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Electrophilic α-*p*-Tolylhydrazonylation of *tert*-Butyl Alkanoates and Tertiary Alkanamides with *tert*-Butyl *p*-Tolylazo Sulfide

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Abstract: The reactions of the enolates of *tert*-butyl alkanoates **2** and *N,N*-dialkylalkanamides **3** with *tert*-butyl *p*-tolylazo sulfide **1** in THF furnish good yields of the corresponding α-*p*-tolylhydrazonylated esters **4** and amides **5**. Results are reported showing the possible transformation of **4** and **5** into the *N*-methylated derivatives **8** and **9** and the subsequent deblocking of the protected carbonyl function to the corresponding 2-oxoalkanoates **10** and 2-oxoalkanamides **11**. Copyright © 1996 Elsevier Science Ltd

Hydrazones are attracting increasing attention in view of their chemical versatility.[1-3] In this context, α-arylhydrazonylated ketones, esters and amides appear particularly valuable as they not only are precursors of a great variety of heterocyclic systems,[4,5] but, more appealingly, they represent key intermediates to target molecules of biological interest, such as *e.g.* α-amino ketones, β-amino alcohols and α-amino acids.

A possible approach to the aforesaid hydrazones is represented by the electrophilic hydrazonylation of the parent carbonyl compounds, which however does not appear as a straightforward task. It is relevant to note that the well known Japp-Klingemann hydrazonylation α to a carbonyl function *via* arenediazonium salts generally requires the activation of a second electronwithdrawing group, such as the removable acetyl or formyl group;[6] further coupling to yield formazans often represents an additional drawback. The reaction of ketene silyl acetals with benzenediazonium tetrafluoroborate in pyridine has been reported[7] to afford α-phenylhydrazonylated esters, whereas the analogous reaction with silyl enol ethers gives only α-arylated ketones.[8]

In the course of our studies on the reactivity of arylazo phenyl and *tert*-butyl sulfides with carbon nucleophiles, we have recently developed[9] an easy and successful α-arylhydrazonylation of potassium ketone enolates by reaction with *tert*-butyl *p*-tolylazo sulfide **1** in DMSO.

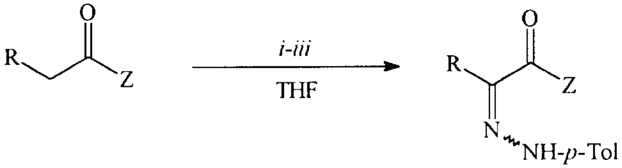
It was then of interest to investigate the possibility of extending this straightforward hydrazonylation method to other carbonyl compounds such as *tert*-butyl alkanoates and tertiary alkanamides; relevant results are herein reported together with some preliminary examples of further manipulation of the products obtained.

RESULTS AND DISCUSSION

Table 1 collects the results obtained from the α-hydrazonylation of some *tert*-butyl alkanoates (**2a-f**) and tertiary alkanamides (**3a-i**) according to Scheme 1.

In line with our previous rationalization,[10] the reactions are believed to proceed (Scheme 2) through a base-induced elimination (eq. 1) of *tert*-butanethiol from **1**, followed by coupling (eq. 2) of the ensuing 1-diazo-4-methylene-2,5-cyclohexadiene intermediate **6** with the enolates **2**$^-$ or **3**$^-$ to give, after acidic quenching, the isolated α-hydrazonylated compounds **4** or **5**.

Scheme 1

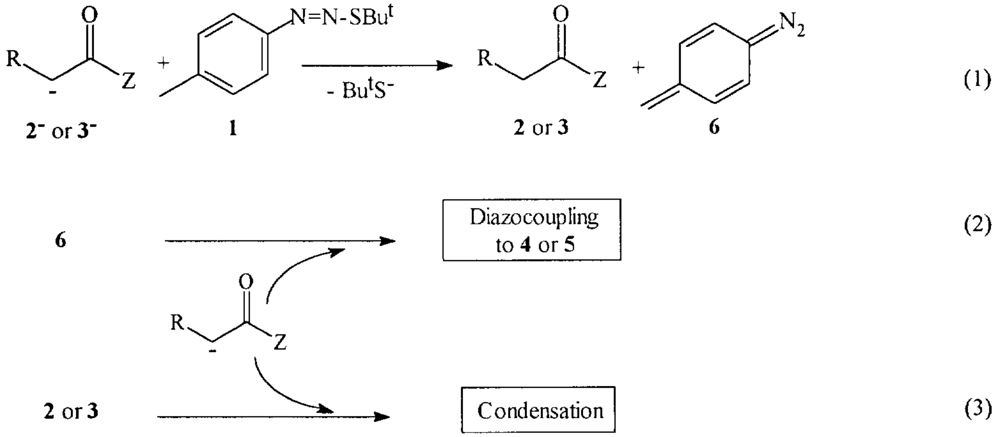


2a-f: Z = OBu^t
3a-i: Z = NR'$_2$

4a-f: Z = OBu^t
5a-i: Z = NR'$_2$

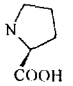
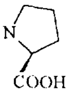
i: KN(SiMe$_3$)$_2$ 0.5 M in toluene or NaN(SiMe$_3$)$_2$ 1M in THF, -78 °C, 30 min; *ii*: *p*-Tol-N=N-SBu^t, -78 °C to r.t.; *iii*: acidic quenching.

