'il devienne un agent réducteur actif dans ces conditions. On présente les critères de RMN du ^1H permettant d'identifier la position de l'acylation des hydrazines et les isomères *E* et *Z*. On a analysé les SM des hydrazides préparés dans le but d'identifier les caractéristiques structurales pertinentes aux fragmentations spécifiques.

Mots clés : 1-acyl-2-arylhydrazine, 1-acyl-2-alkyl-2-arylhydrazine, alkylation réductrice, tétrahydroborate de sodium, acide carboxylique.

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Introduction

The use of carboxylic acids in combination with $NaBH_4$ was found to effect *N*-alkylation of aliphatic as well as aromatic amines (1), nevertheless, the synthetic utility of this method was never developed to date on hydrazines and derivatives. The direct reductive alkylation of phenylhydrazine with carboxylic acid and $NaBH_4$ gave a mixture of products resulting from different multiple alkylations as well as acylation of the hydrazine.[2] In fact, it is well established that alkylation of alkyl- or arylhydrazines occurs preferentially on the substituted nitrogen atom (2), however, this reaction usually requires the use of protecting groups to limit or avoid multiple alkylations. For this reason, it has been performed on hydrazones or acylhydrazines. The resulting alkyl derivatives could be either hydrolyzed to remove the protecting group and give 1,1-disubstituted hydrazines or reduced to yield trisubstituted hydrazines (3). Herein, we focused our attention on arylhydrazides as better substrates for selective alkylation.

Hydrazides are an important class of compounds not only in organic synthesis, but also for industrial applications. Arylhydrazides (**1**) and 1-acyl-2-alkyl-2-arylhydrazines (**3**) were used in the preparation of herbicides (4), antiinflammatory indoles (5), derivatives with antimicrobial (6) or antimycotic activity (7, 8).

We now report the preparation and full characterization of some arylhydrazides (**1**) and their reductive alkylation with carboxylic acids and $NaBH_4$ combination as the method of choice for preparation of 1-acyl-2-alkyl-2-arylhydrazines (**3**). This simple, inexpensive, high-yielding method is also proposed as a one-pot procedure in which the carboxylic acid acts as acylating as well as alkylating agent. The MS and NMR spectra of these hydrazides were carefully discussed because literature data were sparse and scattered.

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[2] G. Verardo et al. Unpublished results.

Results and discussion

1-Acyl-2-arylhydrazines (**1a**–**f**) were readily obtained by heating the corresponding carboxylic acid and arylhydrazines without any condensing agent (9). This direct approach seems scarcely known and even less attended (10, 11). In producing 1-acyl-2-arylhydrazine instead of its isomer 1-acyl-1-arylhydrazine, the carboxylic acid here behaves in the same way as other acylating agents, frequently

Table 1. Physical data of 1-acyl-2-aryl-hydrazines (**1**).

Compound[a]	R	R_1	Yield[b]	mp (°C)[c]
1a	H	H	50%	144[d]
1b	H	Me	85%	129[e]
1c	H	Et	80%	157[f]
1d	H	Pr	75%	110[g]
1e	NO_2	Me	81%	213
1f	Me	Me	75%	132

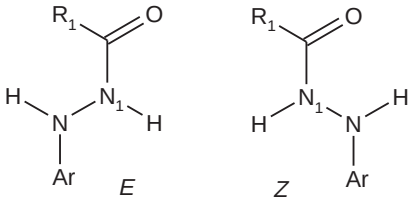
[a]All solid compounds were analyzed for C, H, and N, and results agreed to ±0.5% of theoretical values.
[b]Yield of isolated product.
[c]Midpoint of narrow range.
[d]Literature (4) 145°C.
[e]Literature (5) 129°C.
[f]Literature (5) 157°C.
[g]Literature (5) 96°C.

used for hydrazines, such as esters, anhydrides, and acyl chlorides (12).

All the starting hydrazides **1a–f** were characterized and their properties compared with literature data (Tables 1 and 2). The correct structural identification of the arylhydrazides **1a–f** was essentially based on their ^{1}H NMR features. Upon accurate examination of the available literature data, we made the following observation. Although 1-acyl-1-substituted-hydrazines usually exhibit the *E*/*Z* amide isomerism (Fig. 1), which doubles all the hydrogen resonances, their primary amino group hydrogens appear as singlets at ca. 3.8–4.8 ppm in $CDCl_3$ and 4.2–5.3 ppm in DMSO-d_6 (13).

Completely different NMR features are recognized when the acyl and the aryl (or alkyl) groups are located on different nitrogens (that is, for 1-acyl-2-substituted derivatives). The hydrogen belonging to the amide function shows up as two unequal resonances with a separation of ca. 0.3–0.7 ppm both in $CDCl_3$ (at ca. 7.4 ppm) and in DMSO-d_6 (at ca. 9.0 ppm) (13). Interestingly, the amino proton also reflects

Fig 1.

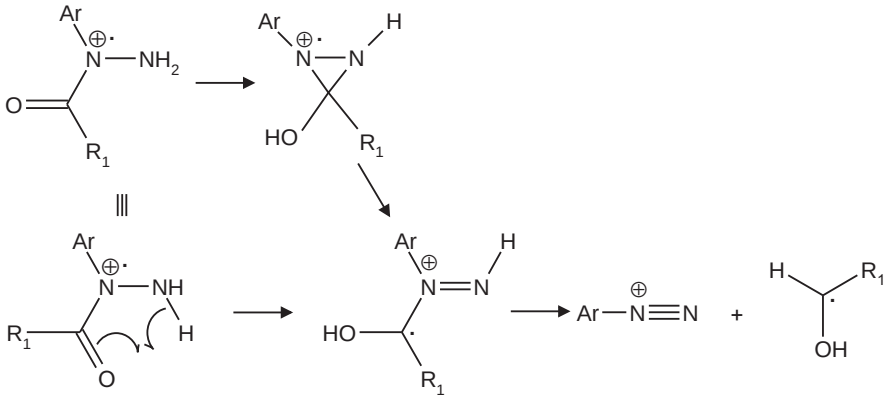


the different environment by showing two peaks at ca. 6.0 ppm in $CDCl_3$ and ca. 8.0 in DMSO-d_6 (13). After comparing these data with the spectra of our 1-acyl-2-arylhydrazines (1) (see Table 2), we confirmed their identification.

