An Efficient and Simple Thallium(III)-Induced Cleavage of the Hydrazino Moiety†

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Hydrazides, which are both derivatives of carboxylic acids and of hydrazine, are easily obtained by various methods[1] and can serve as important starting materials in organic synthesis. We have employed several hydrazides for the preparation of *N*-acyl ethoxymethylene hydrazones, which were used as one-carbon synthons.[2] We then became interested in the oxidative transformations of hydrazides to their corresponding acids or derivatives.

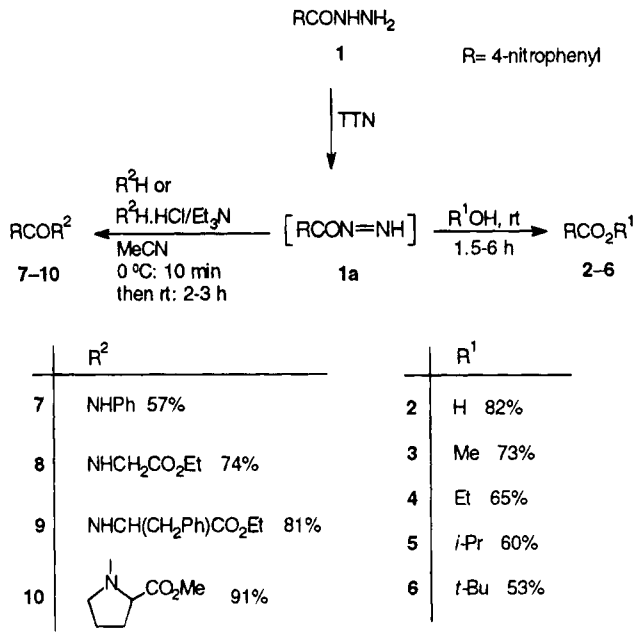
The reaction of hydrazides with most oxidants give the corresponding acids.[3] Although a variety of oxidizing reagents can be used, a serious drawback of those conversions is the formation of undesired side-products. *N,N'*-Diacylhydrazines have been obtained by the oxidation of hydrazides with selenium oxidants,[3g] arylsulfonyl peroxides,[3h] or lead tetraacetate[4] and esters or amides have also been isolated in several cases.[3a,d,f–h] Thallium(III) salts, which are well-known oxidants in organic chemistry,[5] have not yet been employed for the oxidation of the simple hydrazides although the chemical literature has described thallium-induced splitting of carbon-nitrogen bonds: (1) the cleavage of oximes and semicarbazones to obtain aldehydes or ketones,[6] and (2) the preparation of alkynoic esters or allenic esters from 5-pyrazolones and their condensed analogs.[7]

We report here the application of thallium(III) nitrate trihydrate (TTN) for the oxidation of hydrazino moieties leading to different products. Reactions of hydrazides, 4-phenylsemicarbazide, or heterocyclic hydrazines with thallium(III) nitrate resulted in the formation of the corresponding acids, esters, amides, carbamates, ureas, or heterocyclic methyl ethers, depending on the presence of the appropriate nucleophile. Compounds **1**, **11**, **15**, and **20a–c**, respectively, have been selected as typical models.

Results and Discussion

Hydrazide **1** reacted with TTN (molar ratio 1:2) at room temperature in H_2O to give 4-nitrobenzoic acid (**2**) in good yield (Scheme 1). When less than 2 mols of TTN per mol of **1** has been used, a certain amount of the hydrazide remained unchanged, as monitored by TLC. In a separate experiment, a mixture of **1**, 10 mol % of TTN, and 1 mol of $NaBrO_3$ per mol of **1** led under reflux in H_2O to the same product. The reaction of **1** with $NaBrO_3$ did not take place under the conditions employed above. It is indicated therefore that $NaBrO_3$ was consumed by the reoxidation of thallium(I) to thallium(III), which was formed during the reaction.

Scheme 1



When **1** was treated with TTN in MeOH, EtOH, *i*-PrOH, or *t*-BuOH, the corresponding esters **3–6** were isolated. These examples illustrate the transformation of the generally less reactive acid hydrazide to the more reactive ester. Although the formation of methyl or ethyl ester from hydrazides is not especially useful, due to the fact that they can be prepared readily using alternative procedures, the synthesis of analogous isopropyl, *tert*-butyl, and other hindered esters by this method seems to be useful especially since only mild reaction conditions are required.