Scheme 2



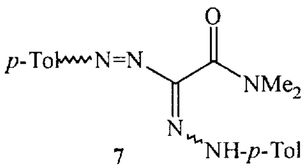
It is well known[11] that the propensity of esters to self-condense makes the generation of their enolates a delicate process. Completeness and rapid deprotonation under mild conditions (low temperature) are required, and better results are obtained when *tert*-butyl esters are used. Employment of very strong, non-nucleophilic hindered bases has been extensively reported[11] as the method of choice. Nevertheless, when considering our system (Scheme 2), the ester is unavoidably regenerated from its enolate in the reaction medium as long as intermediate **6** is formed. Thus, coupling of ester enolate with **6** (eq. 2) suffers from the competitive condensation (eq. 3). In our hands, such a competition could be minimized using (Table 1, entries 1-6) KHMDS as the base and an enolate to **1** ratio of 5: satisfactory results were always obtained, although the ester excess could not be recovered, eventually furnishing the ester self-condensation product.

Table 1. α-(p-Tolyl)hydrazonylation of esters **2a-f** and tertiary alkanamides **3a-i** according to Scheme 1.[a]

Entry	2 or 3	R	Z	4 or 5	Yield %[b]
1	**2a**	H	OBu^t	**4a**	99
2	**2b**	Me	OBu^t	**4b**	95
3	**2c**	Et	OBu^t	**4c**	90
4	**2d**	Ph	OBu^t	**4d**	99
5	**2e**	$PhCH_2$	OBu^t	**4e**	75
6	**2f**	$PhCH_2CH_2$	OBu^t	**4f**	86
7	**3a**	H	NMe_2	**5a**	91
8	**3b**	Me	NMe_2	**5b**	98[c,d]
9	**3c**	Et	NMe_2	**5c**	95[c]
10	**3d**	Et	NEt_2	**5d**	85
11	**3e**	Ph	NEt_2	**5e**	61[d,e]
12	**3f**	H		**5f**	71[c,f]
13	**3g**	Me		**5g**	96[c,d]
14	**3h**	$-(CH_2)_3$-NMe-		**5h**	97
15	**3i**	$-(CH_2)_2$-NMe-		**5i**	50[c,d,g]

a) [**2** or **3** enolate]/[**1**] = 5, unless otherwise specified. b) Yields are based on azosulfide and refer to isolated products. c) $NaN(SiMe_3)_2$ 1M in THF has been used. d) [**3** enolate]/[**1**] = 2.5. e) Unreacted azosulfide (29%) also recovered. f) Unreacted azosulfide (22%) also recovered. g) 80% Yield by ^1H-NMR analysis of the crude reaction mixture.

Hydrazonylation of tertiary alkanamides (Table 1, entries 7-15) could be realized in the same conditions. Nevertheless, alkanamides being less prone to base-promoted self-condensation and the corresponding enolates probably more reactive as bases/nucleophiles, it is also possible (entries 8, 11, 13, 15), within reasonable reaction times and without decreasing the product yields, to use more conveniently a lower (2.5) enolate/**1** ratio, and $NaN(SiMe_3)_2$ as base. In the case of entry 7 (Table 1), however, 5 mol. equiv. of potassium enolate (**3a**$^-$) are necessary in order to avoid the formation, by competitive coupling of **5a**$^-$ with **6**, of the formazan **7**: a by-product which seems to be favoured by both a lower enolate/**1** ratio and the presence of Na^+ as the counter ion (not tabulated results).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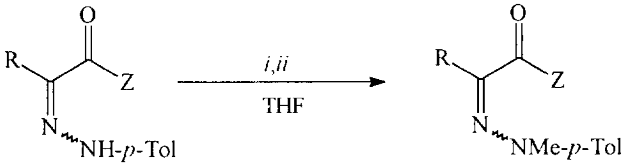
Because of the carboxylic group in the proline moiety, the experiments of entries 12 and 13 (Table 1) require 2 moles of base per mole of amide: the presence of the carboxylate group, on the other hand, does not affect in the least the reaction course. The hydrazones **5f,g** so obtained are particularly interesting because of the chiral center suitably exploitable for stereoselective purposes in further transformations.

Finally, entries 14 and 15 (Table 1) testify to the possibility of hydrazonylating in the same way *N*-methylated γ- and δ-lactams, though **5i** was actually isolated in moderate yield.[12]

Since the α-hydrazonylated esters and amides **4** and **5**, obtained through the method above in generally high yields, are interesting bifunctional compounds,[13] we have started an investigation on possible transformations of these two functionalities.

α-Hydrazono esters and α-hydrazono amides are useful precursors of α-keto esters and α-keto amides,[13a] whose importance as building blocks and as potential biologically-active compounds is testified by a wide literature.[14] Therefore, as a first example, we report on the possible deprotection to give the carbonyl function. It should be pointed out first of all that such a transformation has been best accomplished in the absence of the acidic proton at the nitrogen atom. It was thus found most convenient to employ the *N*-Me derivatives **8** and **9** of the hydrazones **4** and **5** respectively, which were easily obtained (Scheme 3) by metalation at low temperature (-78 °C) with either KHMDS or NaHMDS, followed by reaction with MeI. The yields obtained, collected in Table 2, were always satisfactory if not quantitative.[15]

Scheme 3



4 or **5** **8** or **9**

i: 1.1 mol. equiv. $KN(SiMe_3)_2$ in toluene or $NaN(SiMe_3)_2$ in THF, -78 °C, 30 min; *ii*: MeI (2 mol. equiv.), -78 °C to -30 °C.