Of all the hydrazides **1a–f**, only 1-acetyl-2-(4-nitrophenyl)hydrazine (**1e)** did not show the *E*/*Z* isomerism in the NMR. The H-decoupled ^{13}C-NMR spectra of **1a–f** showed extensive doubling of the several peaks, but again **1e** did not exhibit this feature, a good indication that it was present in a single conformation.

The mass spectra of **1a–f** and of their 1,1-isomers **1a′–f′** differed in a number of features (Table 2 and experimental part). The latter showed weaker parent ions, which underwent extensive fragmentations to the RCO^+ acyl ions and the R^+ ions (likely in a rearranged form, whenever possible). Intense peaks at *m*/*z* 77 and 78 (corresponding to peaks at *m*/*z* 122, 123 for **1e′** and 91, 92 for **1f′** deriving from the substituted phenyl group) were detected. But their most impressive feature was the production of an outstanding peak at *m*/*z* 105 for PhN_2^+ (or the corresponding charged fragment from **1e′** and **1f′**), always accompanied by a weak peak at *m*/*z* 108 for the formula of phenylhydrazine (or the corresponding substituted phenylhydrazine from the parent ions **1e′** and **1f′**). A possible mechanism for the formation of ArN_2^+ involves a few rearrangements before cleavage of the parent ion of **1a′–f′**, eq. [1].

[1]



The 1,2-isomers **1b–f** also yielded all these ions, with the relevant difference that the ion at *m*/*z* 105 (or the corresponding charged fragment from **1e** and **1f**) was hardly discernible and that the ion at *m*/*z* 108 (or the corresponding peak for the formula of substituted phenylhydrazine from the parent ions **1e** and **1f**), due to the loss of ketene from the parent ion, was the base peak. The mass spectrum of **1a** is quite different from **1b–f** as the first most intense peak was the molecular ion (*m*/*z* 136), and the second one was the peak at *m*/*z* 107 ($PhN_2H_2^+$). On the contrary, the ion at *m*/*z* 108 was scarcely present.

Table 2. Spectroscopic and MS data of 1-acyl-2-arylhydrazines (**1**).