Hydrazide **1** was converted into amide **7** on treatment with TTN in MeCN in the presence of $PhNH_2$. This can be useful in that the hydrazide/TTN system could be regarded as an effective acylating agent as is illustrated by the preparation of *N*-protected esters of glycine **8**, L-phenylalanine **9**, and L-proline **10**. It is important to note that racemization was not observed during the formation of **9** and **10**.[8,9]

The reactions mentioned above probably proceed *via* acyl diimide **1a**, postulated earlier,[3g,h] although the formation of the acyl cation has also been suggested.[3d,f] The acyl diimide then reacts with the nucleophile (H_2O, ROH, $PhNH_2$, or ester of an α-amino acid), to give the final product, while nitrogen is evolved. The formation of an acid **2** (up to 1%; 5% in the case of **4**, 14% in the case of **3**, and 20% for **6**) could not be avoided because the thallium reagent used was in the form of a trihydrate.

† Dedicated to Professor Heinz G. Viehe on the occasion of his 65th birthday.

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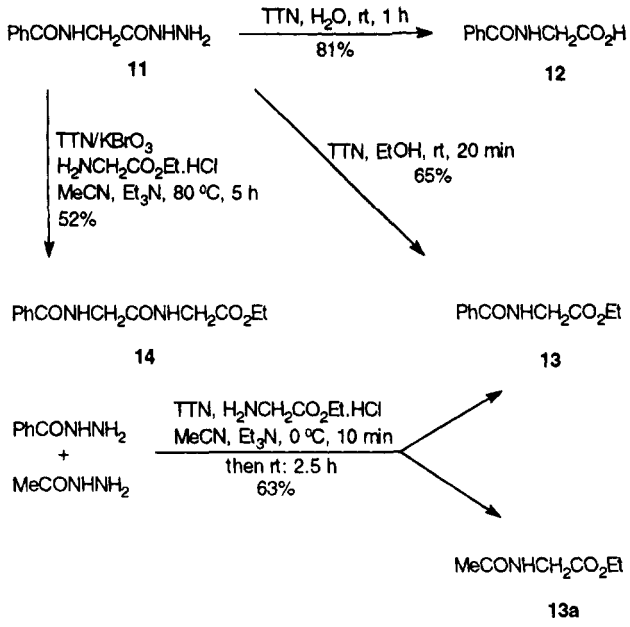
Scheme 2



Amino acid hydrazides are also useful as intermediates in the activation of peptides for bond formation *via* carboxylic acid azides and acyl diimides.[10] They can also serve as semipermanent blocking groups for the carboxy terminal. Our approach enables the removal of the protecting group, the introduction of another, or the formation of a new peptide bond. Examples of these reactions were accomplished using hydrazide **11**, and H_2O, EtOH or glycine ethyl ester as nucleophiles, to obtain **12**, **13**, and **14** under mild conditions (Scheme 2).

Some chemoselective transformations have been described for tetraorganothallium ate complexes.[11] TTN was also found to display a certain level of chemoselectivity in the oxidation of hydrazides. Thus, a mixture of benzoic acid hydrazide and acetic acid hydrazide was treated with TTN in the presence of glycine ethyl ester (molar ratio 1:1:2:1) to give products **13** and **13a** in a ratio of 3:1.

Furthermore, TTN was added to 4-phenylsemicarbazide (**15**) in the presence of the appropriate nucleophile (Scheme 3) to yield products **17**–**19**. The fact that these products were isolated supported the conclusion that regioselective cleavage of the desired carbon–nitrogen bond in **15** took place.

Methyl carbamate **18** or urea **19** were formed in a similar manner to compounds **2**–**10** and **12**–**14**. Aniline, isolated in the form of its hydrochloride **17**, was probably formed by the decarboxylation of unstable carbamic acid **16**.

Another application of the oxidative cleavage of hydrazine moiety involves heterocyclic hydrazines (Scheme 4). The reaction of hydrazines **20a**–**c** with TTN in MeOH was found to be straightforward process, leading to heteroaryl methyl ethers **21a**–**c** in moderate yields.

