(*E*)-3-(2-Alkyl-10*H*-phenothiazin-3-yl)-1-arylprop-2-en-1-ones: preparative, IR, NMR and DFT study on their substituent-dependent reactivity in hydrazinolysis and sonication-assisted oxidation with copper(II)nitrate†

Luiza Găină,[a] Antal Csámpai,*[b] György Túrós,[b] Tamás Lovász,[a] Virág Zsoldos-Mády,[c] Ioan A. Silberg[a] and Pál Sohár*[b,c]

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A series of novel 3(5)-aryl/ferrocenyl-5(3)-phenothiazinylpyrazoles and pyrazolines were obtained by substituent-dependent regioselective condensation of the corresponding (*E*)-3-(2-alkyl-10*H*-phenothiazin-3-yl)-1-aryl/ferrocenylprop-2-en-1-one with hydrazine or methylhydrazine in acetic acid. The different propensity of the primary formed β-hydrazino adducts to undergo competitive retro-Mannich reaction was interpreted in terms of tautomerisation equilibrium constants calculated by DFT using a solvent model. The regioselectivity of the cyclisation reactions with methylhydrazine and the substituent-dependent redox properties of pyrazolines were also rationalized by comparative DFT calculations performed for simplified model molecules. On the effect of ultrasound-promoted oxidation with copper(II)nitrate phenothiazine-containing pyrazolines, enones and oxo-compounds were selectively transformed into sulfoxides. Only one sulfoxide enone was partially converted into an oxirane derivative. The structure of the novel products was determined by IR and NMR spectroscopy including COSY, HSQC, HMBC and DNOE measurements.

Introduction

In the course of our study on ferrocenyl heterocycles,[1b] including phenothiazine derivatives,[2] we synthesized variable new compounds of theoretical, chemical, physical and/or potential biological interest *via* enones.[3] Enones readily react with hydrazines yielding pyrazolines and pyrazoles,[4,5] so it seemed reasonable to apply this reaction to our phenothiazinyl enones, formed by the aldol condensation of formyl phenothiazines with arylmethyl ketones, to obtain novel pyrazole/pyrazoline derivatives substituted with phenothiazinyl and aryl (including ferrocenyl) groups (Scheme 1).

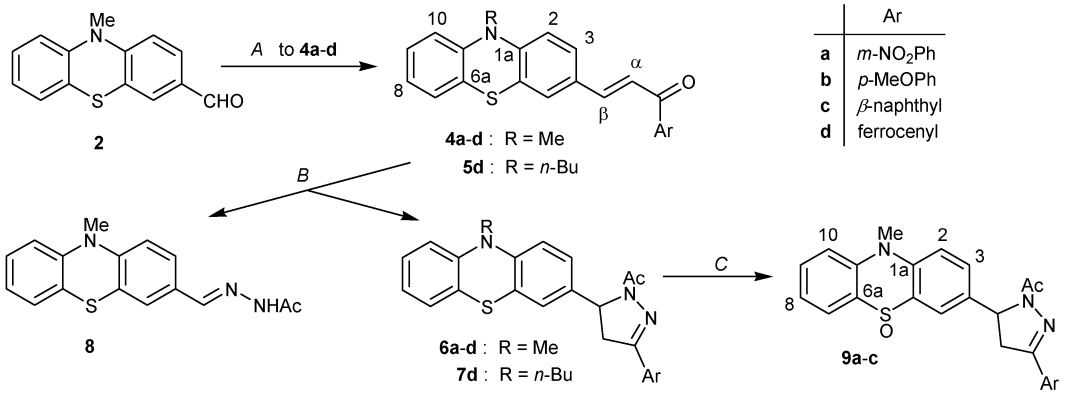
[a]*Department of Organic Chemistry, Babeş-Bolyai University, str. Arany János 11, RO-40028, Cluj-Napoca, Romania*
[b]*Institute of Chemistry, Eötvös Loránd University, P. O. B. 32, H-1518, Budapest-112, Hungary*
[c]*Research Group for Structural Chemistry and Spectroscopy, Hungarian Academy of Sciences, Eötvös Loránd University, P. O. B. 32, H-1518, Budapest-112, Hungary*

† Study on ferrocenes, part 19. For part 18 see ref. 1*a*.

Results and discussion

1. Synthesis of new phenothiazinyl enones

The procedure already established for obtaining enone **4a** by the condensation of 10-methyl-phenothiazin-3-carboxaldehyde **2** with *m*-nitroacetophenone[3] was extended to the preparation of analogues using *p*-methoxyacetophenone, 2-acetylnaphthalene and acetylferrocene. The corresponding enones **4b**–**d** and **5d** were thus obtained in 60–97% yield.



A: CH_3COAr, EtOH, 10 % NaOH, RT; *B*: $NH_2NH_2.H_2O$, AcOH, reflux; *C*: $Cu(NO_3)_2.3H_2O$, CH_2Cl_2, sonication, RT

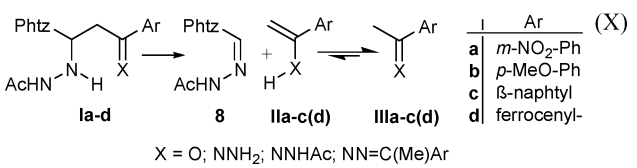
Scheme 1

2. Reactions of enones with hydrazine hydrate

2.1 Cyclisations. Cyclisations were first attempted in ethanol, but TLC analysis showed the formation of multi component mixtures. Boiling acetic acid proved to be a suitable solvent in which enones **4a**–**d** and **5d** gave 1-acetyl-3-aryl-5-phenothiazinylpyrazolines **6a**–**d** and **7d** (Scheme 1) in good yields (75–85%). Spontaneous aromatisation was obviously prevented by the electron-withdrawing *N*-acetyl group present in the products. The increased redox potential of **6a**–**d** and **7d** is also reflected in their attempted oxidation reactions discussed later.

2.2 Retro-Mannich type reaction and its theoretical interpretation

A common characteristic side reaction, with the exception of precursors containing ferrocenyl substituent (**4d** and **5d**), was the formation of *N*-acetyl-*N*′-[(10-methylphenothiazine-3-yl)methylene]hydrazine (**8**) as by-product. Klimova *et al.* reported similar fragmentation reactions accompanying enone cyclisations with thiosemicarbazides.[6] Fang *et al.* have demonstrated that certain isolated β-phenylhydrazino adducts undergo such fragmentation with a proposed concerted mechanism affording phenylhydrazones.[7] It must be pointed out that, although the concerted mechanism seems reasonable for this reaction, in the lack of conclusive evidence stepwise transformation can also be taken into consideration. In keeping with these precedents our reactions must involve the formation of a β-adduct [**I**: X = O; NNH_2; NNHAc; NN=C(Me)Ar] and its subsequent fragmentation affording **8** and an enol or enhydrazine/enhydrazone intermediate (**II**) which finally undergoes tautomerisation to **III** (Scheme 2). Of course, the methyl ketone (**III**: X = O) can react with a hydrazine component present in the reaction mixture yielding a hydrazone or azine product (**III**: X = NNH_2; NNHAc; NN=C(Me)Ar). Accordingly, a significant amount (14%) of *N*,*N*′-bis[1-(*m*-nitrophenyl)ethylene]hydrazine (**IIIa**, X = NN=C(Me)-*m*-NO_2Ph) could also be isolated from the reaction mixture obtained after the reaction of enone **4a**. As in the case of **4d** and **5d**, such fragmentation was not observed even in trace amounts, a particular inhibition must be attributed to the ferrocenyl group. Since fragmentation **I** → **II**, taking place either with concerted mechanism or in a stepwise manner, is eventually associated with the tautomerisation of the ArC(=X)CH_2 moiety of the β-adduct, we tried to approach the observed substrate-dependence through the calculated substrate-dependence of oxo-enol tautomerisation **III** ↔ **II**. The computations were carried out by the Gaussian program package[8] at B3LYP/6–31G(d,p) level of DFT using IEFPCM solvent model[9] adequately representing the applied reaction conditions (solvent: AcOH, $\varepsilon = 6.15$). On the optimized structures, frequency calculations gave the change in free energy values (ΔG), and the series of K(**II**/**III**) constants were obtained as $\exp(-\Delta G/RT)$ (Table 1). The comparison of K(**II**/**III**) values



Scheme 2

Table 1 Free energy (G)[a] and equilibrium of aryl methyl ketones **IIIa**–**d** and the corresponding enols **IIa**–**d** (see Scheme 2) and their equilibrium calculated by B3LYP/6–31G(d,p) in acetic acid ($\varepsilon = 6.15$) using IEFPCM solvent model