Product	IR (KBr) ν (cm^{-1})	^{1}H NMR δ, *J* (Hz)	^{13}C NMR δ	MS (70 eV) *m*/z (%)
1a	3310 s, 3204 s, 3072 s, 3026 s, 2907 m, 1690 vs, 1663 vs, 1604 s, 1505 s, 1394 vs, 1200 m, 874 s, 755 vs, 702 vs	6.65–6.85 (m, 3H, H_{arom}), 7.10–7.25 (m, 2H, H_{arom}), 8.11 (d, 1H, HC=O, *J* = 10.5, rotamer A), 8.13 (s, 1H, HC=O, rotamer B), 7.80 (app d, 1H, N-H, *J* = 2.7, rotamer A), 8.01 (s, 1H, N-H, rotamer B), 9.45 (d, 1H, N-H, *J* = 10.8, rotamer A), 9.72 (app d, 1H, N-H, *J* = 2.2, rotamer B)[b]	149.3, 149.4, 155.8, 156.6, 165.8, 166.1, 185.8, 186.5, 197.7, 204.8[b]	136 (M^+, 100), 108 (12), 107 (73), 92 (12), 91 (16), 78 (10), 77 (50), 65 (19), 64 (10), 51 (20), 39 (10)
1b	3270 s, 3072 m, 1670 vs, 1617 vs, 1500 s, 1485 vs, 1437 vs, 1372 s, 1300 s, 1250 s, 1010 s, 766 vs, 700 vs	2.03 (s, 3H, CH_3, rotamer A), 2.09 (s, 3H, CH_3, rotamer B), 5.84 (br s, 1H, N-H, rotamer A), 6.18 (app d, 1H, N-H, *J* = 3.9, rotamer B), 6.72–6.96 (m, 3H, H_{arom}), 7.15 (br s, 1H, N-H, rotamer A), 7.19–7.33 (m, 2H, H_{arom}), 7.63 (s, 1H, N-H, rotamer B)[a]	19.1, 20.9, 112.4, 113.48, 121.2, 121.2, 129.1, 129.5, 147.0, 147.8, 170.2, 176.9[a]	150 (M^+, 62), 108 (100), 107 (37), 93 (27), 92 (28), 91 (12), 78 (13), 77 (43), 65 (12), 51 (14), 43 (19), 39 (10)
1c	3310 vs, 3270 vs, 3039 s, 2980 s, 2940 s, 1650 vs, 1609 vs, 1557 vs, 1497 vs, 1464 vs, 1227 s, 1150 s, 1043 s, 944 s, 760 vs, 694 vs	1.05–1.25 (m, 3H, CH_3), 2.27 (q, 2H, CH_2, *J* = 7.5, rotamer A), 2.45 (q, 2H, CH_2, *J* = 7.5, rotamer B), 5.80 (br s, 1H, N-H, rotamer A), 6.15 (br s, 1H, N-H, rotamer B), 6.70–6.95 (m, 3H, H_{arom}), 7.03 (br s, 1H, N-H, rotamer A), 7.15–7.30 (m, 2H, H_{arom}), 7.50 (br s, 1H, N-H, rotamer B)[a]	8.0, 8.9, 23.9, 26.9, 111.7, 112.9, 120.6, 128.5, 128.8, 146.5, 147.4, 173.2[a]	164 (M^+, 68), 108 (100), 107 (31), 93 (50), 92 (18), 78 (19), 77 (37), 66 (17), 65 (15), 57 (16), 54 (19), 51 (14), 39 (11)
1d	3296 vs, 3236 vs, 3085 s, 3045 s, 2966 s, 2940 s, 2880 m, 1681 vs, 1642 vs, 1622 vs, 1576 vs, 1510 vs, 1445 s, 1120 s, 957 s, 760 vs, 694 vs, 502 vs	0.89 (t, 3H, CH_3, *J* = 7.3), 1.50–1.85 (m, 2H, CH_2), 2.10 (t, 2H, CH_2, *J* = 7.5, rotamer A), 2.33 (t, 2H, CH_2, *J* = 7.5, rotamer B), 5.85 (br s, 1H, N-H, rotamer A), 6.30 (br s, 1H, N-H, rotamer B) 6.60–6.90 (m, 3H, H_{arom}), 7.10–7.30 (m, 2H, H_{arom}), 7.38 (br s, 1H, N-H, rotamer A), 8.15 (br s, 1H, N-H, rotamer B)[a]	14.9, 19.3, 20.2, 34.3, 37.3, 113.6, 114.6, 122.1, 130.3, 130.5, 148.6, 149.3, 174.7, 180.8[a]	178 (M^+, 27), 108 (100), 107 (18), 93 (78), 92 (20), 78 (13), 77 (30), 71 (16), 66 (28), 65 (20), 51 (12), 43 (35), 41 (66), 39 (25)
1e	3315 vs, 3290 vs, 3091 m, 3006 m, 2933 m, 1655 vs, 1592 vs, 1504 vs, 1320 vs, 1257 vs, 1115 vs, 1008 s, 837 vs, 749 s	1.98 (s, 3H, CH_3), 6.79 (app d, 2H, H_{arom}, *J* = 8.7), 8.08 (app d, 2H, H_{arom}, *J* = 8.7), 9.01 (s, 1H, N-H), 9.97 (s, 1H, N-H)[b]	20.5, 110.5, 125.8, 138.0, 154.9, 169.2[b]	195 (M^+, 26), 154 (8), 153 (100), 123 (9), 108 (10), 107 (10), 106 (12), 43 (32)
1f	3289 vs, 3252 vs, 3026 s, 1666 vs, 1600 vs, 1547 vs, 1520 vs, 1381 vs, 1241s, 1150 m, 1000 s, 824 vs, 751 vs	1.90 (s, 3H, CH_3, rotamer A), 2.02 (s, 3H, CH_3, rotamer B), 2.23 (s, 3H, CH_3, rotamer A), 2.24 (s, 3H, CH_3, rotamer B), 5.85 (br s, 1H, N-H, rotamer A), 6.19 (br s, 1H, N-H, rotamer B), 6.50–6.70 (m, 2H, H_{arom}), 6.85–7.00 (m, 2H, H_{arom}), 7.46 (br s, 1H, N-H, rotamer A), 8.26 (br s, 1H, N-H, rotamer B)[a]	19.7, 21.1, 21.3, 113.1, 114.2, 130.2, 130.4, 130.9, 145.5, 146.2, 171.2, 177.9[a]	164 (M^+, 90), 121 (64), 122 (100), 121 (91), 107 (27), 106 (62), 91 (30), 77 (32), 65 (13), 43 (18)

[a]Solvent:$CDCl_3$.
[b]Solvent: DMSO-d_6.

The GC–MS analysis of the intact reaction mixtures, after removal of excess acid, showed that the 1,1-isomer was usually present in small concentrations (<5%). In the course of the GC analyses we observed that 1-acyl-2-arylhydrazines (**1**) isomerized extensively to the 1,1-isomer when they were injected using CH_2Cl_2 as solvent. We assumed that this was the result of the formation of HCl in the injector, kept at 250°C, which catalyzed the 1,2-migration of the acyl group.

We submitted the 1-acyl-2-arylhydrazines **1b–f** to reductive alkylation using an excess of either the same (R_1 = R_2, eq. [2]), or different ($R_1 \neq R_2$, eq. [2]) carboxylic acids and $NaBH_4$.

[2]

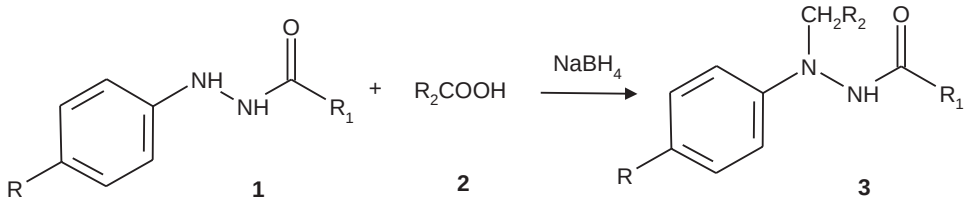


Table 3. Physical data of 1-acyl-2-alkyl-2-aryl-hydrazines (**3**).

Compound[a]	R	R_1	R_2	Yield[b]	mp (°C)[c]
3a	H	Me	H	15%	94[d]
3b	H	Me	Me	76%	87
3c	H	Me	Et	77%	93
3d	H	Me	Pr	80%	94
3e	H	Et	H	20%	80
3f	H	Et	Et	76%	72
3g	H	Pr	Pr	70%	90[e]
3h	NO_2	Me	Me	67%	144[f]
3i	Me	Me	Me	71%	100

[a]All solid compounds were analyzed for C, H, and N, and results agreed to ±0.5% of theoretical values.
[b]Yield of isolated product.
[c]Midpoint of narrow range.
[d]Literature (8) 94°C.
[e]Recrystallized at –20°C.
[f]Literature (11) 144°C.