For the successive transformation of **8** and **9** into the corresponding 2-oxo-derivatives, we chose the oxidative cleavage by ozonolysis at low temperature. Actually, among the numerous carbonyl deblocking procedures[16] recently developed, ozonolysis at low temperature has the following advantages: extremely mild and neutral conditions, short reaction times, ease of endpoint detection, and, last but not least, very satisfactory yields.[17] The feasibility of such an ozonolysis method on some hydrazones **8** and **9** (Scheme 4) is shown by the results collected in Table 3. As expected,[17b] *N*-methyl-*N*-nitroso-*p*-toluidine in yields comparable with those of **10** and **11** was also isolated as coproduct.

Table 2. α-(*N*-Methyl-*N*-*p*-tolylhydrazono)-esters **8** and -amides **9** obtained according to Scheme 3.

Entry	4 or 5	R	Z	8 or 9	Yield %[a]
1	**4b**	Me	OBu^t	**8b**	85
2	**4c**	Et	OBu^t	**8c**	98
3	**4d**	Ph	OBu^t	**8d**	98
4	**5a**	H	NMe_2	**9a**	97
5	**5b**	Me	NMe_2	**9b**	99
6	**5c**	Et	NMe_2	**9c**	99
7	**5e**	Ph	NEt_2	**9e**	99
8	**5h**	$-(CH_2)_3-NMe-$		**9h**	81

a) Yields of isolated products.

Scheme 4

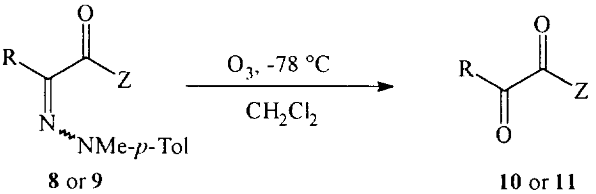


Table 3. Ozonolysis of α-hydrazono esters **8** and α-hydrazono amides **9**.

Entry	8 or 9	R	Z	10 or 11	Yield %[a]
1	**8b**	Me	OBu^t	**10b**	75
2	**8c**	Et	OBu^t	**10c**	99
3	**8d**	Ph	OBu^t	**10d**	97
4	**9b**	Me	NMe_2	**11b**	74
5	**9c**	Et	NMe_2	**11c**	80
6	**9e**	Ph	NEt_2	**11e**	76

a) Yields refer to products isolated by chromatography.

EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus and are uncorrected. Distillations were performed with a Kugelröhr apparatus, the quoted boiling point referring to the oven temperature. ^{1}H-NMR spectra were taken in $CDCl_3$ (unless otherwise stated) on a Varian Gemini 200 spectrometer; TMS was used as internal standard and chemical shifts are reported as δ values (ppm). The ozonizations were performed with a Fischer Ozon-Generator. Optical rotation of **5g** was obtained on a JASCO DIP-181 polarimeter at 589 nm. IR spectra (nujol mull) were recorded on a Perkin-Elmer 881 infrared spectrophotometer.

Materials

Petroleum ether and light petroleum refer to the fractions with bp 40-60 °C and 80-100 °C, respectively. Methylene chloride for the ozonolysis was distilled over P_2O_5 before use. THF was distilled from KOH and then from benzophenone ketyl under argon just before use. $KN(SiMe_3)_2$ (0.5M in toluene) and $NaN(SiMe_3)_2$ (1M in THF) were commercial products, used as received. Starting esters and amides were properly dried before use; **2a**,**b**; **3a**,**b**,**h**,**i** were commercial products while **2c-f** and **3c-g** were synthesized by standard literature methods. Column (or preparative plate) chromatographies were performed on silica gel using petroleum ether and gradients (or appropriate mixtures) with CH_2Cl_2 or Et_2O as eluants, the solvents being distilled before use. (*Z*)-*tert*-Butyl *p*-tolylazo sulfide (**1**) was synthesized from commercial *p*-toluidine as previously reported.[10]

General procedure for the α-hydrazonylation of esters 2a-f and amides 3a-i with (Z)-tert-butyl p-tolylazo sulfide 1

Reactions were realized under argon, using flame-dried glassware. To a stirred solution of **2** or **3** in THF (12 mmol in 12 ml) at -78 °C, an equimolar amount of $KN(SiMe_3)_2$ 0.5M in toluene was slowly added. After stirring for 30 minutes at the same temperature, azosulfide **1** in THF (2.4 mmol in 12 ml) was dropped into the reaction mixture and the temperature allowed to reach 25 °C. When $NaN(SiMe_3)_2$ was used, concentrations were: [**1**] = 0.1M, [enolate] = 0.5M, or 0.25M when stated (see Table 1). Progress of the reaction was followed by TLC and the endpoint (generally after 2-5 h) estimated by the disappearance of **1**. The usual workup involved pouring of the reaction mixture into ice/3% HCl followed by extraction with ether, washing and drying (Na_2SO_4) of the combined extracts, and solvent evaporation under reduced pressure. Column chromatography of the residue allowed separation of the reaction products. Sometimes the product could be easily taken-up and filtered with petroleum ether after distillation of the starting ester or amide excess.