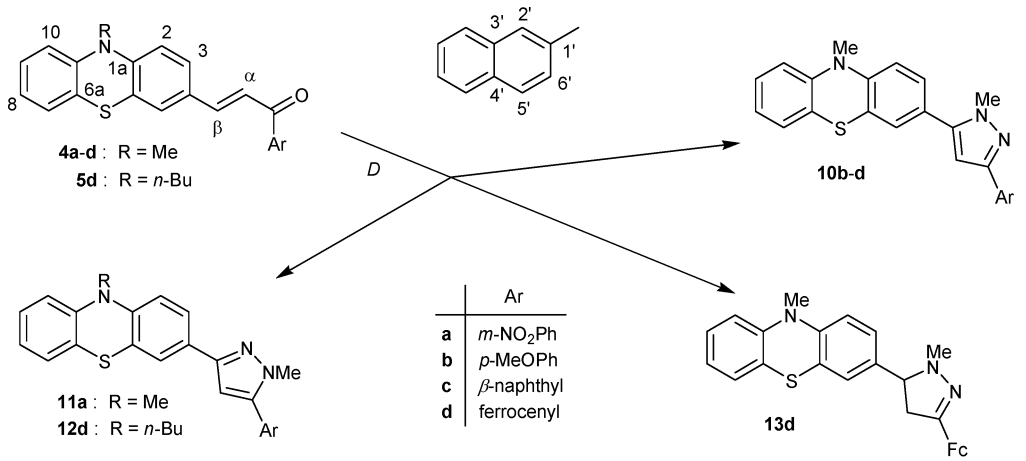
	G(**III**) (au)	G(**II**) (au)	ΔG(**II**–**III**)/kJ mol^{-1}	K(**II**/**III**)
a	−589.317091	−589.298461	48.92	3.04×10^{-9}
b	−499.311991	−499.288729	61.11	2.29×10^{-11}
c	−538.419438	−538.397319	58.20	7.37×10^{-11}
d	−1803.218399	−1803.193065	78.41	2.23×10^{-14}

[a] Zero-point energy (ZPE, kJ mol^{-1}): 366.88 for **IIIa**; 446.42 for **IIIb**; 482.71 for **IIIc**; 540.13.88 for **IIId**; 365.28 for **IIa**; 444.68 for **IIb**; 481.15 for **IIc**; 537.79 for **IId**.

unambiguously shows that **Id** → **IId** (related to **IIId** → **IId**) must be much less favoured process (at least by three orders of magnitude) than fragmentations **Ia**–**c** → **IIa**–**c**. This view can probably be extended to the corresponding intermediates with X = NNH_2; NNHAc; NN=C(Me)Ar moieties.

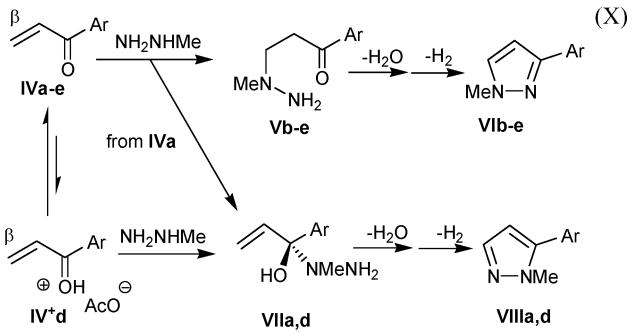
3. Substituent-dependent cyclisations with methylhydrazine and their theoretical interpretation

The cyclisations with methylhydrazine under the same conditions provided in most cases aromatic products, that is, 1-methyl-3-aryl-5-phenothiazinyl pyrazoles, **10b**–**d**, **11a** and **12d** (Scheme 3). Pyrazoline **13d** was only formed as a by product. Apparently, the electron-deficient acetylated nitrogen is mainly responsible for the increased resistance to oxidation in the above cases. (This difference in reactivity will be discussed later.) The yields of pyrazoles were lower, 54–65% than those of *N*-acetylpyrazolines. A general problem was raised by the positional isomerism in the forming pyrazol(in)es as reported for a number of analogous reactions.[4a–e] The majority of products (**10b**–**d**, **13d**) have the 1-Me-5-phenothiazinyl (Ptz) substitution pattern while 1-Me-3-Ptz substitution was evidenced by NMR (see later) for **11a** and **12d**. In order to get quantitative information on the relative reactivity of the electrophilic centres of our precursor enones in acetic acid solution we carried out again density functional (DFT) calculations for simplified models **IVa**–**e** (Scheme 4) and their *O*-protonated forms (**IV**$^+$**a**–**e**) at B3LYP/6–31G(d,p) level using an IEFPCM solvent model (Table 2). In each case the geometry optimization was followed by calculation of the energy and population of the frontier molecular orbitals.[10,11] Molecular reactivity indices such as electronic chemical potential[12a–l] [$\mu = (E_{HOMO} + E_{LUMO})/2$], chemical hardness[12a–l] [$\eta = (E_{LUMO} - E_{HOMO})/2$] and natural charges [$\rho$(NBO)][13] are also listed in Table 2. The local electrophilicity of the carbonyl- and β-carbon atoms were characterized by their local LUMO electron deficiency (Σc^2_{LUMO}) and the LUMO energy in the neutral and *O*-protonated counterparts. The relative proton affinities of **IVa**–**d** ($\Delta\Delta G$) and equilibrium constants (K_a) for the process **IV** + AcOH ↔ **IV**$^+$ + AcO^- were obtained from the thermodynamic results of frequency calculations carried out on the same level of DFT with the same solvent model. The electron chemical potential values (μ), representing the escaping tendency of molecular electrons, clearly reflect the relative electrophilicity of the studied models. According to general expectations, *m*-nitrophenyl derivative **IVa** is characterized by the lowest μ value (−5.00 eV) and ferrocenyl vinyl ketone **IVd** is the less electrophilic model ($\mu = -3.58$ eV).



D: NH_2NHMe, AcOH, reflux;

Scheme 3



Ar: *m*-NO_2Ph (**a**); *p*-MeOPh (**b**); b-naphthyl (**c**); ferrocenyl (**d**); Ph (**e**)

Scheme 4

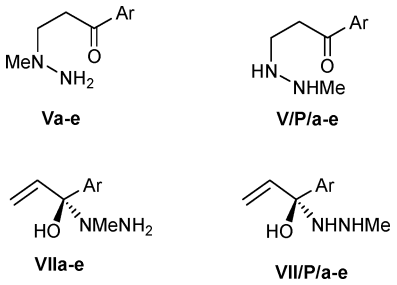


Fig. 1

It is worth noting that even protonated ferrocenyl vinyl ketone (**IVd**$^+$) is not as electrophilic as the neutral vinyl *m*-nitrophenyl ketone **IVa**. Although **IV**$^+$ cations are expected to be involved in charge controlled reactions,[14] protonation decreases molecular hardness (η) values also increasing the efficiency of orbital interactions. On the other hand, considering the natural charge values on C=O/C-β carbon atoms in the electrophilic species (Table 2) and on NHMe/NH_2 nitrogen atoms in methylhydrazine ($\rho = -0.547/\rho = -0.767$), charge controlled additions would dominantly give allylalcohol intermediates **VII/P/a–e** (Fig. 1) which would finally be converted into the "normal" regioisomeric pyrazoles (**VI**, Scheme 4) in all cases. The free energy values (G) of four types of possible adducts (**Va–e**, **V/a–e**, **VIIa–e** and **VII/a–e**, Fig. 1) were also obtained by DFT frequency calculations performed on the optimized structures at B3LYP/6–31G(d,p) level of theory using IEFPCM solvent model (Table 3, solvent: AcOH, $\varepsilon = 6.15$). The ΔG values show that β-adducts are much more stable than the corresponding allylalcohols [see ΔG(**VII–V**) and ΔG(**VII/P–V/P**) in columns 7 and 8]. Regioselectivity would be less influenced by the relative stability of NHMe- and NH_2 adducts—as reflected from ΔG(**V–V/P**) and ΔG(**VII–VII/P**) values (Table 3, columns 3 and 6). Nevertheless, the dominance of thermodynamic control in the primary addition step would finally result in the preferred formation of pyrazoles with the "unexpected" 1-Me-3-Ptz substitution pattern in all cases. The observed regioselectivity can be successfully interpreted by the relative weighting of LUMO in the neutral and protonated model enones **IVa–e** and **IV**$^+$**a–e**, respectively.