In the former case the reaction can be easily carried out in a stepwise, one-pot procedure. The synthetic route reported herein promised to be an easy way to obtain monoalkylated arylhydrazides compared to previously described methods, mostly affording fair yields of impure products (14–18). Most of the alkylated products (**3**), prepared and characterized herein, were never synthesized before. The results are summarized in Table 3, and the spectroscopic and MS properties are collected in Table 4.

The structural identification of products **3a**–**i** were based both on chemical degradation and spectroscopic investigations. It was reported that treatment of azo compounds with Zn in aqueous HCl effected the reductive cleavage of the NN double bond (19). It is reasonable to conclude that the conversion went through the intermediacy of hydrazines. We applied this treatment to **3b** and **3d** and obtained *N*-ethyl and *N*-butylaniline, respectively, as the only aromatic amines, as determined by GC–MS analysis. The ^{1}H NMR spectra of **3b** and **3d** showed two relatively sharp singlets each at 7.66, 8.32 ppm and 7.50, 8.10 ppm, respectively, in $CDCl_3$ for the *E* and *Z* amide hydrogens. This assignment turned out to be correct upon comparison with the range for this proton in the spectra of **1a**–**f** (7.03–7.46 ppm and 7.50–8.26 ppm in $CDCl_3$). The ^{13}C NMR spectra were consistent with the data obtained from the proton spectra. As expected, the IR spectra for **3b** and **3d** showed single NH bands. The common features in the mass spectra of **3b** and **3d** are illustrated in Scheme 1. The outlined patterns of fragmentations were found in all other *N*-alkyl arylhydrazides **3a**, **c**, **e**–**i**. Analogously, the ^{1}H and ^{13}C NMR spectra of these compounds repeated quite consistently the features outlined above for **3b** and **3d**.

A likely mechanism of the reductive alkylation of 1-acyl-2-arylhydrazines **1** with the carboxylic acids **2** implies the reduction of **2** to aldehydes **4** by the action of some borohydride species formed in solution (20) and subsequent condensation of aldehydes with **1** to an easily reducible iminium ion **5** (Scheme 2). This rationale is consistent with the formation of traces of ethanal-phenylhydrazone from the reaction of phenylhydrazine with acetic acid and $NaBH_4$ (see footnote 2) as detected by GC–MS and confirmed the observation made by Gribble et al. (1). The proposed mechanism turned out to be correct when we tested the reaction between 1-acyl-2-phenylhydrazine (**1b**) and butanal in the presence of $NaBH_4$ (21) (see experimental part). The reaction afforded 1-acyl-2-butyl-2-phenylhydrazine (**3d**) in 50% yield together with some unreacted 1-acyl-2-phenylhydrazine.

The reductive alkylation of 1-aryl-2-acylhydrazines with carboxylic acids and $NaBH_4$ is a valid alternative method to the usual reductive alkylation with carbonyl compounds due to the high yields and easy procedure. The reaction implied the use of few and readily available reagents. The carboxylic acid plays the role of solvent, acylating agent, source of entering alkyl group, modifier of $NaBH_4$ reactivity, and acid catalyst.

When we applied our procedure of reductive alkylation with carboxylic acids and $NaBH_4$ to phenylhydrazine hydrochloride, after neutralization with the minimum amount of 10% aqueous NaOH, we observed the formation of the corresponding 1-acyl-2-phenylhydrazine only, but no formation of the alkylated product. This result was consistent with decomposition of acyloxyborohydride species in the presence of water as reported in literature (22).

Moreover, $NaBH_4$ is a mild and selective reagent. The GC–MS analysis revealed that neither any amide was reduced nor N—N bond was cleaved by $NaBH_4$. Even in 6 M H_2SO_4 at 80°C, sodium borohydride left 1-acetyl-2-butyl-2-phenylhydrazine (**3d**) unchanged; only some 2-butyl-2-phenylhydrazine was detected as the usual hydrolysis product obtainable under acidic conditions.

While the reductive alkylation of *N*-acyl-*N*′-arylhydrazines was applicable to **1b**–**f**, the only exception was **1a**, which resisted *N*′-ethylation by acetic acid – $NaBH_4$ under the standard condition.

Experimental

Phenylhydrazine hydrochloride, (4-methylphenyl)hydrazine hydrochloride, phenylhydrazine, (4-nitrophenyl)hydrazine, and $NaBH_4$ pellets were purchased from Aldrich, Italy, Milan. Solvents were used as received. The GC–MS analyses were performed with a Fisons Trio 2000 mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 35–500 u. Injector temperature was kept at 250°C, and the column (Supelco SPB^{TM}-5, 30 m long, 0.32 mm i.d.) temperature was programmed from 60 to 300°C with a gradient of 10°C/min. The GC analyses performed, keeping the injector at 250°C on pure 1-acyl-2-arylhydrazines (**1**), showed, at times, the formation of isomeric 1-acyl-1-arylhydrazines; the reaction was relevant when very dilute CH_2Cl_2 solutions were used, but did not occur with other solvents. The IR spectra were obtained with a Nicolet FT-IR Magna 550 spectrophotometer using KBr technique for solids in the range 4000–400 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at room temperature on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively. The NMR peak locations are reported as δ-values from TMS (^{1}H NMR) and the central peak of $CDCl_3$ or DMSO-d_6 (^{13}C NMR). Some ^{1}H multiplets are characterized by the term app (apparent): this refers only to their

Table 4. Spectroscopic and MS data of 1-acyl-2-alkyl-2-arylhydrazines (**3**).