The use of large amounts of TTN (2 mol per mol of the substrate) could be avoided in some cases by the addition of the appropriate cooxidant. Thus, 1 mol of $NaBrO_3$ or $KBrO_3$ and 10 mol % of TTN have been used for the cleavage of the hydrazino moiety in compounds **1** and **11**.

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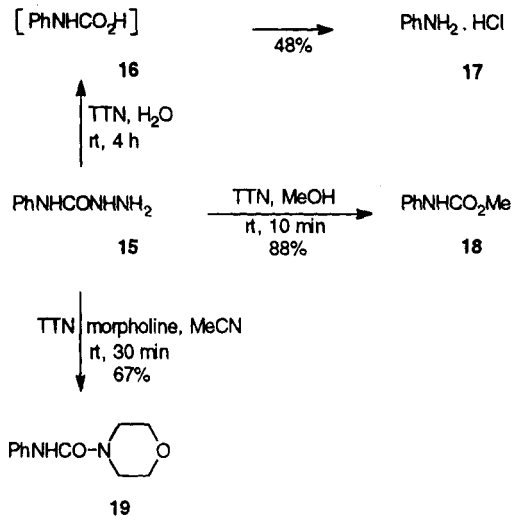
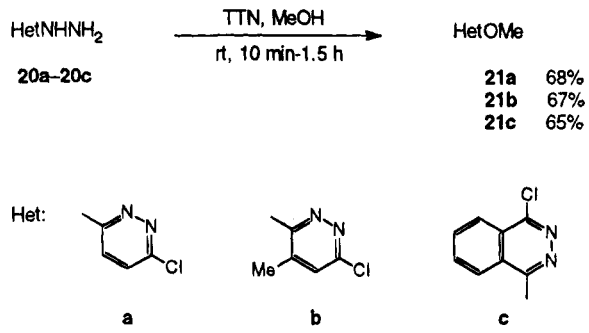
Scheme 3



Scheme 4



The reactions require higher temperatures or longer reaction times compared to those with 2 mol of TTN per mol of the substrate and do not occur in the absence of TTN. On the other side, our attempts to employ $NaBrO_3$ or $KBrO_3$ in the presence of TTN, to transform compounds **15** or **20a-c** to the products, shown in Schemes 3 and Scheme 4, were unsuccessful.

In conclusion, we would like to emphasize that reactions described above take place at relatively mild reaction conditions, which prevent the racemization of the substrates. This approach can be widely employed for the cleavage of the hydrazino moiety of simple hydrazides, hydrazides of α-amino acids, hydrazines, and 4-substituted semicarbazides.

WARNING: Thallium and its compounds are toxic and must be handled with care.[11]

Experimental Section

Melting points were determined on a hot stage and are uncorrected. ^{1}H NMR spectra were obtained with TMS as an internal standard. TLC was carried out on Fluka silica gel plates (F_{254}). Fluka silica gel 60 (220–440 mesh) was used for column chromatography. Merck silica gel 60 P F_{254} with gypsum was applied to prepare the chromatotron plates.

Chemicals were used as received from Fluka (TTN, sodium bromate, potasium bromate, benzoic acid hydrazide, 4-phenylsemicarbazide, 2-propanol, *tert*-butyl alcohol, acetonitrile, triethylamine, aniline, glycine ethyl ester hydrochloride, L-phenylalanine ethyl ester hydrochloride, L-proline methyl ester hydrochloride, and morpholine), from Merck (TTN, acetic acid hydrazide, methanol, and absolute ethanol), or from Aldrich (4-nitrobenzoic acid hydrazide).

The products, isolated in the experiments described below, were identified by IR and ^{1}H NMR to those of samples, prepared by published methods, or with commercially available materials.

4-Nitrobenzoic Acid (2). Method A: A solution of TTN (622 mg, 1.4 mmol) in H_2O (2 mL) was added to a suspension of 4-nitrobenzoic acid hydrazide (**1**, 127 mg, 0.7 mmol) in H_2O (5 mL) and stirred at rt for 1 h, $NaHCO_3$ was added to reach pH 5–6, the reaction mixture was kept at 0 °C for 2 h, and the acid **2** (96 mg; 82%) was recovered by filtration (mp 237–238 °C). The product was identical with commercially available compound (Fluka purum, mp 237–239 °C).