The population data (Table 2) suggest that without protonation, only the nitrophenyl model **IVa** has increased carbonyl reactivity in the orbital-controlled[14] addition towards the more nucleophilic methylated nitrogen of methyl-hydrazine ($\Sigma\ c^2_{HOMO} = 0.488$ on *N*HMe and 0.155 on NH_2 as calculated by the same method), but enones **IVb–e** with larger $\Sigma\ c^2_{LUMO}$ values on C-β are more likely to undergo conjugate addition with the reagent, which is also preferred under thermodynamic control [*cf.* ΔG(**VII–V**) in Table 3]. Population analysis of LUMOs (Table 2) shows substantially higher carbonyl reactivity for each *O*-protonated model (**IV**$^+$**a–e**). Enhanced carbonyl reactivity of **IV**$^+$**a–e** is also reflected from the increased positive values of natural charge [*cf.* ρ(NBO) on *C*=O for **IVa–e** and **IV**$^+$**a–e** in Table 2].

On the basis of these results it can be stated that the conjugate addition of methylhydrazine at C-β finally yielding the expected pyrazole (**IV** → **V** → **VI**) is preferred over the nucleophilic addition to the carbonyl group in neutral enones **IVb–e**, while **IVa** and each cation of type **IV**$^+$ are susceptible to react with the nucleophile at the carbonyl group to give the corresponding hydrazinoacetal **VII** which is then transformed into the regioisomeric pyrazoline **VIII**. In accord with the expectations, much lower LUMO energy (*i.e.* larger electron affinity) and electronic chemical potential (μ) values

Table 2 HOMO and LUMO values, electronic chemical potential (μ), chemical hardness (η), natural charges and local LUMO electron deficiency on C=O/C-β atom pairs and equilibrium constants (K_a) calculated by B3LYP/6–31G(d,p) for enone models (**IVa–e**) and their *O*-protonated forms (**IV⁺a–e**) in acetic acid ($\varepsilon = 6.15$) using an IEFPCM solvent model[a]

IV/IV⁺	E_{HOMO}/eV	E_{LUMO}/eV	μ/eV	η/eV	ρ(NBO) on C=O	ρ(NBO) on C-β	Σ c^2_{LUMO} on C=O[b]	Σ c^2_{LUMO} on C-β[b]	$\Delta\Delta G^{c,d}$/kJ mol^{-1}	K_a(IV/IV⁺)[e]
a	−7.25	−2.75	−5.00	2.50	0.542	−0.320	**0.169**[f]	0.159[g]	−19.28	7.58×10^{-34}
	−8.29	−4.12[f]	−6.20	2.09	0.601	−0.246	*0.277*	0.181[f]		
b	−6.30	−1.91	−4.10	2.19	0.529	−0.339	0.184	**0.201**	+14.07	6.17×10^{-28}
	−7.15	−3.55	−5.35	1.80	0.551	−0.293	*0.261*	0.172		
c	−6.01	−2.17	−4.09	1.92	0.535	−0.332	0.157	**0.167**	+10.29	1.26×10^{-28}
	−6.60	−3.78	−5.19	1.41	0.572	−0.242	*0.257*	0.171		
d	−5.43	−1.73	−3.58	1.85	0.527	−0.347	0.205	**0.240**	+19.91	6.62×10^{-27}
	−6.29	−3.33	−4.81	1.48	0.515	−0.296	*0.279*	0.202		
e	−6.93	−2.05	−4.49	2.44	0.536	−0.333	0.184	**0.194**	0	1.98×10^{-30}
	−7.72	−3.80	−5.76	1.96	0.587	−0.271	*0.273*	0.178		

[a] Relevant values for $MeNHNH_2$: ρ(NBO)/Σ $c^2_{HOMO} = -0.547/0.488$ on Me*N*H and $-0.767/0.155$ on NH_2, resp.; $\mu = -3.54$ eV and $\eta = 4.22$ eV. [b] The larger value referring to preferred electrophilic centrum is indicated by bold (for **IV**) or italics (for **IV⁺**). [c] Proton affinities relative to that of **IVe**. [d] *G* [au]/ZPE [kJ mol^{-1}]: −627.393321/380.80 for **IVa**; −627.802682/410.64 for **IVa⁺**; −537.389487/460.10 for **IVb**; −537.811120/490.76 for **IVb⁺**; −576.493481/496.31 for **IVc**; −576.914194/526.61 for **IVc⁺**; −1841.293123/553.81 for **IVd**; −1841.717582/584.66 for **IVd⁺**; −422.889050/374.26 for **IVe**; −423.305819/404.46 for **IV⁺e**; −229.071648/159.10 for AcOH; −228.590313/127.38 for AcO^-. [e] Calculated from proton affinities. [f] For **IVa** the values of LUMO + 1 concentrated on the enone moiety ($E = -2.26$ eV) were calculated instead of those of LUMO concentrated on the nitro group (Σ c^2_{LUMO} on N = 0.257, on C-carbonyl = 0.014 and on C-β = 0.017). [g] For **IVa⁺** Σ c^2_{LUMO+1} on $N = 0.0003$.

Table 3 Free energy values[a] of regioisomeric methylhydrazine adducts of model enones **IVa–e** (**Va–e**, **V/P/a–e**, **VIIa–e** and **VII/P/a–e**, see Fig. 1) calculated by B3LYP/6–31G(d,p) in acetic acid ($\varepsilon = 6.15$) using IEFPCM solvent model. ("**P**" designates the adducts formed by the addition of the primary amino group.)

	G(**V**) (au)	*G*(**V/P**) (au)	Δ*G*(**V–V/P**)/kJ mol^{-1}	*G*(**VII**) (au)	*G*(**VII/P**) (au)	Δ*G*(**VII–VII/P**)/kJ mol^{-1}	Δ*G*(**VII–V**)/kJ mol^{-1}	Δ*G*(**VII/P–V/P**)/kJ mol^{-1}
a	−778.528923	−778.534460	14.54	−778.498876	−778.504389	14.48	78.89	78.96
b	−688.523877	−688.527206	8.74	−688.488520	−688.494625	16.03	92.84	85.55
c	−727.630853	−727.636562	14.99	−727.598014	−727.604449	16.90	86.22	84.32
d	−1992.427064	−1992.433278	16.32	−1992.395265	−1992.398879	9.49	83.49	90.32
e	−574.024732	−574.030205	14.37	−573.991003	−573.997271	16.46	88.56	86.47

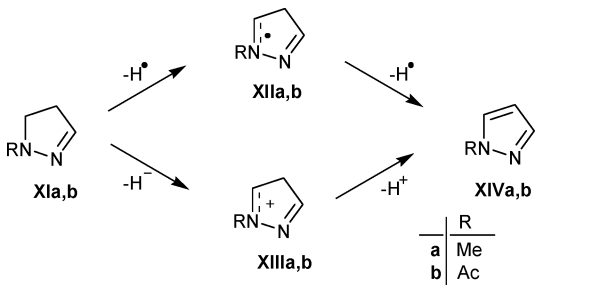
[a] ZPE [kJ mol^{-1}]: 604.76 for **Va**; 684.20 for **Vb**; 720.42 for **Vc**; 778.96 for **Vd**; 598.37 for **Ve**; 604.84 for **V/Pa**; 684.36 for **V/Pb**; 720.62 for **V/Pc**; 779.55 for **V/Pd**; 598.45 for **V/Pe**; 602.06 for **VIIa**; 680.85 for **VIIb**; 716.89 for **VIIc**; 774.79 for **VIId**; 601.78 for **VII/Pa**; 680.27 for **VII/Pb**; 716.53 for **VII/Pc**; 775.25 for **VII/Pd**; 594.73 for **VII/Pe**.

were obtained for **IV⁺a–e** than for their neutral counterparts **IVa–e** which are less sensitive to nucleophilic attack. The comparison of these data characterizing the electronic properties of Ar substituents suggests that addition of **IVd** → **Vd** (Ar = ferrocenyl) is much slower than addition of neutral enones with less electron-donating aryl substituents (**IVb**,**c**,**e** → **Vb**,**c**,**e**: Scheme 4). On the other hand, according to the relative proton affinity values and equilibrium constants obtained for the process **IV** + AcOH ↔ $\mathbf{IV}^+$ + AcO^- (Table 2) **IVd** has far the best chance to be transformed into the more electrophilic protonated form **IV⁺d** (*e.g.* **IVd** is more basic than anisyl derivative **IVb** by more than one magnitude). Although **IV⁺d** must be present in low concentration in the reaction mixture, its enhanced reactivity, which is reflected in electron chemical potential, chemical hardness and LUMO energy ($\mu = -4.81$ eV *vs.* −3.58 eV for **IVd**; $\eta = 1.48$ eV *vs.* 1.85 eV for **IVd**; $E_{LUMO} = -3.33$ eV *vs.*–1.73 eV for **IVd**), significantly increases the possibility of the primary addition at the carbonyl group.