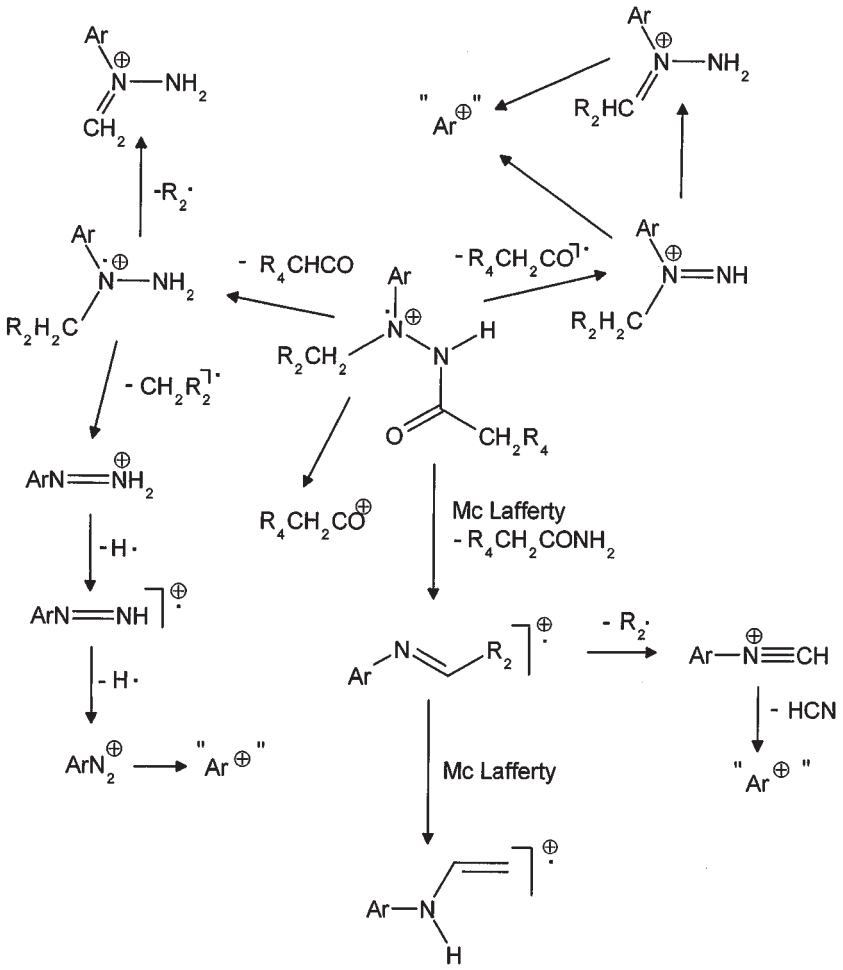
Product	IR (KBr) ν (cm^{-1})	^{1}H NMR δ, *J* (Hz)	^{13}C NMR δ	MS (70 eV) *m/z* (%)
3a	3256 vs, 3019 s, 2880 m, 2808 m, 1675 vs, 1605 vs, 1530 vs, 1504 vs, 1377 s, 1281 vs, 1220 s, 1120 s, 1038 s, 756 vs, 694 vs	1.93 (s, 3H, CH_3, rotamer A), 2.01 (s, 3H, CH_3, rotamer B), 3.03 (s, 3H, N-CH_3, rotamer A), 3.08 (s, 3H, N-CH_3, rotamer B), 6.65–6.95 (m, 3H, H_{arom}), 7.13–7.31 (m, 3H, $2H_{arom}$ + N-H, rotamer A), 8.05 (br s, 1H, N-H, rotamer B)[a]	18.9, 20.8, 40.5, 41.9, 112.9, 113.2, 119.5, 120.5, 128.9, 129.2, 149.1, 149.2, 169.2, 176.9[a]	164 (M^+, 42), 122 (45), 121 (100), 107 (33), 106 (19), 105 (60), 104 (12), 93 (8), 92 (33), 78 (9), 77 (60), 65 (8), 51 (16), 43 (16)
3b	3263 vs, 3032 m, 2986 m, 2940 m, 2861 m, 1683 vs, 1598 vs, 1551 s, 1499 vs, 1387 vs, 1295 s, 1269 s, 1144 m, 1045 m, 755 vs, 702 vs	1.05–1.22 (m, 3H, CH_3), 1.94 (s, 3H, CH_3, rotamer A), 1.98 (s, 3H, CH_3, rotamer B), 3.33–3.55 (m, 2H, N-CH_2), 6.70–6.95 (m, 3H, H_{arom}), 7.10–7.35 (m, 2H, H_{arom}), 7.66 (br s, 1H, N-H, rotamer A), 8.32 (br s, 1H, N-H, rotamer B)[a]	11.8, 12.4, 20.3, 21.8, 47.3, 49.8, 114.3, 115.2, 120.4, 121.7, 130.1, 130.5, 149.6, 149.9, 170.9, 177.9[a]	178 (M^+, 44), 136 (21), 135 (85), 121 (51), 120 (15), 119 (100), 107 (91), 105 (10), 104 (24), 79 (11), 78 (12), 77 (96), 51 (24), 43 (22)
3c	3270 vs, 3030 m, 2964 s, 2935 s, 2880 m, 1665 vs, 1600 vs,1532 vs, 1500 vs, 1370 vs, 1288 vs, 1236 m, 1194 m, 1140 m, 1045 m, 756 vs, 670 vs	0.95 (t, 3H, CH_3, *J* = 7.4, rotamer A), 0.97 (t, 3H, CH_3, *J* = 7.4, rotamer B), 1.55–1.70 (m, 2H, CH_2), 2.01 (s, 3H, CH_3, rotamer A), 2.03 (s, 3H, CH_3, rotamer B), 3.32–3.47 (m, 2H, N-CH_2), 6.75–6.92 (m, 3H, H_{arom}), 7.21–7.35 (m, 3H, $2H_{arom}$ + N-H)[a]	11.3, 19.0, 19.1, 19.7, 20.9, 54.0, 56.6, 112.9, 113.7, 119.4, 120.5, 129.1, 129.3, 148.5, 148.9, 169.2, 176.4[a]	192 (M^+, 43), 163 (13), 150 (8), 149 (33), 134 (12), 133 (75), 132 (30), 122 (11), 121 (100), 108 (7), 107 (54), 106 (25), 105 (14), 104 (36), 91 (10), 79 (9), 78 (10), 77 (68), 51 (14), 43 (30), 41 (11)
3d	3235 s, 3035 m, 2964 m, 2923 m, 1654 vs, 1602 s, 1542 vs, 1496 vs, 1458 s, 1374 s, 1291 s, 1219 m, 994 m, 746 s	0.91–1.00 (m, 3H, CH_3), 1.25–1.45 (m, 2H, CH_2, rotamer A), 1.47–1.63 (m, 2H, CH_2, rotamer B), 1.97 (s, 3H, CH_3, rotamer A), 2.00 (s, 3H, CH_3, rotamer B), 3.35–3.45 (m, 2H, N-CH_2), 6.72–6.95 (m, 3H, H_{arom}), 7.15–7.45 (m, 2H, H_{arom}), 7.50 (br s, 1H, N-H, rotamer A), 8.10 (br s, 1H, N-H, rotamer B)[a]	13.8, 13.8, 19.1, 20.1, 20.6, 20.7, 27.7, 28.4, 51.9, 54.6, 112.8, 113.7, 119.1, 120.4, 129.0, 129.2, 148.5, 148.9, 169.4, 176.4[a]	206 (M^+, 19), 163 (17), 132 (15), 122 (10), 121 (100), 120 (15), 119 (55), 118 (10), 107 (24), 106 (33), 105 (12), 104 (27), 91 (10), 78 (10), 77 (65), 51 (14), 43 (20), 41 (18)