To the isolated samples an (*E*)-geometry around the C=N double bond was attributed on the basis of the chemical shift value (δ 7-8) of the hydrazone N<u>H</u> proton as compared with that of the (Z)-isomer (δ *ca.* 12); the latter isomer is in fact characterized in $CDCl_3$ by the formation of an intramolecular H-bonding between NH and CO which brings about the observed high deshielding of the N<u>H</u> proton.

tert-Butyl (p-tolylhydrazono)acetate **4a**, mp 146.0-147.0 °C (light petroleum); ^{1}H-NMR: 1.55 (9H, s), 2.29 (3H, s), 6.97 (1H, d, *J* 1.1 Hz), 7.11 (4H, m) and 8.21 (1H, br s); ^{13}C-NMR: 20.67, 28.22, 81.20, 113.89, 126.63, 129.82, 131.59, 140.39 and 163.52; IR: 1688 (CO st.), 1614 cm^{-1} (CN st.). Found: C, 66.4; H, 7.8; N, 11.8% ($C_{13}H_{18}N_2O_2$ requires: C, 66.6; H, 7.8; N, 12.0%). (*Z*)-isomer: ^{1}H-NMR: 1.53 (9H, s), 2.29 (3H, s), 6.51 (1H, s), 7.09 (4H, s) and 12.30 (1H, br s); ^{13}C-NMR: 20.71, 28.20, 81.60, 113.77, 119.39, 129.81, 131.78, 140.87 and 163.78; IR: 1673 (CO st.), 1613 cm^{-1} (CN st.).

tert-Butyl 2-(p-tolylhydrazono)propionate **4b**, mp 113.1-114.1 °C (petroleum ether); ^{1}H-NMR: 1.57 (9H, s), 2.05 (3H, s), 2.30 (3H, s), 7.09 (4H, app. s) and 7.56 (1H, br s); ^{13}C-NMR: 19.88, 27.92, 28.21, 81.01, 113.85, 128.12, 129.78, 131.17, 141.23 and 164.34. Found: C, 67.5; H, 7.9; N, 11.2% ($C_{14}H_{20}N_2O_2$ requires: C, 67.7; H, 8.1; N, 11.3%). (*Z*)-isomer: ^{1}H-NMR: 1.54 (9H, s), 2.09 (3H, s), 2.28 (3H, s), 7.06 (4H, app. s) and 12.00 (1H, br s); ^{13}C-NMR: 20.67, 27.79, 28.21, 81.73, 113.28, 126.05, 129.73, 130.60, 141.56 and 163.71.

tert-Butyl 2-(p-tolylhydrazono)butyrate **4c**, mp 105.5-106.5 °C (petroleum ether); ^{1}H-NMR: 1.12 (3H, t, *J* 7.6 Hz), 1.56 (9H, s), 2.29 (3H, s), 2.53 (2H, q, *J* 7.6 Hz), 7.08 (4H, app. s) and 7.75 (1H, br s); ^{13}C-NMR: 9.71, 17.41, 20.68, 28.24, 80.90, 113.79, 129.79, 131.06, 138.01, 141.33 and 164.09. Found: C, 68.3; H, 8.0; N, 10.3% ($C_{15}H_{22}N_2O_2$ requires: C, 68.7; H, 8.4; N, 10.7%). (*Z*)-isomer: ^{1}H-NMR: 1.14 (3H, t, *J* 7.4 Hz), 1.54 (9H, s), 2.28 (3H, s), 2.46 (2H, q, *J* 7.4 Hz), 7.07 (4H, app. s) and 12.00 (1H, br s); ^{13}C-NMR: 12.23, 20.68, 26.75, 28.26, 81.62, 113.38, 129.73, 130.55, 141.80 and 163.52.

tert-Butyl phenyl(p-tolylhydrazono)acetate **4d**, mp 90.0-90.6 °C (EtOH-H_2O); ^{1}H-NMR: 1.54 (9H, s), 2.28 (3H, s), 7.00 and 7.07 (2H each, AA'BB', *J* 8.8 Hz), 7.32 (2H, m), 7.49 (3H, m) and 7.99 (1H, br s); ^{13}C-NMR could not be taken because of fast (*E*) to (*Z*) stereomutation in solution; IR: 1699 (CO st.), 1613 cm^{-1} (CN st.). Found: C, 73.2; H, 7.2; N, 8.9% ($C_{19}H_{22}N_2O_2$ requires: C, 73.5; H, 7.2; N, 9.0%). (*Z*)-isomer: mp 85.2-85.7 °C (EtOH); ^{1}H-NMR: 1.57 (9H, s), 2.31 (3H, s), 7.10 and 7.18 (2H each, AA'BB', *J* 8.7 Hz), 7.31 (3H, m), 7.66 (2H, m) and 12.39 (1H, br s); ^{13}C-NMR: 20.74, 28.27, 82.66, 114.07, 127.11, 127.63, 128.46, 128.61, 129.80, 131.64, 137.15, 141.17 and 163.34; IR: 1666 (CO st.), 1612 cm^{-1} (CN st.).