The above discussed view about the relative possibilities of alternative reaction pathways is in accord with the experimental results as under the applied conditions 3-nitrobenzoyl enone **4a** (modelled by **IVa**) yields exclusively pyrazole **11a** with unexpected substituent pattern, while the presence of strongly electron-releasing ferrocenyl group in the enone precursor **5d** (R = *n*-Bu) increases the chance of *O*-protonation and, consequently the formation of analogous pyrazole **12d**. The reason of the different regioselectivity observed for the cyclisation of 10-methylphenothiazinylenone **4d** (R = Me) is not clear at the moment, but the alternative reaction pathway can not be ruled out completely considering the formation of a substantial amount of tarry materials and the relatively low yields of the "normal" regioisomers **10d** and **13d** (18 and 27%, respectively). The cyclisations of **4b**,**c** to **10b**,**c** presumably proceed *via* the generally accepted mechanism[7] involving the primary conjugate addition of methylhydrazine on the unprotonated enones.

4. Theoretical interpretation of different redox properties of *N*-acetyl- and *N*-methylpyrazolines

The spectacular difference in the propensity of *N*-acetyl- and *N*-methylpyrazolines to undergo spontaneous dehydrogenation under the conditions of cyclisation reactions discussed above was also studied by DFT calculations, which were performed for simplified models **XIa**,**b**–**XIVa**,**b** (Scheme 5) at B3LYP/6–31G(d,p) level of theory using IEFPCM solvent model (solvent: AcOH, $\varepsilon = 6{,}15$). Two possible mechanisms involving radical and cationic intermediates **XIIa**,**b** and **XIIIa**,**b**, respectively, were taken into account. Concluding from the highly significant substrate dependence we assume that the rate-determining step is the loss of a hydrogen atom or a hydride anion from the saturated carbon atom adjacent to the substituted nitrogen generating the corresponding intermediate. The free energy values of the models were resulted from frequency calculations carried out on the optimized structures (Table 4). Comparison of the substituent-dependent changes in free energy associated with the formation of the possible intermediates (listed in row 3) shows that—in keeping with general expectations—the *N*-methyl group renders a higher degree of stabilization both to radical (**XII**) and cationic (**XIII**) intermediates than does the *N*-acetyl group (by 9.04 kJ mol^{-1} and 94.29 kJ mol^{-1}, respectively). The difference is more than ten times larger for the formation of cationic intermediates than obtained for the formation of radical intermediates, suggesting that the ionic mechanism might be better adopted to the experimental observations. As the cyclisation reactions with methylhydrazine were conducted under inert conditions, we cannot unambiguously identify the possible oxidant at the moment. Finally, from thermodynamic point of view, aromatisation of *N*-methylpyrazoline is also preferred over that of *N*-acetylpyrazoline by 47.18 kJ mol^{-1} (Table 4: row 3).



Scheme 5

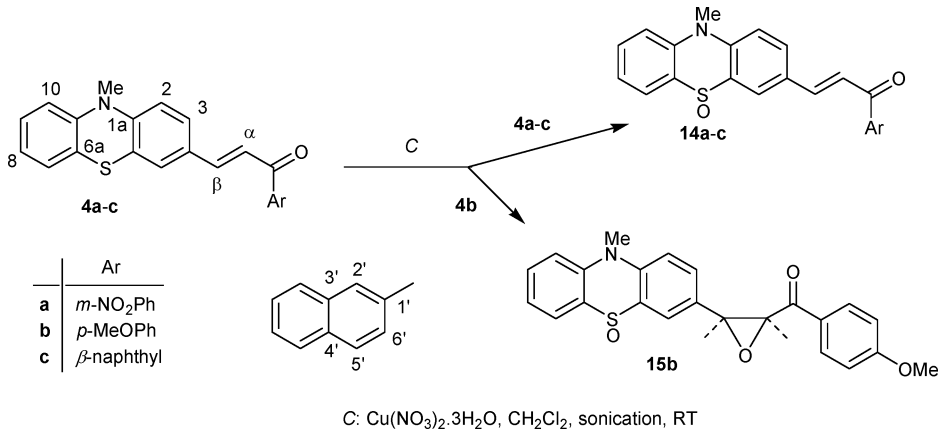
5. Sonication-assisted oxidation reactions with copper(II) nitrate trihydrate

In order to get pyrazoles without an *N*-substituent, we envisaged oxidation of **6a**–**d** and **7d** followed by facile deacylation of the resulting aromatic products. Preliminary experiments using classical oxidation agents, including attempts with high redox potential quinones (*e.g.* DDQ) failed. This is why we resorted to the sonication-assisted oxidation with copper(II) nitrate, a procedure successfully applied to aromatisation of pyrazolines.[15] Instead of the expected dehydrogenation reaction, on the effect of the "*in situ*" generated nitrogen dioxide[16] oxidation of sulfur atom occurred to give sulfoxides **9a**–**c** (Scheme 1). This finding refers to the preference of primary single electron transfer from the phenothiazinyl ring[16] over the hydrogen-abstraction from

Table 4 Free energy values[a] of model pyrazolines **XIa**,**b**, radicals **XIIa**,**b**, cations **XIIIa**,**b** and pyirazoles **XIVa**,**b**, (see Scheme 5) calculated by B3LYP/6–31G(d,p) in acetic acid ($\varepsilon = 6.15$) using IEFPCM solvent model

	G(**XI**) (au)	*G*(**XII**) (au)	*G*(**XIII**) (au)	*G*(**XIV**) (au)	Δ*G*(**XII**–**XI**)[b]/kJ mol^{-1}	Δ*G*(**XIII**–**XI**)[b]/kJ mol^{-1}	Δ*G*(**XIV**–**XI**)[b]/kJ mol^{-1}
a	−266.623705	−265.987472	265.866276	265.461863	1670.54	1988.77	3050.63
b	−379.979412	−379.339739	379.186074	378.799602	1679.58	2083.06	3097.81
a–**b**					−9.04	−94.29	−47.18

[a] ZPE [kJ mol^{-1}]: 318.02 for **XIa**; 343.01 for **XIb**; 276.14 for **XIIa**; 303.88 for **XIIb**; 286.44 for **XIIIa**; 307.91 for **XIIIb**; 258.65 for **XIVa**; 282.99 for **XIVb**. [b] In the third row for columns 5–7: ΔΔ*G*(**a**–**b**).

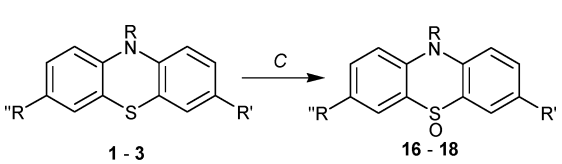


C: $Cu(NO_3)_2.3H_2O$, CH_2Cl_2, sonication, RT

Scheme 6

the pyrazolyl moiety.[15] Unfortunately the ferrocenyl-substituted substrates underwent decomposition under the applied conditions. However, the relatively short reaction time, the high yields of sulfoxides **9a**–**c** (sometimes reaching 95%) and the simplicity of the reaction conditions made us to subject phenothiazinyl enones to this procedure of *S*-oxidation, not mentioned so far in the literature. By means of this method, **4a–c** were smoothly converted into their sulfoxide derivatives (**14a**–**c** Scheme 6), without sulfone contaminations. Besides *S*-oxidation, enone **4b** partially underwent subsequent epoxidation on the double bond, yielding oxirane **15b** (Scheme 6). The primary oxidation of the sulfur atom probably decreases the electron-donating ability of the phenothiazine unit, indirectly decreasing the chance of electrophilic epoxidation on the attached double bond. This deactivation must be partially compensated by the electron-donating anisyl group in sulfoxide **14b**, the precursor of **15b**. In a separate experiment, **14b** was subjected to prolonged oxidative procedure (10 h) affording oxirane **15b** in good yield (85%).

We also tested this protocol on simpler 10-alkylphenothiazines **1**–**3** and found that *S*-oxidation took place selectively resulting in sulfoxides **16**–**18** irrespective of the ring substituents (Scheme 7). It is also worth pointing out that the formyl group in **2** proved to be resistant to oxidation under the employed conditions which is capable of oxidizing even the highly deactivated diacetyl derivative **3** (Scheme 7). To the best of our knowledge this is the first example for the sulfoxidation of a 3,7-diacylphenothiazine. Due to its simplicity and potential to produce sulfoxides with high yields and chemoselectivity, this method represents an advantageous alternative to the classical *S*-oxidation reactions applied so far in phenothiazine chemistry.[17]



C: $Cu(NO_3)_2.3H_2O$, CH_2Cl_2, sonication, RT

Scheme 7

6. Structure

The spectral data (Tables 5–8) of our new compounds are self-explanatory concerning the supposed structures and only a few additional remarks are necessary.