3e	3256 s, 3052 m, 2992 m, 1675 vs, 1616 vs, 1543 s, 1510 vs, 1346 s, 1273 s, 1194 m, 1128 m, 766 s, 707 s	1.05–1.25 (m, 3H, CH_3), 2.30 (q, 2H, CH_2, *J* = 7.5, rotamer A), 2.41 (q, 2H, CH_2, *J* = 7.5, rotamer B), 3.10 (s, 3H, N-CH_3, rotamer A), 3.11 (s, 3H, N-CH_3, rotamer B), 6.70–6.95 (m, 3H, H_{arom}), 7.05 (br s, 1H, N-H, rotamer A), 7.15–7.40 (m, 2H, H_{arom}), 7.95 (br s, 1H, N-H, rotamer B)[a]	8.5, 9., 24.4, 27.4, 40.6, 42.2, 112.8, 113.2, 119.5, 120.5, 129.0, 129.3, 149.3, 149.5, 172.9, 179.0[a]	178 (M^+, 38), 122 (70), 121 (100), 107 (43), 106 (32), 105 (63), 104 (23), 93 (9), 92 (26), 79 (10), 78 (14), 77 (71), 65 (8), 52 (8), 51 (22), 39 (8)
3f	3210 s, 3040 s, 2980 s, 2887 m, 1675 vs, 1602 vs, 1504 vs, 1471 vs, 1379 s, 1240 s, 1194 s, 1148 m, 930 m, 753 vs, 687 s	0.93 (t, 3H, CH_3, *J* = 7.4, rotamer A), 0.94 (t, 3H, CH_3, *J* = 7.4, rotamer B), 1.06 (t, 3H, CH_3, *J* = 7.4, rotamer A), 1.18 (t, 3H, CH_3, *J* = 7.4, rotamer B), 1.52–1.70 (m, 2H, CH_2), 2.13–2.43 (m, 2H, CH_2), 3.20–3.45 (m, 2H, N-CH_2), 6.73–6.95 (m, 3H, H_{arom}), 7.10–7.30 (m, 3H, $2H_{arom}$ + N-H, rotamer A), 7.70 (br s, 1H, N-H, rotamer B)[a]	8.4, 9.7, 11.3, 11.4, 18.9, 19.8, 24.3, 27.4, 54.0, 56.7, 112.8, 113.7, 119.1, 120.4, 129.0, 129.3, 148.7, 150.0, 172.9, 179.3[a]	206 (M^+, 24), 150 (12), 149 (30), 133 (68), 122 (10), 121 (100), 120 (16), 107 (40), 106 (43), 105 (12), 104 (32), 91 (11), 78 (12), 77 (74), 57 (9), 51 (15), 43 (15), 41 (12)
3g	3243 s, 3045 m, 2973 s, 2947 s, 2887 s, 1675 vs, 1609 vs, 1550 s, 1510 vs, 1458 s, 1379 s, 1300 m, 1227 m, 1150 m, 1100 m, 977 m, 750 vs	0.80–1.00 (m, 6H, CH_3), 1.20–1.80 (m, 6H, CH_3), 2.05–2.35 (m, 2H, CH_2), 3.25–3.45 (m, 2H, N-CH_2), 6.65–6–95 (m, 3H, H_{arom}), 7.05–7.30 (m, 3H, H_{arom} + N-H, rotamer A), 8.00 (br s, 1H, N-H, rotamer B)[a]	13.8, 17.7, 19.0, 20.1, 27.5, 28.5, 32.8, 36.0, 51.9, 54.7, 112.8, 113.8, 119.0, 120.4, 128.9, 129.3, 148.7, 149.0, 172.3, 178.6[a]	234 (M^+, 16), 191 (10), 164 (19), 147 (10), 132 (13), 122 (9), 121 (100), 120 (10), 119 (47), 107 (12), 106 (27), 104 (11), 77 (32), 43 (10), 41 (12)