tert-Butyl 3-phenyl-2-(p-tolylhydrazono)propionate **4e**, mp 119.4-120.3 °C (petroleum ether); ^{1}H-NMR: 1.57 (9H, s), 2.26 (3H, s), 3.96 (2H, s), 6.99 (4H, AA'BB', *J* 8.5 Hz), 7.26 (5H, m) and 7.83 (1H, br s); ^{13}C-NMR: 20.64, 28.20, 31.02, 81.16, 113.84, 126.96, 128.00, 129.16, 129.68, 131.35, 134.36, 135.49, 140.95 and 164.41. Found: C, 73.6; H, 7.1; N, 8.2% ($C_{20}H_{24}N_2O_2$ requires: C, 74.0; H, 7.5; N, 8.6%). (*Z*)-isomer: mp 93.7-94.4 °C (petroleum ether); ^{1}H-NMR: 1.39 (9H, s), 2.29 (3H, s), 3.75 (2H, s), 7.09 (4H, app. s), 7.25 (5H, m) and 12.11 (1H, br s); ^{13}C-NMR: 20.69, 28.06, 39.94, 81.93, 113.59, 125.98, 128.07, 128.61, 128.79, 129.76, 130.97, 139.73, 141.45 and 163.37.

tert-Butyl 4-phenyl-2-(p-tolylhydrazono)butyrate **4f**, mp 103.1-103.6 °C (petroleum ether); ^{1}H-NMR: 1.55 (9H, s), 2.27 (3H, s), 2.83 (4H, app. t), 6.85 and 7.03 (2H each, AA'BB', *J* 8.4 Hz) and 7.26 (6H in all, m and br s, partly overlapped); ^{13}C-NMR: 20.65, 27.26, 28.20, 32.26, 80.92, 113.77, 126.69, 128.31, 128.89, 129.60, 131.03, 135.98, 141.17, 141.30 and 164.12. Found: C, 74.5; H, 7.9; N, 8.4% ($C_{21}H_{26}N_2O_2$ requires: C, 74.5; H, 7.8; N, 8.3%). (*Z*)-isomer: mp 120.1-121.0 °C (petroleum ether); ^{1}H-NMR: 1.53 (9H, s), 2.29 (3H, s), 2.74 (2H, m), 2.91 (2H, m), 7.07 (4H, app. s), 7.26 (5H, m) and 12.08 (1H, br s); ^{13}C-NMR: 20.69, 28.24, 34.60, 35.33, 81.80, 113.53, 125.80, 128.34, 128.58, 129.75, 130.82, 141.60, 142.22 and 163.45.

N,N-Dimethyl(p-tolylhydrazono)acetamide **5a**, mp 191.0-192.0 °C (toluene); ^{1}H-NMR (DMSO-d_6): 2.21 (3H, s), 2.91 (3H, s), 3.20 (3H, s), 6.92 and 7.06 (2H each, AA'BB', *J* 8.4 Hz), 7.44 (1H, s) and 10.63 (1H, br s). Found: C, 64.5; H, 7.5; N, 20.6% ($C_{11}H_{15}N_3O$ requires C, 64.35; H, 7.4; N, 20.5%). (*Z*)-isomer: mp 146.3-147.5 °C (petroleum ether); ^{1}H-NMR (DMSO-d_6): 2.23 (3H, s), 2.91 (3H, s), 3.15 (3H, s), 7.07 (5H in all, AA'BB' and s, partly overlapped) and 13.26 (1H, br s).

N,N-Dimethyl-2-(p-tolylhydrazono)propionamide **5b**, mp 113.4-114.6 °C (light petroleum); ^{1}H-NMR: 2.08 (3H, s), 2.29 (3H, s), 3.17 (6H, br s), 6.98 and 7.08 (2H each, AA'BB', *J* 8.5 H) and 7.26 (1H, br s); ^{1}H-NMR (DMSO-d_6): 1.99 (3H, s), 2.20 (3H, s), 2.92 (3H, br s), 3.15 (3H, br s), 7.01 and 7.05 (4H in all, AA'BB', *J* 8.8 Hz) and 9.17 (1H, br s). Found: C, 65.4; H, 7.6; N, 19.1% ($C_{12}H_{17}N_3O$ requires C, 65.7; H, 7.8; N, 19.2%).

N,N-Dimethyl-2-(p-tolylhydrazono)butyramide **5c**, orange oil; ^{1}H-NMR: 1.17 (3H, t, *J* 7.6 Hz), 2.28 (3H, s), 2.54 (2H, q, *J* 7.6 Hz), 3.06 (3H, s), 3.23 (3H, s), 6.97 and 7.07 (2H each, AA'BB', *J* 8.5 Hz) and 7.39 (1H, br s). Found: C, 66.8; H, 8.4; N, 18.1% ($C_{13}H_{19}N_3O$ requires C, 66.9; H, 8.2; N, 18.0%).

N,N-Diethyl-2-(p-tolylhydrazono)butyramide **5d**, mp 99.2-100.2 °C (light petroleum); ^{1}H-NMR: 1.18 and 1.22 [9H in all, t (*J* 7.6 Hz) and m, partly overlapped], 2.28 (3H, s), 2.53 (2H, q, *J* 7.6 Hz), 3.50 (4H, m), 6.95 and 7.07 (2H each, AA'BB', *J* 8.7 Hz) and 7.31 (1H, br s); ^{1}H-NMR (DMSO-d_6): 1.01 and 1.10 [9H in all, t (*J* 7.6 Hz) and m, partly overlapped], 2.19 (3H, s), 2.49 (2H, q, *J* 7.6 Hz), 3.38 (4H, m), 7.00 (4H, app. s) and 9.18 (1H, br s). Found: C, 69.3; H, 8.7; N, 15.8% ($C_{15}H_{23}N_3O$ requires C, 68.9; H, 8.9; N, 16.1%). (*Z*)-isomer: mp 105.9-106.5 °C (petroleum ether); ^{1}H-NMR (DMSO-d_6): 1.08 (9H, t, *J* 7.4 Hz), 2.18 (3H, s), 2.34 (2H, q, *J* 7.4 Hz), 3.17 (2H, br q), 3.42 (2H, br q), 6.98 (4H, app. s) and 8.80 (1H, br s).