The position of the NAc group in **6a**–**d** and **7d** is proved by HMBC experiments (for **6a**–**c** and **7d**) which demonstrate ^3J(C,H) coupling between the H of pyrazoline-CH and the carbonyl carbon of the acetyl group and between the CH_2-hydrogens and C-1 of the aryl or ferrocenyl moiety (Ar, Scheme 1), respectively.

The chemical non-equivalence of C/H-2,5 and C/H-3,4 atom pairs in **6d**, **7d** and **13d** is due to molecular asymmetry (the presence of a chirality center). Of course, in the spectra of **10d** and **12d**, which do not contain chiral atoms, the aforementioned H and C atom pairs give identical signals.

Besides the IR, ^{1}H- and ^{13}C-NMR characteristics of the azomethine, acetyl and NH groups the structure of compound **8** is confirmed by the significant downfield shift of H-3 and H-5 signals (by *ca.* 0.4–0.5 ppm compared to **6a**–**d** and **7d**) as a consequence of summarized *–I–* and anisotropic effects of the vicinal C=N double bond.

In case of **9a**–**c**, the pyrazolyl methine carbon and the S atom of the sulfinyl group, the two chirality centres, make possible the presence of two diastereomers. In the ^{1}H- and ^{13}C-NMR spectra of **9a**–**c** all resonances appear as doubled signals of equal intensity proving the formation of a 1 : 1 mixture of diastereomers containing the pyrazolyl methine proton and sulfinyl oxygen in *syn* and *anti* arrangements. This observation is an indirect proof of the presence of an SO group (besides of the *v*SO IR band, *cf.* Table 8).

Similarly the *ab ovo*, more probable, chemically-expected position of the NMe group in **10b**–**d** and **13d** is proved by HMBC measurements. For **10b**, the supposed regioisomeric structure is also supported by NOE experiments. Intensity enhancements were observed on the H-3 and H-5 signals of phenothiazine ring when the Hs of the NMe group were irradiated.

HMBC results confirmed the unexpected regioisomeric structures for **11a** and **12d**. Accordingly, we detected NOE between the Hs of NMe group and H-2,5 of the substituted Cp ring of ferrocene for compound **12d**.

In the ^{1}H- and ^{13}C-NMR spectra of **15b** the signals of two saturated methine groups appear in the interval characteristic

Table 5 ^{1}H NMR data[a] of compounds **6a–d**, **7d**, **8**, **9a–c**, **10b–d**, **11a**, **12d**, **13d**, **14a–c**, **15b** and **16–8**[b]

Compound	CH_3[c] s (3H)	CH_3[d] s (3H)	OCH_3[e] s (3H)	CH_2/=CH[f] dd/s (2/1H)	CH dd (1H)	H-2,6/5 Ar or substituted Cp ring[g]	H-3,5/4	H-4/1″-5″ Ar/Cp[h]	H-2 Phenothiazine ring	H-3	H-5	H-7	H-8	H-9	H-10
6a	2.44	3.35	—	3.18, 3.76	5.56	8.54, 8.07	–, 7.63	8.28	6.76	7.07	6.97	7.09	6.92	7.16	6.79
6b	2.40	3.34	3.86	3.10, 3.68	5.48	7.68	6.94	—	6.74	7.07	6.99	7.10	6.91	7.15	6.78
6c	2.47	3.34	—	3.27, 3.82	5.55	7.93[i]	8.08[i]	7.88	6.76	7.10	7.03	7.10	6.91	7.15	6.78
6d	2.36	3.33	—	2.94, 3.59	5.43	4.55, 4.69	4.40, 4.41	4.17	6.76	7.07	7.03	7.10	6.90	7.15	6.78
7d	2.37	0.93	3.82	2.95, 3.60	5.45	4.56, 4.68	~4.42	4.18	6.81	7.05	7.01	7.14	6.88	7.10	6.83
8	2.39	3.41	—	7.66	—	—	—	—	6.80	7.40	7.50	7.16	6.97	7.20	6.84
9a	2.42	3.69	—	3.26, 3.85[j]	5.69	8.56	—	8.25	7.35[j]	7.45	~7.6[j]	7.85	7.22	~7.6[j]	~7.35[j]
	2.43	3.71		3.32, 3.85[j]	5.72	8.05	~7.6			~7.6[j]	7.85				
9b	2.40	3.72	3.87	3.22, 3.77	5.63	7.72	6.97	—	7.33[j]	7.45	7.70	7.87	7.24	7.60	7.36[j]
	2.41	3.75	3.88	3.30, 3.80	5.64		6.98		7.37[j]	7.63	7.89	7.91	7.25		
9c	2.46	3.72	—	3.40, 3.93[j]	5.71	~7.88[i]	8.09[i]	7.98	7.36[j]	7.49	7.75	~7.88	7.24	7.60	7.34[j]
	2.47	3.75		3.48, 3.93[j]	5.72		8.11[i]		7.37	7.68	7.93		7.26		7.36
10b	3.90	3.44	3.86	6.49	—	7.75	6.95	—	6.89	7.25[j]	7.25[j]	7.18	6.99	7.22	6.87
10c	3.96	3.45	—	6.67	—	8.28[i]	7.99[i]	7.89	6.91	7.29	7.27	7.18	6.99	7.22	6.87
10d	3.84	3.43	—	6.29	—	4.67	4.26	4.10	6.86	7.25	7.24	7.17	6.97	7.21	6.88
11a	3.97	3.43	—	6.64	—	8.36, 7.81	–7.69	8.30	6.86	7.64	7.63	7.17	6.95	7.19	6.84
12d	4.00	0.96	3.89	6.52	—	4.53	4.39	4.19	6.89[j]	7.61	7.58	7.15[j]	6.92	7.16[j]	6.88[j]
13d	2.73	3.40	—	2.90, 3.20	3.84	4.63, 4.46	4.31, 4.33	4.17	6.83[j]	7.27	7.28	7.16	6.94	7.18	6.83[j]
14a	—	3.80	—	7.54	7.89	8.81, 8.33	–7.70	8.40	7.30	7.90	8.22	7.91[j]	7.29	7.64	7.28
14b	—	3.78	3.90	7.56	7.82[j,k]	8.06	6.99	—	7.39	7.84[j]	8.21	7.96	7.31	7.65	7.41
14c	—	3.78	—	7.73	7.91[j,k]	8.60[i]	8.13[i]	7.96	7.42	7.89	8.30	7.99	7.33	7.66	7.41
15b	—	3.65	3.73	4.97, 4.99	4.83,[k] 4.85[k]	7.72	6.73	—	7.20[j]	7.58[j]	7.64, 7.65	7.85	7.21[j]	7.57[j]	7.30
16	—	3.79	—	—	—	—	—	—	7.40	7.64	7.95	7.95	7.27[l]	7.64	7.40
17	—	3.80	—	—	9.97[m]	—	—	—	7.46	8.08	8.39	7.94	7.34	7.65	7.45
18	2.68	1.65	4.45	—		—	—	—	7.58	8.29	8.58	8.58	—	8.29	7.58