Table 4 (*concluded*).

Product	IR (KBr) ν (cm^{-1})	^{1}H NMR δ, *J* (Hz)	^{13}C NMR δ	MS (70 eV) *m/z* (%)
3h	3270 s, 3091 m, 2990 m, 2947 m, 1682 vs, 1590 vs, 1504 vs, 1326 vs, 1280 vs, 1201 s, 1128 vs, 825 s, 746 s, 687 s	1.16 (app t, 3H, CH_3, *J* = 7.0), 1.96 (s, 3H, CH_3, rotamer A), 1.99 (s, 3H, CH_3, rotamer B), 3.50–3.78 (m, 2H, N-CH_2), 6.76 (app d, 2H, H_{arom}, *J* = 9.3, rotamer A), 6.84 (app d, 2H, H_{arom}, *J* = 9.5), 10.4 (br s, 1H,N-H)[b]	11.4, 20.3, 45.9, 110.4, 110.6, 125.6, 137.3, 137.8, 153.4, 154.8, 168.4, 169.0[b]	223 (M^+, 15), 181 (35), 180 (30), 166 (62), 164 (100), 152 (46), 149 (11), 134 (22), 122 (11), 121 (11), 106 (13), 77 (11), 43 (20)
3i	3197 m, 3086 m, 2987 s, 2931 s, 1695 vs, 1616 vs, 1520 vs, 1403 vs, 1340 vs, 1256 vs, 1194 s, 1137 m, 1083 s, 1026 m, 822 vs, 762 s	1.05 (t, 3H, CH_3, *J* = 7.1, rotamer A), 1.06 (t, 3H, CH_3, *J* = 7.1, rotamer B), 1.89 (s, 3H, CH_3, rotamer A), 1.91 (s, 3H, CH_3, rotamer B), 2.10 (s, 3H, CH_3, rotamer A), 2.15 (s, 3H, CH_3, rotamer B), 3.25–3.40 (m, 2H, N-CH_2), 6.55–6.75 (m, 2H, H_{arom}), 6.85–7.00 (m, 2H, H_{arom}), 7.45 (br s, 1H, N-H, rotamer A), 8.05 (br s, 1H, N-H, rotamer B)[a]	11.2, 11.7, 19.8, 20.8, 21.3, 47.0, 49.5, 114.2, 114.9, 129.4, 130.1, 130.4, 130.7, 146.9, 147.1, 170.2, 177.2[a]	192 (62), 150 (20), 149 (100), 135 (40), 134 (17), 133 (98), 121 (92), 120 (20), 118 (28), 91 (81), 77 (41), 65 (20), 43 (18)

[a]Solvent: $CDCl_3$.
[b]Solvent: DMSO-d_6.

Scheme 1.

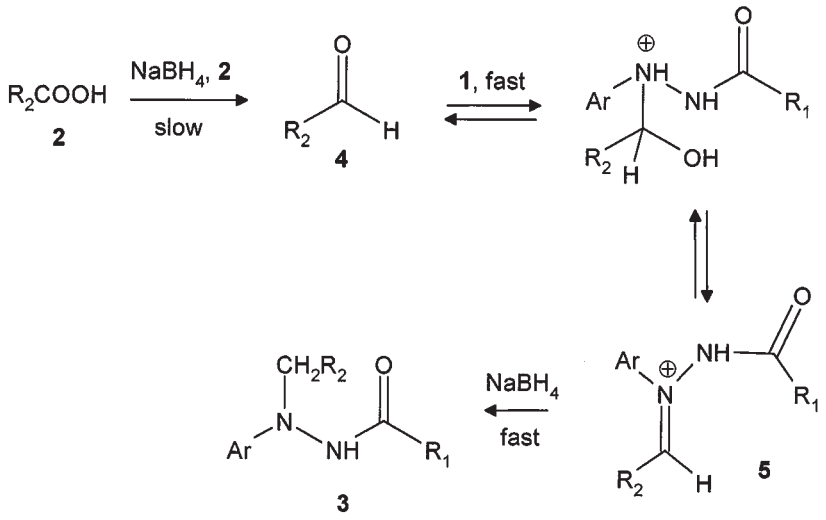


appearance and may be an oversimplification. Elemental analysis were performed with a Carlo Erba Mod. 1106 elemental analyzer.

Preparation of 1-formyl-2-phenylhydrazine (1a)

1-Formyl-2-phenylhydrazine (**1a**) was prepared as described procedure (9) by heating a mixture of

Scheme 2.



phenylhydrazine (5 mL, 46 mmol) and 50% HCOOH (18 mL, 240 mmol) at 120°C for 15 min. After the mixture was allowed to stand at rt, crystals of product precipitated; the resulting solid was recrystallized from EtOH and hexane.

Preparation of 1-acyl-2-arylhydrazines (1b–e)

The arylhydrazine (30 mmol) was added at rt to the appropriate carboxylic acid (**2**, 750 mmol), and the resulting mixture was stirred at 80°C for 1.5 h. Most of the acid was distilled off; the warm residue was treated with Et_2O or hexane and the crystals of the desired products **1b**–**e** precipitated. The products were further purified by recrystallization from hexane and the minimum amount of EtOH. Their physical and spectroscopic data are collected in Tables 1 and 2.

Procedure A

*Preparation of 1-acyl-2-alkyl-2-arylhydrazines (**3b**–**d**, **3f**–**i**)*

Sodium borohydride (pellets, 1.5 g, 40 mmol) was added portionwise to a mixture of 1-acyl-2-phenylhydrazine (**1**, 13 mmol) in carboxylic acid (**2**, 200 mmol) at ca. 60°C under vigorous stirring. The reaction usually required about 1 h for completion and could be considered completed soon after the sodium borohydride pellets were completely dissolved. The solvent was then partly distilled off under reduced pressure and, after neutralization of the residue with $NaOH–Na_2CO_3$ solution at ca. 0°C, the product was extracted with CH_2Cl_2 (20 mL × 5). Whenever after addition of $NaBH_4$ a too dense mixture resulted, distillation of the solvent was avoided and only a treatment with $NaOH–Na_2CO_3$ solution followed by CH_2Cl_2 extraction was performed. After the combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure, the product was crystallized from hexane by the addition of the minimum amount of EtOH. The physical and spectroscopic data of **3** are shown in Tables 3 and 4.