Method B: A mixture of **1** (36.2 mg, 0.2 mmol), $NaBrO_3$ (30.2 mg, 0.2 mmol) and TTN (8.9 mg, 0.02 mmol) in H_2O (2 mL) was refluxed for 1.5 h. The reaction mixture was kept at 0 °C for 2 h, and the acid **2** (26.7 mg, 80%) was recovered by filtration.

Methyl 4-Nitrobenzoate (3). Method A: A solution of TTN (293.3 mg, 0.66 mmol) in MeOH (2 mL) was added dropwise at rt to **1** (60 mg, 0.33 mmol) in MeOH (3 mL), stirred for 2 h, evaporated to dryness, dissolved in H_2O (3 mL), neutralized with Na_2CO_3, extracted with $CHCl_3$ (3 × 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to obtain the ester **3** (44 mg, 73%, mp 95–97 °C). The product **3** was identical with the sample from commercial source (Fluka purris., mp 94–96 °C). The aqueous solution was acidified with HNO_3 to pH 5 and kept at 0 °C overnight, and the crystals were separated by filtration to yield the acid **2** (7.5 mg, 14%).

Method B: A mixture of **1** (36.2 mg, 0.2 mmol), $NaBrO_3$ (30.2 mg, 0.2 mmol), and TTN (8.9 mg, 0.02 mmol) was stirred in MeOH (2 mL) at rt for 13 h, evaporated under reduced pressure, treated with H_2O (2 mL), extracted with $CHCl_3$ (3 × 10 mL), dried over Na_2SO_4, and concentrated to afford **3** (19 mg, 52%).

Ethyl 4-Nitrobenzoate (4). A solution of TTN (542 mg, 1.22 mmol) in absolute EtOH (3 mL) was added to a suspension of **1** (110 mg, 0.61 mmol) in absolute EtOH (3 mL), stirred at rt for 4 h, concentrated *in vacuo*, treated with H_2O (2 mL), neutralized with $NaHCO_3$, extracted with $CHCl_3$ (3 × 30 mL), dried over Na_2SO_4, and evaporated to dryness to give **4** (77 mg, 65%, mp 57–58 °C), which was identical with commercially available compound (Fluka purum, mp 55–57 °C). The aqueous solution was acidified with HNO_3 to pH 5 and kept at 0 °C overnight, and the crystals were separated by filtration to yield the acid **2** (5.1 mg, 5%).

Isopropyl 4-Nitrobenzoate (5). The synthesis was performed under the same conditions as for **4** using *i*-PrOH instead of absolute EtOH (reaction time: 6h ; yield: 60%, mp 109–110 °C). Ester **5** was identical with the compound obtained by published procedure (lit.[12a] mp 108.5 °C).

***tert*-Butyl 4-Nitrobenzoate (6).** As described above for the synthesis of **3** (method A) employing *t*-BuOH instead of MeOH (reaction time: 6 h). *tert*-Butyl ester **6** was isolated in 53% yield (mp 114–116 °C), along with 20% of the acid **2**. *tert*-Butyl ester **6** was identical with the product prepared according to known procedure (lit.[12a] mp 115.5 °C).

***N*-Phenyl 4-Nitrobenzamide (7).** A solution of TTN (392 mg, 0.88 mmol) in MeCN (2 mL) was added to a mixture of **1** (79.5 mg, 0.44 mmol) and aniline (82 mg, 0.88 mmol) in MeCN (1 mL) and stirred at rt for 3 h. Thallium(I) salts were then removed by filtration. The filtrate was evaporated to dryness, treated with H_2O (2 mL), and neutralized with $NaHCO_3$ to yield the solid material **7** (61 mg, 57%, mp 207–210 °C), identical with the compound obtained from 4-nitrobenzoyl chloride and aniline[12b] (mp 209–211 °C).

***N*-(4-Nitrobenzoyl)glycine Ethyl Ester (8).** A solution of TTN (311 mg, 0.7 mmol) in MeCN (2 mL) was added dropwise at 0 °C to a mixture of glycine ethyl ester hydrochloride (57 mg, 0.41 mmol), Et_3N (182 mg, 1.8 mmol), and **1** (63 mg, 0.35 mmol) in MeCN (2 mL). The reaction mixture was stirred at 0 °C for 10 min, and then at rt for 2 h. The solid material was filtered off, and the filtrate was evaporated to dryness, dissolved in H_2O (2 mL), neutralized with $NaHCO_3$, extracted with $CHCl_3$ (3 × 15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from Et_2O/EtOH to afford **8** (60 mg, 74%, mp 140–142 °C), which was identical with product prepared as described in the literature (lit.[12c] mp 144 °C).