N,N-Diethyl-2-(p-tolylhydrazono)phenylacetamide **5e**, mp 152.6-153.7 °C (light petroleum-toluene); ^{1}H-NMR: 1.00 (3H, t, *J* 7.2 Hz), 1.33 (3H, t, *J* 7.1 Hz), 2.29 (3H, s), 3.22 (2H, q, *J* 7.1 Hz), 3.64 (2H, q, *J* 7.2 Hz), 7.05 and 7.10 (4H in all, AA'BB', *J* 8.5 Hz), 7.36 (3H, m), 7.65 (2H, m) and 7.96 (1H, br s). Found: C, 73.6; H, 7.6; N, 13.8% ($C_{19}H_{23}N_3O$ requires C, 73.8; H, 7.5; N, 13.6%).

N-(p-Tolylhydrazono)acetyl-L-proline **5f**, the product has been isolated as a mixture of (*E*)- and (*Z*)-isomers, with broad mp 162.2-166.5 °C (toluene-petroleum ether); the ^{1}H-NMR is complicated because of the presence, in solution, of four species (two conformers for each stereoisomer); ^{1}H-NMR (DMSO-d_6): 1.93 (3H, m), 2.17, 2.22 and 2.23 (4H in all, m, s, s, partly overlapped), 3.50, 3.71 and 3.84 (2H in all, three app. t), 4.33, 4.81 and 4.98 [1H in all, three dd (*J ca.* 4 and 9 Hz)], 6.67, 6.92, 6.95, 7.02, 7.07, 7.09, 7.21 and 7.33

(5H in all, eight s), 10.63, 10.80, 13.25 and 13.27 (1H in all, 4 s) and 12.60 (1H, br s). Found: C, 60.9; H, 6.4; N, 15.4% ($C_{14}H_{17}N_3O_3$ requires C, 61.1; H, 6.2; N, 15.3%).

N-[2-(p-Tolylhydrazono)propionyl]-L-proline **5g**, mp 178.8-180.5 °C (AcOEt-petroleum ether); $[\alpha]^{25}_D$ -37.7° (c 1 in AcOEt); ^{1}H-NMR (DMSO-d_6): 1.60-2.40 [10H in all, m, s (2.01) and s (2.22), partly overlapped], 3.51 and 3.91 (2H in all, two apparent t), 4.31 and 5.02 [1H in all, two dd (*J ca.* 4 and 8 Hz)], 7.06 (4H, m), 9.15 and 9.39 (1H in all, two s) and 12.44 (1H, br s). Found: C, 62.0; H, 6.4; N, 14.3% ($C_{15}H_{19}N_3O_3$ requires C, 62.2; H, 6.6; N, 14.5%).

N-Methyl-3-(p-tolylhydrazono)piperidin-2-one **5h**, mp 180.1-180.6 °C (CH_2Cl_2-petroleum ether); ^{1}H-NMR: 2.04 (2H, app. quint.), 2.28 (3H, s), 2.55 (2H, t, *J* 6.8 Hz), 3.09 (3H, s), 3.39 (2H, t, *J* 5.6 Hz), 7.07 and 7.15 (2H each, AA'BB', *J* 8.8 Hz) and 7.64 (1H, br s). Found: C, 67.2; H, 7.1; N, 17.8% ($C_{13}H_{17}N_3O$ requires C, 67.5; H, 7.4; N, 18.2%).

N-Methyl-3-(p-tolylhydrazono)pyrrolidin-2-one **5i**, mp 231.5-232.9 °C (MeOH-AcOEt); ^{1}H-NMR (DMSO-d_6): 2.21 (3H, s), 2.71 (2H, t, *J* 6.4 Hz), 2.86 (3H, s), 3.48 (2H, t, *J* 6.4 Hz), 7.04 and 7.06 (4H in all, AA'BB', *J* 8.8 Hz) and 9.41 (1H, br s). Found: C, 66.2; H, 7.0; N, 18.9% ($C_{12}H_{15}N_3O$ requires C, 66.3; H, 7.0; N, 19.3%).

N,N-dimethyl 2-(p-tolylazo)-2-(p-tolylhydrazono)acetamide **7**, mp 208.0-208.2°C (EtOH); the ^{1}H-NMR showed the presence, in solution, of two stereoisomers **A** and **B** (66:43 molar ratio). ^{1}H-NMR (DMSO-d_6): 2.27 [3H (**A**), s], 2.34 and 2.38 [3H (**A**) and 6H (**B**), two s, partly overlapped], 2.72 [3H (**A**), s], 2.83 [3H (**B**), s], 2.96 [3H (**B**), s], 3.01 [3H (**A**), s], 7.15 [4H (**B**), AA' of AA'BB', *J* 8.4 Hz], 7.27 and 7.33 [4H (**B**), BB' of AA'BB', and 4H (**A**), AA' of AA'BB', *J* 8.4 Hz], 7.62 [4H (**A**), BB' of AA'BB', *J* 8.4 Hz], 10.51 [1H (**A**), br s] and 11.75 [1H (**B**), br s]. Found: C, 67.0; H, 6.8; N, 21.3% ($C_{18}H_{21}N_5O$ requires C, 66.8; H, 6.6; N, 21.7%).