[a] Measuring frequency: 500 MHz. Solvent: $CDCl_3$. Chemical shifts in ppm ($\delta_{TMS} = 0$ ppm), coupling constants in Hz. Assignments were supported by HMQC (except for **9a** and **18**), HMBC (except for **6d**, **9a**, **16** and **18**) and for **6c**, **7d**, **9c** and **15b** also by 2D-COSY measurement. [b] Further ^{1}H-NMR signals, 2-naphthyl substituent, H-5,8: 7.85 and 7.87 (**6c**), 7.88 (2H, **9c**), 7.83 and 7.84 (**10c**), 7.92[j] and 8.02 (**14c**), H –6,7: ~7.55 (2H, **6c** and **9c**), 7.49 and 7.46 (**10c**), 7.63 and 7.60 (**14c**); CH_2, β- and γ- to the N, *qi* (2H) and *sx* (2H): 1.76 and 1.43 (**7d**), 1.83 and 1.49 (**12d**); NH: s (1H): 9.34 (**8**). [c] Ac (**6a–d**, **7d**, **8**, **9a–c** and **18**), NCH_3, pyrazole (**10b–d**, **11a** and **12d**) or pyrazoline ring (**13d**). [d] *N*-Substituent in phenothiazine ring, triplet, *J*: 7.4 (**7d**, **12d**), 7.2 (**18**). [e] NCH_2 (2H, **7d**, **12d**, **18**). [f] Singlet (1H) for **8**, **10b–d**, **11a** and **12d**, 2 × *dd* (2H) for **6a–d**, **7d** and **13d**, 17.7, 4.8 and 12.0 (**6a**), 17.6, 4.5 and 11.7 (**6b**), 17.8, 3.8 and 11.1 (**6c**), 17.4, 4.1 and 11.6 (**6d** and **7d**), 16.0, 14.5 and 9.6 (**13d**), *dd* and *d* for **9a–c**, *J*: 17.7, 4.8 and 17.7, *d* (α to C=O) for **14a–c**, *J*: 15.5, 2 × *d* for **15b**, *J*: 7.1 and 6.6. [g] For **6d**, **7d**, **10d**, **12d** and **13d**. [h] Unsubstituted Cp ring for **d**-type compounds. [i] In positions 1 and 3 (β-naphthyl). [j] Overlapping signal. [k] =CH (**14a–c**) or –OCH– (**15b**), β to C=O, *d* or 2 × *d* (for *J* see footnote f). [l] H-4,8 (2H). [m] CHO.

Table 6 ^{13}C NMR chemical shifts[a] of compounds **6a–d**, **7d**, **8**, **9a–c**, **10b–d**, **11a**, **12d**, **13d**, **14a–c**, **15b** and **16–18**[b,c]

		C-3	C-4	C-5				C-1	C-2,6/5	C-3,5/4	
Compound	C=O (Ac)[d]	Pyrazole/pyrazoline ring			CH_3 (Q)	CH_3 (Ac) or NMe[e]	OCH_3 or NCH_2[f]	Aryl group[g] or substituted Cp ring[h]			C-4/1–5 Ar/Cp[i]
6a	169.4	151.8	42.4	60.1	35.7	22.4	—	133.7	121.8, 132.4	149.0, 130.2	125.0
6b	169.0	154.0	42.7	59.5	35.7	22.4	55.8	124.46[j]	128.6	114.6	161.8
6c	169.3	154.2	42.5	59.8	35.7	22.5	—	134.6	127.7, 123.7	129.4, 128.3	133.4
6d	168.6	156.3	43.9	58.9	35.7	22.4	—	75.8	67.6, 68.1	70.7, 70.9	69.8
7d	168.6	156.3	43.9	58.9	14.2	22.3	47.5	75.9	67.6, 68.1	70.7, 70.8	69.8
8	173.8	142.8[k]	—	—	35.9	20.8	—	—	—	—	—
9a	169.5	59.97	42.33	151.9	35.76	22.4	—	132.5	121.74, 121.82	149.0	125.07
		60.01	42.37	152.1	35.80			133.5	132.6, 133.5	131.3	
9b	169.1	59.38	42.5	154.0	35.74	22.3	55.8	124.2[j]	128.67	114.65	161.9
		59.44	42.6	154.2	35.77			124.3[j]	128.73	114.67	
9c	169.4	59.6	42.4	154.3	35.8	22.4	—	134.65	128.90, 123.66	127.8, 129.1	133.4
		59.7	42.5	154.5				134.69	129.0, 123.69	129.2	
10b	—	150.8	102.9	144.5	35.8	37.9	55.7	126.7	127.2	114.4	159.7
10c	—	150.9	103.7	144.8	35.8	38.0	—	131.3	124.3, 124.4	134.1, 128.7	133.5
10d	—	150.1	103.8	144.0	35.8	37.8	—	79.1[l]	66.9	68.8	69.9
11a	—	150.4	104.0	142.9	35.8	38.2	—	132.7	123.8, 134.8	148.9, 130.3	123.7
12d	—	149.7	102.7	142.8	14.2	38.2	47.6	75.5	68.7	69.3	70.0
13d	—	151.6	45.2	73.0	35.8	42.2	—	77.6[m]	66.9, 67.5	69.8, 70.1	69.7
14a	188.3	145.0[n]	120.3[n]	—	36.0	—	—	139.8	123.6, 134.5	148.8, 130.4	127.5
14b	188.7	142.2[n]	121.6[n]	—	36.0	—	56.0	131.5	131.3	114.3	163.9
14c	190.2	143.0[n]	121.7[n]	—	36.0	—	—	133.5	130.5, 124.9	135.91[j] 129.0	135.94[j]
15b	197.2	50.9[n]	42.1[n]	—	35.6	—	55.8	130.1	131.0	114.1	163.9
16	—	—	—	—	35.8	—	—	—	—	—	—
17	189.9	—	—	—	36.4	—	—	—	—	—	—
18	195.6	—	—	—	12.6	26.8	44.0	—	—	—	—

[a] In ppm ($\delta_{TMS} = 0$ ppm) at 125.7 MHz. Solvent: $CDCl_3$. [b] Assignments were supported by DEPT, HMQC (except for **9a** and **18**) and HMBC (except for **6d**, **9b**, **16** and **18**) measurements. [c] Further lines: CCH_2C (β- and γ- to N in): 29.4 and 20.6 (**7d** and **12d**), $C_{Ar}H$ (terminal benzene ring of the β-naphthyl group): 127.2, 127.5,[o] 128.8 and 129.0 (**6c**), 127.23,[j] 127.28,[j] 128.92;[j] 131.3 and 131.4.6 (**9c**), 126.1, 126.5, 128.1 and 128.6 (**10c**), 127.2, 128.2, 128.9 and 130.0 (**14c**). [d] Ketone (COR) group (**14a–c** and **15b**) or formyl group (**17**). [e] For **10b–d**, **11a**, **12d** and **13d** in pyrazole or pyrazoline ring (**13d**). [f] For **7d**, **12d** and **18**. [g] Numbering of the β-naphthyl moiety (**c**-type compounds) see Scheme 3. [h] For ferrocenyl-(**d**-type) compounds. [i] Unsubstituted Cp ring. [h,j] Interchangeable assignments (for **6b** and **9b** see also Table 2b). [k] C=N group. [l] Identified by HMBC. [m] In overlap with a line of the solvent. [n] α/β-Carbon to the phenothiazine of the enone (**14b**) or oxirane (**15b**) group. [o] Two overlapping lines (see also Table 2b).

Table 7 ^{13}C NMR chemical shifts[a] of phenothiazine carbons in compounds **6a–d**, **7d**, **8**, **9a–c**, **10b–d**, **11a**, **12d**, **13d**, **14a–c**, **15b** and **16–18**[b]

Compd.	C-1a	C-2	C-3	C-4	C-5	C-5a	C-6a	C-7	C-8	C-9	C-10	C-10a
6a	146.0	114.6	125.5	136.1	124.4	124.8	123.3	127.5	123.0	128.0	114.5	145.9
6b	146.1	114.5	125.6	136.8	124.6	124.46[c]	123.5	127.5	122.9	127.9	114.4	145.7
6c	146.0	114.6	125.6	136.7	124.7	124.6	123.5	127.5[d]	122.9	127.9	114.4	145.8
6d	146.0	114.6	125.2	136.9	124.5	124.6	123.4	127.5	122.9	127.9	114.5	145.7
7d	145.5	115.8	124.9	136.7	124.7	126.0		127.6	122.7	127.8	115.7	145.2
8	147.8	114.3	127.57	128.6	125.4	124.5	123.2	127.64	123.4	128.0	114.8	145.4
9a	139.85[c,e]	115.9[c,e]	130.3	135.4	132.0	125.13[c]	124.7[c]	127.3	122.47	133.3	116.4[c]	140.05[c]
			132.4	135.6	133.4[e]	125.5[c]	124.8[c]	129.3	122.50	133.4[e]	116.8[c]	140.09[c]
9b	140.16[c]	116.1[c]	130.2	136.1	127.4	125.01[c]	124.99[c]	131.3	122.35	133.3[e]	115.9[c,e]	139.7[c,e]
	140.20[c]	116.7[c]	132.3	136.2	129.5	125.6	124.95[c]	131.4	122.39			
9c	139.8[c,e]	115.9[c,e]	130.2	136.0	127.5	125.07[c]	124.92[c]	128.3[e]	122.37	133.3[e]	116.2[c]	140.15[c]
			132.3	136.1	129.6	125.62[c]	124.97[c]		122.42		116.7 [c]	140.18[c]
10b	146.4	114.38	127.6[c]	124.4[c]	128.3[c]	125.4[c]	123.3	127.7	123.2	128.1	114.7	145.7
10c	146.5	114.4	128.3	125.2	127.6	124.5	123.2	127.7	123.3	128.1	114.7	145.7
10d	146.4	114.7	128.2	123.3[e]	127.6	125.4	124.4	127.7	123.3[e]	128.1	114.3	145.7
11a	146.0[c]	114.54[e]	127.86	127.9	124.6	124.2	123.6	127.6	122.9	127.9	114.48[c]	145.9[c]
12d	144.9	115.8[c]	124.7	128.4	124.8	125.5	125.1	127.6[c]	122.7	127.8[e]	115.7[c]	145.6
13d	146.1	114.52[c]	126.9	135.0	126.5	124.3	123.6	127.6	122.9	127.9	114.48[c]	145.8
14a	141.7	116.8	133.4[d]	128.6	132.3	124.7	124.3	131.4	123.3	133.8	116.5	139.6
14b	141.2	116.5	133.0	129.4	131.43	125.6	125.3	131.48	123.0	133.5	116.2	139.8
14c	141.3	116.5	133.0	129.3	131.54[c]	125.6	125.2	131.58[c]	123.1	133.3	116.2	139.7
15b	139.0	116.0	133.1	133.5	131.36	124.6	125.0	131.28	122.1	132.0	115.8	140.1
16	140.3	11.9	133.2	122.3	131.5	125.2	125.2	131.5	122.3	133.2	115.9	140.3
17	144.1	116.6[c]	133.1	130.5	134.8	125.5	125.2	131.5	123.88	133.7	116.7[c]	139.3
18	140.9	116.4	133.2[c,e]	132.0	133.7[c,e]	124.4	124.4	133.7[c,e]	132.0	133.2[c,e]	116.4	140.9