***N*-(4-Nitrobenzoyl)-L-phenylalanine Ethyl Ester (9).** Prepared in 81% yield as described above for the synthesis of **8**, employing L-phenylalanine ethyl ester hydrochloride instead of glycine ethyl ester hydrochloride (reaction time: 10 min at 0 °C, and then 3 h at rt). The crude ester **9**, which was crystallized from cyclohexane, mp 104–106 °C, $\alpha^{20}_D = -58.0°$ ($c = 0.805$ in EtOH), was identical with the compound described in the literature: lit.[8] mp 104–106 °C, $\alpha^{25}_D = -58.1°$ ($c = 1.2$ in EtOH).[8]

***N*-(4-Nitrobenzoyl)-L-proline Methyl Ester (10).** Obtained in 91% yield as described above for the preparation of **8**, using L-proline methyl ester hydrochloride instead of glycine ethyl ester hydrochloride (reaction time: 10 min at 0 °C, then 3 h at rt). Methyl ester **10**, crystallized from cyclohexane, mp 108–110 °C, $\alpha^{20}_D = -82.9°$ ($c = 0.8$ in EtOH), was identical with the product described in the literature: lit.[9] mp 107–109 °C, $\alpha^{22}_D = -83°$ ($c = 1.2$ in EtOH).[9]

***N*-Benzoylglycine (12).** Method A: A solution of TTN (738 mg, 1.66 mmol) in H_2O (4 mL) was added at rt to a suspension of *N*-benzoylglycine hydrazide[12d] (**11**, 160 mg, 0.83 mmol) and stirred at rt for 1 h. The pH of the reaction mixture was adjusted with $NaHCO_3$ to reach pH 5–6 and the mixture was kept at 0 °C for 3 h, to give **12** (120 mg, 81%), which was recovered by filtration (mp 188–189 °C). The product was identical the compound, obtained as described in the literature (lit.[12e] mp 187 °C).

Method B: A mixture of **11** (38.6 mg, 0.2 mmol), $NaBrO_3$ (30.2 mg, 0.2 mmol), and TTN (8.9 mg, 0.02 mmol) in H_2O (2 mL) was refluxed for 2.5 h, extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford **12** (33 mg, 92%).

***N*-Benzoylglycine Ethyl Ester (13).** A solution of TTN (480 mg, 1.08 mmol) in absolute EtOH (2 mL) was added to **11** (104 mg, 0.54 mmol) in absolute EtOH (6 mL) and stirred at rt for 20 min. The solid material was removed by filtration. The filtrate was evaporated to dryness, treated with H_2O (2 mL), extracted with $CHCl_3$ (3 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield **13** (73 mg, 65%, mp 57–59 °C). Ester **13** was identical with the product prepared according to literature procedure (lit.[12e] mp 60 °C).

A Mixture of 13 and *N*-Acetylglycine Ethyl Ester (13a). A solution of TTN (1.698 g, 3.82 mmol) in MeCN (5 mL) was added at 0 °C to a solution of benzoic acid hydrazide (260 mg, 1.91 mmol), acetic acid hydrazide (141.5 mg, 1.91 mmol), glycine ethyl ester hydrochloride (266.7, 1.91 mmol), and Et_3N (793 mg, 7.85 mmol) in MeCN (10 mL). The reaction mixture was kept at 0 °C for 10 min and at rt for 2.5 h. The insoluble material was removed by filtration. The filtrate was evaporated under reduced pressure and an oily product purified by column chromatography (eluent: petroleum ether/ethyl acetate 2:3) to give the mixture of **13** and **13a** in a ratio of 3:1 as estimated by ^1H NMR (230 mg, 63% yield). This mixture was identical with the sample prepared from 0.3 mmol of **13**[12e] and 0.1 mmol of **13a** (Aldrich).