α-(N-Methyl-N-p-tolylhydrazono)-esters 8 and -amides 9

In a flame-dried two-neck flask the hydrazone **4** or **5** was dissolved under argon in THF at -78 °C and metalated with 1.1 mol. equiv. of KHMDS. NaHMDS could be sometimes alternatively used without significant differences. Concentrations were usually *ca.* 0.1-0.13M in **4** or **5**. After 30 minutes MeI (2 mol. equiv.) was added by siringe and the reaction mixture allowed to reach -30 °C. At the end of reaction (as judged by TLC analysis), the mixture was poured into brine: the usual workup yielded a crude residue which in most cases did not require chromatographic purification. It was possible in the case of compounds **8** to isolate both (*E*)- and (*Z*)-isomers, stereochemical assignment being based on the greater deshielding of the alkyl hydrogens α to the hydrazono function in the (*E*)- with respect to the (*Z*)-isomer.

tert-Butyl 2-(N-methyl-N-p-tolylhydrazono)propionate **8b**, yellow oil; (*E*)-isomer: ^{1}H-NMR: 1.56 (9H, s), 1.96 (3H, s), 2.30 (3H, s), 3.40 (3H, s), 7.01 and 7.10 (2H each, AA'BB', *J* 8.6 Hz); (*Z*)-isomer: ^{1}H-NMR: 1.47 (9H, s), 1.62 (3H, s), 2.41 (3H, s), 3.63 (3H, s), 7.27 and 7.67 (2H each, AA'BB', *J* 8.2 Hz). Found: C, 68.3; H, 8.6; N, 10.9% ($C_{15}H_{22}N_2O_2$ requires C, 68.7; H, 8.4; N, 10.7%).

tert-Butyl 2-(N-methyl-N-p-tolylhydrazono)butyrate **8c**, mp 63.0-64.0 °C (pentane); (*E*)-isomer: ^{1}H-NMR: 1.22 (3H, t, *J* 7.5 Hz), 1.45 (9H, s), 2.27 (3H, s), 2.55 (2H, q, *J* 7.5 Hz), 3.09 (3H, s), 6.92 and 7.07 (2H each, AA'BB', *J* 8.6 Hz); (*Z*)-isomer: ^{1}H-NMR: 1.05 (3H, t, *J* 7.5 Hz), 1.57 (9H, s), 2.30 (3H, s), 2.50 (2H, q, *J* 7.5 Hz), 3.36 (3H, s), 7.04 and 7.10 (2H each, AA'BB', *J* 8.8 Hz). Found: C, 69.6; H, 8.8; N, 10.0% ($C_{16}H_{24}N_2O_2$ requires C, 69.5; H, 8.7; N, 10.1%).

tert-Butyl phenyl(N-methyl-N-p-tolylhydrazono)acetate **8d**, orange oil; (*E*)-isomer: ^{1}H-NMR: 1.56 (9H, s), 2.30 (3H, s), 3.37 (3H, s), 7.11 (4H, s), 7.37 (3H, m) and 7.72 (2H, m); (*Z*)-isomer: ^{1}H-NMR: 1.54 (9H, s), 2.30 (3H, s), 2.96 (3H, s), 7.11 (2H, AA' of AA'BB', *J* 8.7 Hz) and 7.32 (7H in all, BB' of AA'BB' and m, partly overlapped). Found: C, 74.2; H, 7.7; N, 8.6% ($C_{20}H_{24}N_2O_2$ requires C, 74.0; H, 7.5; N, 8.6%).

N,N-Dimethyl(N-methyl-N-p-tolylhydrazono)acetamide **9a**, mp 50.2-51.3 °C (pentane); ^{1}H-NMR: 2.29 (3H, s), 2.95 (3H, s), 3.03 (3H, s), 3.28 (3H, s), 6.77 (1H, s), 7.09 and 7.15 (4H in all, AA'BB', *J* 8.8 Hz). Found: C, 65.3; H, 7.9; N, 19.5% ($C_{12}H_{17}N_3O$ requires C, 65.7; H, 7.8; N, 19.2%).

N,N-Dimethyl-2-(N-methyl-N-p-tolylhydrazono)propionamide **9b**, mp 53.1-54.0 °C (petroleum ether); ^{1}H-NMR: 2.06 (3H, s), 2.29 (3H, s), 3.05 (3H, s), 3.16 (3H, s), 3.18 (3H, s), 6.90 and 7.09 (2H each, AA'BB', *J* 8.3 Hz). Found: C, 67.1; H, 8.4; N, 18.0% ($C_{13}H_{19}N_3O$ requires C, 66.9; H, 8.2; N, 18.0%).