[a] In ppm ($\delta_{TMS} = 0$ ppm) at 125.7 MHz. Solvent: $CDCl_3$. [b] Assignments were supported by DEPT, HMQC (except for **9a** and **18**) and HMBC (except for **6d**, **9a**, **16** and **18**). [c] Interchangeable assignments (See Table 2a for compound **6b** and **9b**). [d] Overlapping lines (See Table 2a). [e] Two coalesced lines.

Table 8 Characteristic IR frequencies [cm^{-1}] of compounds **6a–d**, **7d**, **8**, **9a–c**, **10b–d**, **11a**, **12d**, **13d**, **14a–c**, **15b** and **16–18**[a,b]

Compound	νC=O band	νC=C band	Bands of the phenothiazine moiety		νSO band	γ $C_{Ar}H$ band	ν_{as}Cp–Fe–Cp band
6a	1661	1608	1466	1257	—	817, 752	—
6b	1646	1607	1465	1258	—	840, 808, 743	—
6c	1662	1602	1465	1256	—	836, 805, 752	—
6d	1646	1601	1465	1253	—	856, 755	487
7d	1658	1601	1464	1248	—	818, 747	491
8	1695	1601	1466	1254	—	808, 744	—
9a	1667	1591	1464	1261	1049, 1027	811, 757, 739	—
9b	1653	1606	1463	1250	1046, 1022	815, 755	—
9c	1661	1589	1464	1260	1049, 1027	819, 753	—
10b	—	1611	1465	1248	—	834, 821, 783, 764	—
10c	—	1601	1460	1260	—	802, 705	—
10d	—	1606	1462	1259	—	818, 750	489
11a	—	1606	1466	1260	—	798, 752, 737	—
12d	—	1606	1454	1285	—	823, 758	505, 488
13d	—	1603	1464	1251	—	815, 747	495
14a	1656	1586	1466	1218	1021	813, 754	—
14b	1654	1602, 1585	1463	1259	1020	834, 805	—
14c	1654	1586	1465	1261	1020	810, 747	—
15b	1654	1601, 1588	1464	1256	1057	813, 753	—
16	—	1584	1457	1261	1020	765	—
17	1682	1605, 1086	1462	1260	1046, 1025	764, 751	—
18	1674	1589	1479	1249	1024	826	—

[a] In KBr discs. [b] Further bands: νNH: 3200–2800 diffuse band (**8**); $\nu_{as}NO_2$ and ν_sNO_2: 1498 and 1332 (**6a**), 1530 and 1350 (**9a** and **11a**), 1526 and 1354 (**14a**); νC–O (oxirane ring): 876 and 839 (**15b**).

for oxiranes[18a] instead of the signals of olefinic CH=CH moiety arising from the parent enone sulfoxide **14b**. The absence of the C=C double bond in **15b** is also reflected in the significant upfield shifts of the signal of *ortho*-Hs of the aryl group and H-3 and H-5 signals of the phenothiazinyl group.

In accordance with the above stated structural difference, the carbonyl lines of **14b** and **15b** appear at 188.7 and 197.2 ppm, respectively, in the ranges expected for compounds containing benzophenone- and acetophenone-type –C(sp^2)–CO–C(sp^2) and C(sp^3)–CO–C(sp^2) moieties.[18b]

The signals of the oxirane-Hs of **15b** appear doubled with similar intensities while neither the other ^{1}H-NMR signals nor the carbon lines without exception are doubled. From the AB-type spectrum of the oxirane-Hs, the coupling constants of the two components

are 6.6 and 7.1 Hz, respectively, characteristic of *cis* isomers.[18c] It means that the relative configurations of the carbons in the oxirane ring do not differ in the two components. Thus the existence of the latter requires the presence of a third chiral centrum provided by the sulfoxide structure. Accordingly, in the IR spectrum of **15b**, a very intense *v*SO band (1027 cm^{-1}) appears and the mass spectrum proved the molecular formulae ($C_{23}H_{19}NO_4S$) in keeping with the sulfoxide structure.

Experimental

Melting points (uncorrected) were obtained with an Electrothermal IA 9200 digital melting point apparatus. Elemental analyses were performed by a VARIO EL III instrument. IR spectra were recorded in KBr pellets with a BRUKER IFS 55 FT-spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX 400-(only for **4b**,**c**) and 500 spectrometers at 400/500 (^{1}H) and 100/125 (^{13}C) MHz, using TMS as internal reference with the deuterium signal of the solvent as the lock. *J* Values are given in Hz. The spectral data of **4b**,**c** are listed in the experimental part. The standard Bruker micro program NOEMULT.AU to generate NOE was used with a selective pre-irradiation time. DEPT spectra were run in a standard manner, using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs INV4GS and INV4GSLPLRND, respectively. The mass spectra of **IIIa** (X = NN=C(Me)-*m*-NO_2Ph), **14a**,**b** and **16** were obtained by a Bruker Esquine 3000+ ion trap mass spectrometer equipped with electrospray ionisation source.

Phenothiazine derivatives **1**–**3**, **4a**,**d** and **5d** were prepared according to described procedures.[2,3,19,20] Acetylferrocene, methylhydrazine, hydrazine hydrate, 2-acetylnaphthalene, *m*-nitroacetophenone, *p*-methoxyacetophenone and phenothiazine were purchased from Sigma-Aldrich.

General procedure for the preparation of enones 4b,c

To the stirred solution of the appropriate 10-alkyl-3-formyl-phenothiazine (1 mmol) and *p*-methoxyacetophenone (0.150 g, 1 mmol) or 2-acetylnaphthalene (0.146 g, 1 mmol) in ethanol (20 cm^3) 10% methanolic solution of NaOH (1 cm^3) was added dropwise over 3 min at 25 °C. The mixture was stirred for 8 h at 40–50 °C. The product precipitated on cooling was filtered and washed with cold ethanol (3 cm^3) then purified by column chromatography on silica using dichloromethane as eluent.

(*E*)-3[1-(4-Methoxyphenyl)-1-oxo-2-propen-3-yl]-10-methyl-10*H*-phenothiazine (4b). Orange powder (0.355 g, 95%); mp 197–200 °C (from EtOH); (found: C, 74.0; H, 5.2; N, 3.8, S 8.55, $C_{23}H_{19}NO_2S$ requires C, 74.0; H, 5.1; N, 3.75, S 8.6%); ν_{max}(KBr)/cm^{-1} 1668, 1600, 1588, 1498, 1454, 1332, 1259, 810, 757 and 738; δ_H (400 MHz; $CDCl_3$): 3.40 (3 H, s), 3.88 (3 H, s), 6.79 (1 H, d, $J = 8.4$), 7.40 (1 H, d, $J = 8.4$), 7.43 (1 H, s), 7.14 (1 H, d, $J = 7.6$), 6.96 (1 H, t, $J = 8.0$), 7.18 (1 H, t, $J = 8.0$), 6.82 (1 H, d, $J = 8.0$), 7.69, (1 H d, $J = 15.6$), 7.41 (1 H d, $J = 15.6$), 8.03, (2 H, d, $J = 8.8$ Hz) and 6.97 (2 H d, $J = 8.8$). δ_C (100 MHz; $CDCl_3$): 35.5, 55.5, 113.8, 114.1, 114.4, 119.7, 122.6, 123.0, 123.9, 126.2, 127.2, 127.7, 129.0, 129.5, 130.7, 131.3, 142.9, 144.8, 147.6, 163.3 and 188.5.