***N*-(Benzoylglycyl)glycine Ethyl Ester (14).** A mixture of glycine ethyl ester hydrochloride (530.5 mg, 3.8 mmol), **11** (733.5 mg, 3.8 mmol), and Et_3N (475 mg, 4.7 mmol) in MeCN (10 mL) was treated with a solution of TTN (169 mg, 0.38 mmol) in MeCN (2 mL). $KBrO_3$ (634.6 mg, 3.8 mmol) was added, and the reaction mixture was refluxed for 5 h. The solid material was removed by filtration. The filtrate was evaporated *in vacuo*, extracted with $CHCl_3$ (4 × 20 mL), concentrated under reduced pressure, and purified on a chromatotron (eluent: $CHCl_3$/MeOH 50:1) to afford **14** (518 mg, 52%, mp 116–118 °C), which was identical with the compound prepared as described in the literature (lit.[12f] mp 119–120 °C).

Aniline Hydrochloride (17). A mixture of 4-phenylsemicarbazide (**15**, 151 mg, 1 mmol) and TTN (889 mg, 2 mmol) in H_2O (5 mL) was stirred at rt for 4 h. Na_2CO_3 was added to reach pH 8. The reaction mixture was kept at rt for 10 min and extracted with Et_2O (3 × 15 mL). The ethereal solution was saturated with HCl gas, kept at −10 °C for 2 h. The solid

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product **17**, which was recovered by filtration (62 mg, 48%, mp 198–199 °C), was identical with commercially available material (Fluka puriss. p.a., mp 199–200 °C).

***N*-Phenylcarbamic Acid Methyl Ester (18).** A solution of TTN (813 mg, 1.83 mmol) in MeOH (6 mL) was added dropwise while stirring at rt to **15** (138 mg, 0.915 mmol) in MeOH (2 mL). The reaction mixture was then stirred at rt for 10 min. The insoluble material was removed by filtration. The filtrate was concentrated *in vacuo*, treated with H_2O (2 mL), neutralized with $NaHCO_3$, extracted with $CHCl_3$ (5 × 15 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give **18** (133 mg, 88%, mp 45–47 °C), identical with the product prepared by known procedure (lit.[12g] mp 47 °C).

***N*-(Phenylcarbamoyl)morpholine (19).** A solution of TTN (955.5 mg, 2.15 mmol) in MeCN (6 mL) was added dropwise at rt to a mixture of **15** (162.3 mg, 1.075 mmol) and morpholine (140 mg, 1.61 mmol) in MeCN (2 mL) and stirred for 30 min. The insoluble material was removed by filtration. The filtrate was evaporated to dryness, treated with H_2O (2 mL), neutralized with Na_2CO_3, extracted with $CHCl_3$ (3 × 15 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield **19** (148 mg, 67%, mp 157–159 °C), which was identical with the compound obtained by the addition of morpholine to phenyl isocyanate (lit.[12h] mp 159.3–160 °C).

3-Chloro-6-methoxypyridazine (21a). A solution of TTN (444 mg, 1 mmol) in MeOH (10 mL) was added dropwise to a mixture of 3-chloro-6-hydrazinopyridazine[12i] (**20a**, 72.5 mg, 0.5 mmol) in MeOH (2 mL) and stirred at rt for 10 min. The reaction mixture was evaporated to dryness, treated with H_2O (2 mL), neutralized with Na_2CO_3, extracted with $CHCl_3$ (3 × 15 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give **21a** (49.3 mg, 68%, mp 89–90 °C), identical with the product prepared as described earlier (lit.[12j] mp 91 °C).

3-Methoxy-4-methyl-6-chloropyridazine (21b). This compound was prepared in 67% yield under conditions as for **21a** using 3-hydrazino-4-methyl-6-chloropyridazine (**20b**)[12k] instead of **20a** (reaction time: 20 min). Product **21b** (mp 117–119 °C) was identical with the compound obtained by known procedure (lit.[12l] mp 118–119.5 °C).

1-Chloro-4-methoxyphthalazine (21c). The synthesis of **21c** was performed in 65% yield as described above for **21a** employing 1-chloro-4-hydrazinophthalazine (**20c**)[12m] instead of **20a** (reaction time: 1.5 h). Methoxy derivative **21c** (mp 109–110 °C) was identical with the product obtained according to the literature (lit.[12m] mp 108 °C).

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