N,N-Dimethyl-2-(N-methyl-N-p-tolylhydrazono)butyramide **9c**, mp 49.1-49.7 °C (petroleum ether); (*E*)-isomer: ^{1}H-NMR: 1.23 (3H, t, *J* 7.5 Hz), 2.28 (3H, s), 2.58 and 2.59 (2H, two q, partly overlapped, *J* 7.4 and

7.5 Hz), 2.82 (3H, s), 2.95 (3H, s), 3.11 (3H, s), 6.97 and 7.07 (2H each, AA'BB', *J* 8.7 Hz); (*Z*)-isomer: ^{1}H-NMR: 1.02 (3H, t, *J* 7.6 Hz), 2.29 (3H, s), 2.56 (2H, q, *J* 7.6 Hz), 3.06 (3H, s), 3.12 (3H, s), 3.18 (3H, s), 6.88 and 7.09 (2H each, AA'BB', *J* 8.3 Hz). Found: C, 67.8; H, 8.7; N, 16.8% ($C_{14}H_{21}N_3O$ requires: C, 68.0; H, 8.5; N, 17.0%).

N,N-Diethyl(N-methyl-N-p-tolylhydrazono)phenylacetamide **9e**, oil, bp 200 °C (oven)/1mm Hg; ^{1}H-NMR: 0.96 (3H, X_3 of ABX_3, *J* 7.2 Hz), 1.26 (3H, X_3 of ABX_3, *J* 7.1 Hz), 2.31 (3H, s), 3.22 (2H, AB of ABX_3, J_{AB} 14.4 Hz, $J_{AX} = J_{BX}$ 7.2 Hz), 3.44 and 3.48 [4H in all, s and B of ABX_3 (J_{AB} 13.8 Hz, J_{BX} 7.1 Hz), partly overlapped], 3.62 (1H, A di ABX_3, J_{AB} 13.8 Hz, J_{AX} 7.1 Hz), 7.11 and 7.19 (4H in all, AA'BB', *J* 8.9 Hz), 7.35 (3H, m) and 7.72 (2H, m). Found: C, 74.7; H, 7.9; N, 13.2% ($C_{20}H_{25}N_3O$ requires C, 74.3; H, 7.8; N, 13.0%).

1-Methyl-3-(N-methyl-N-p-tolylhydrazono)piperidin-2-one **9h**, mp 89.5-90.5 °C (light petroleum); ^{1}H-NMR 1.83 (2H, m), 2.31 (5H in all, s and m partly overlapped), 3.09 (3H, s), 3.35 (5H in all, s and m partly overlapped), 6.94 and 7.08 (2H each, AA'BB', *J* 8.4 Hz). Found: C, 68.7; H, 7.9; N, 16.9% ($C_{14}H_{19}N_3O$ requires C, 68.5; H, 7.8; N, 17.1%).

Ozonolysis of (N-methyl-N-p-tolylhydrazono)-esters 8 and -amides 9

The reactions were carried out, as described for *N,N*-dimethylhydrazones[17b] on *ca.* 0.4 mmol of **8** or **9** in anhydrous CH_2Cl_2 (20 ml), under a gentle stream of ozone. The expected 2-oxoesters **10** and 2-oxoamides **11** were separated from the coproduct *N*-methyl-*N*-nitroso-*p*-toluidine [mp 50.0-51.1 °C (lit.:[9] mp 52-53 °C)] by chromatography on column or on preparative plate, further purified by distillation (Kugelröhr) and identified by ^{1}H-NMR.

tert-Butyl 2-oxopropanoate **10b**, oil; bp 50 °C (oven)/5 mm Hg (lit.:[18] 63-65 °C/22 mm Hg); ^{1}H-NMR: 1.55 (9H, s) and 2.42 (3H, s).

tert-Butyl 2-oxobutanoate **10c**, oil; bp 50 °C (oven)/5 mm Hg (lit.:[19] 55-60 °C/6-7 mm Hg); ^{1}H-NMR: 1.11 (3H, t, *J* 7.2 Hz), 1.55 (9H, s) and 2.80 (2H, q, *J* 7.2 Hz).

tert-Butyl 2-oxophenylpropanoate **10d**,[20] oil; bp 175 °C (oven)/5 mm Hg ; ^{1}H-NMR: 1.64 (9H, s),7.51 (2H, m), 7.65 (1H, m) and 7.98 (2H, app. d).

N,N-Dimethyl-2-oxopropanamide **11b**, oil; bp 80 °C (oven)/5 mm Hg (lit.:[21] b.p. 53.8 °C/4-5 mm Hg); ^{1}H-NMR: 2.43 (3H, s), 2.99 (3H, s) and 3.03 (3H, s).

N,N-Dimethyl-2-oxobutanamide **11c**, oil; bp 75 °C (oven)/5 mm Hg (lit.:[14c] 80-85 °C/0.6 mm Hg); ^{1}H-NMR: 1.13 (3H, t, *J* 7.3 Hz), 2.81 (2H, q, *J* 7.3 Hz), 2.99 (3H, s) and 3.00 (3H, s).

N,N-Diethyl-2-oxophenylpropanamide **11e**, oil; bp 190 °C (oven)/1 mm Hg (lit.:[22] b.p. 183-185 °C/18 mm Hg); ^{1}H-NMR: 1.16 (3H, t, *J* 7.1 Hz), 1.29 (3H, t, *J* 7.2 Hz), 3.25 (2H, q, *J* 7.1 Hz), 3.57 (2H, q, *J* 7.2 Hz), 7.50 (2H, m), 7.64 (1H, m) and 7.94 (2H, dd, *J* 1.4 and 8.4 Hz).

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