*Preparation of 1-acyl-2-methyl-2-phenylhydrazine (**3a**, **3e**)*

Procedure A was followed except that warming was prevented, keeping the temperature at 0–5°C, and that the amounts of reagents used were 13 mmol of 1-acyl-2-phenylhydrazine (**3**), 400 mmol of HCOOH, and 70 mmol of $NaBH_4$ (pellets). In the case of **3a**, twice crystallization from hot Et_2O was necessary to purify the desired product impure of 1-acetyl-2-formyl-2-phenylhydrazine.

In the case of **3e**, the reaction mixture containing 30% of unreacted reagent, was isolated in neutral form as explained in Procedure A and treated again with HCOOH and $NaBH_4$. At the end of reaction GC–MS analysis revealed the presence of product **3e** and a trace of unreacted **1c**. The reaction mixture was treated as in Procedure A. The physical and spectroscopic data of **3a** and **3e** are reported in Tables 3 and 4.

Procedure B

*One-pot preparation of 1-acetyl-2-ethyl-2-(4-methylphenyl)hydrazine (**3i**). Preparation of 1-acetyl-2-(4-methylphenyl)hydrazine (**1f**)*

(4-Methylphenyl)hydrazine hydrochloride (2.1 g, 13 mmol) was heated at 80°C for 15 h in acetic acid (20 mL, 320 mmol) with sodium acetate (1.1 g, 14 mmol) to allow the formation of 1-acetyl-2-(4-methylphenyl)hydrazine (**1f**), as revealed by GC–MS. The temperature was allowed to decrease to 60°C when $NaBH_4$ pellets (2.2 g, 58 mmol) were added portionwise. After all pellets were dissolved, GC–MS analysis revealed 1-acetyl-2-ethyl-2-(4-methylphenyl)-hydrazine (**3i**) as the sole volatile product. The reaction mixture was treated as described in Procedure A. Procedure B was repeated, obviously without the addition of $NaBH_4$, in order to obtain 1-acetyl-2-(4-methylphenyl)hydrazine (**1f**); it was recrystallized from EtOH and hexane. The physical and spectroscopic data of **1f** are reported in Tables 1 and 2 and **3i** in Tables 3 and 4.

*Reductive alkylation of 1-acyl-2-phenylhydrazine (**1b**) with butanal and $NaBH_4$*

A solution of aqueous 3 M H_2SO_4 (1.4 mL, 0.46 mmol) and butanal (0.18 mL, 2 mmol) in THF (3 mL) was slowly added to an open vessel containing a solution of 1-acetyl-2-phenylhydrazine (**1b**, 0.2 g, 1.33 mmol) in THF (10 mL) and MeOH (1.3 mL), while $NaBH_4$ pellets (0.17 g, 4.5 mmol) were added portionwise at 0°C (±5°C) under magnetic

stirring. The mixture was stirred for an additional hour at rt, diluted with H_2O, made strongly alkaline with NaOH (cooling), and extracted with CH_2Cl_2. After solvents were distilled off, 1-acetyl-2-butyl-2-phenylhydrazine (**3d**, 40% yield) and 1-acetyl-2-phenylhydrazine (**1b**, 43% yield) were separated by crystallization from Et_2O.

*Reductive cleavage of 1-acetyl-2-ethyl-2-phenylhydrazine (**3b**) and of 1-acetyl-2-butyl-2-phenylhydrazine (**3d**)*

Treatment of 0.22 mmol of either 1-acetyl-2-ethyl-2-phenylhydrazine (**3b**) or of 1-acetyl-2-butyl-2-phenylhydrazine (**3d**) in 37% HCl (3 mL) with Zn dust (0.6 g, 9.2 mmol) at 70°C for ca. 16 h gave *N*-ethylaniline and *N*-butylaniline, respectively, as the sole GC–MS products. The original products were completely transformed.

Mass spectra of 1-acyl-1-arylhydrazines

1-Formyl-1-phenylhydrazine (**1a′**), MS, *m*/*z*: 136 (M^+, 16), 107 (11), 106 (13), 105 (80), 93 (26), 92 (8), 91 (8), 78 (20), 77 (100), 66 (7), 51 (19), 39 (7); 1-acetyl-1-phenylhydrazine (**1b′**), MS, *m*/*z*: 150 (M^+, 10), 108 (18), 107 (7), 105 (49), 93 (18), 92 (6), 78 (13), 77 (64), 51 (23), 43 (100); 1-propionyl-1-phenylhydrazine (**1c′**), MS, *m*/*z*: 164 (M^+, 4), 119 (5), 108 (10), 105 (53), 93 (25), 78 (41), 77 (100), 66 (10), 57 (93), 52 (14), 51 (39), 50 (16), 39 (11); 1-butyril-1-phenylhydrazine (**1d′**), MS, *m*/*z*: 178 (M^+, 7), 108 (21), 105 (26), 93 (27), 78 (18), 77 (68), 71 (89), 66 (9), 51 (25), 43 (100), 41 (77), 39 (21); 1-acetyl-1-(4-nitrophenyl)hydrazine (**1e′**), MS, *m*/*z*: 195 (M^+, 6), 153 (20), 123 (4), 122 (6), 76 (13), 74 (6), 50 (14), 43 (100), 41 (12); 1-acetyl-1-(4-methylphenyl)hydrazine (**1f′**), MS, *m*/*z*: 164 (M^+, 10), 122 (13), 119 (96), 107 (9), 106 (15), 92 (13), 91 (100), 77 (8), 65 (25), 43 (99).

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