(*E*)-10-Methyl-3[1-(2-naphthyl)-1-oxo-2-propen-3-yl]-10*H*-phenothiazine (4c). Yellow powder; (0.382 g, 97%); mp 162–163 °C (from EtOH); (found C 79.4, H 4.9, N 3.5, S 8.25, $C_{26}H_{19}NOS$ requires C 79.4, H 4.9, N 3.6, S 8.15%); ν_{max}(KBr)/cm^{-1} 1652, 1597, 1586, 1455, 1261, 813 and 762; δ_H (400 MHz; $CDCl_3$): 3,41 (3 H, s), 6.82 (1 H d, $J = 8.8$), 6.84 (1 H, d, $J = 8.4$), 6.97 (1 H, t, $J = 8.4$), 7.15 (1 H, d, $J = 7.7$), 7.19 (1 H, d, $J = 8.4$), 7.45 (1 H, d, $J = 8.4$), 7.49 (1 H d, $J = 1.6$), 7.56 (1 H, d, $J = 15.4$), 7.58–7.62 (2 H, m), 7.70 (1 H, d, $J = 15.4$), 7.90 (1 H dd, $J = 7.2$ and 1.6), 7.93 (1 H, dd, $J = 8.8$ and 1.6), 8.01 (1 H, dd, $J = 8.1$ and 1.6), 8.09 (1 H, dd, $J = 8.4$ and 1.6) and 8.53 (1 H, dd, $J = 8.1$ and 1.6). δ_C (100 MHz; $CDCl_3$): 35.6, 114.1, 114.4, 119.9, 122.6, 123.1, 124.0, 124.5, 126.3, 126.7, 127.3, 127.7, 127.8, 128.3, 128.5, 129.4 (two overlapping lines), 129.8, 132.6 (two overlapping lines), 135.4, 135.8, 143.7, 144.8, 147.9 and 190.1.

General procedure for the preparation of compounds 6a–d, 7d, 8, 10b–d, 11a, 12d, 13d. Hydrazine hydrate (0.145 g, 30 mmol) for compounds **6a**–**d** and **8** or methyl hydrazine (0.136 g, 30 mmol) for compounds **7d**, **10b**–**d**, **11a**, **12d** and **13d** was added to chalcones **4a**–**d** and **5d** (1.5 mmol) suspended in acetic acid (50 cm^3). The reaction mixture was heated under reflux for 5–8 h then solvent was evaporated *in vacuo*. The solid residue was washed with water and filtered off. Purification was made by column chromatography on silica using toluene as eluent and the products were re-crystallised from EtOH–*n*-hexane (2 : 1) if otherwise not stated.

3-[1-Acetyl-3-(nitrophenyl)-4,5-dihydropyrazol-5-yl]-10-methyl-10*H*-phenothiazine (6a). Yellow powder, (0.527 g, 79%); mp 155–156 °C; (found C 64. 9, H 4.6, N 12.6, S 7.2; $C_{24}H_{20}N_4O_3S$ requires C 64.85, H 4.5, N 12.6, S 7.2%).

3-[1-Acetyl-3-(4-methoxyphenyl)-4,5-dihydropyrazol-5-yl]-10-methyl-10*H*-phenothiazine (6b). Yellowish-white powder, (0.535 g 83%); mp 137–138 °C; (found C 69.95, H 5.4, N 9.8, S 7.65; $C_{25}H_{23}N_3O_2S$ requires C 69.9, H 5.4, N 9.8, S 7.5%).

3-[1-Acetyl-3-(2-naphthyl)-4,5-dihydropyrazol-5-yl]-10-methyl-10*H*-phenothiazine (6c). Reddish-white powder; (0.573 g, 85%); mp 170–171 °C; (found C 74.8, H 5.2, N 9.4, S 7.0; $C_{28}H_{23}N_3OS$ requires C 74.8, H 5.2, N 9.35, S 7.1%).

3-[1-Acetyl-3-(ferrocen-1-yl)-4,5-dihydropyrazol-5-yl]-10-methyl-10*H*-phenothiazine (6d). Brown powder; (0.571 g, 75%); mp 180–182 °C; (found C 66.2, H 5.0, N 8.3, S 6.45; $C_{28}H_{25}FeN_3OS$ requires C 66.3, H 5.0, N 8.3, S 6.3%).

3-[1-Acetyl-3-(ferrocen-1-yl)-4,5-dihydropyrazol-5-yl]-10-(*n*-butyl)-10*H*-phenothiazine (7d). Brown plates; (0.659 g, 80%); mp 93–95 °C; (found C 67.8, H 5.7, N 7.7, S 5.7; $C_{31}H_{31}FeN_3OS$ requires C 67.75, H 5.7, N 7.6, S 5.8%).

(*E*)-*N*′-[(10-Methyl-10*H*-phenothiazine-3-yl)methylene]acetohydrazide (8). This compound was separated from **6a**–**c** as yellowish-white powder; (0.044 g, 10%, from **4a** and **4b**, respectively, and 0.066 g, 15% from **4c**) mp 226–227 °C (from EtOH); (found C 64.65, H 5.1, N 14.15, S 10.95; $C_{16}H_{15}N_3OS$ requires C 64.6, H 5.1, N 14.1, S 10.8%).

***N*,*N*′-Bis[1-(*m*-nitrophenyl)ethylene]hydrazine (IIIa, X = NN=C(Me)-*m*-NO_2Ph)[21].** The mixture obtained from the reaction of **4a** was cooled in ice-water to obtain this compound as precipitated pale yellow crystals; (0.034 g, 14%); mp 198–200 °C (from EtOH);

(found C 59.1, H 4.4, N 17.0; $C_{16}H_{14}N_4O_4$ requires C 58.9, H 4.3, N 17.2%); ν_{max} (KBr)/cm^{-1} 3093, 1610, 1526, 1432, 1345, 737, 678 and 669; δ_H (500 MHz, $CDCl_3$) 2.41 (3 H, s), 7.64 (1 H, t, $J = 7.9$), 8.28 (1 H, dd, $J = 7.9$ and 1.9), 8.30 (1 H, dd, $J = 7.9$ and 1.9) and 8.75 (1 H, t, $J = 1.9$); δ_C (125 MHz, $CDCl_3$) 15.1, 124.4, 129.5, 132.4, 139.6, 149.0 and 156.8. MS (electrospray) 325.1 (ESI−), 327.1 (ESI+).

10-Methyl-3-[3-(4-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl]-10*H*-phenothiazine (10b). Yellow powder; (0.360 g, 60%); mp 152–153 °C, (found C 72.2, H 5.3, N 10.5, S 8.2; $C_{24}H_{21}N_3OS$ requires C 72.15, H 5.3, N 10.5, S 8.0%).

10-Methyl-3-[1-methyl-3-(naphthalen-2-yl)-1*H*-pyrazol-5-yl]-10*H*-phenothiazine (10c). White powder; (0.409 g, 65%), mp 240–241 °C; (found C 77.3, H 5.1, N 10.05, S 7.7; $C_{27}H_{21}N_3S$ requires C 77.3, H 5.05, N 10.0, S 7.6%).

10-Methyl-3-[1-methyl-3-(ferrocen-1-yl]-1*H*-pyrazol-5-yl)-10*H*-phenothiazine (10d). This compound was separated from **13d** as yellow powder; (0.129 g, 18%); mp 147–148 °C; (found C 68.0, H 4.9, N 8.8 S 6.7; $C_{27}H_{23}FeN_3S$ requires C 67.9, H 4.9, N 8.8, S 6.7%).

10-Methyl-3-[1-methyl-3-(3-nitrophenyl)-1*H*-pyrazol-5-yl]-10*H*-phenothiazine (11a). Ochre powder; (0.336 g, 54%); mp 176–177 °C; (found C 66.7, H 4.4, N 13.6, S 7.9; $C_{23}H_{18}N_4O_2S$ requires C 66.65, H 4.4, N 13.5, S 7.7%).

10-(*n*-Butyl)-3-[1-methyl-3-(ferrocenyl)-1*H*-pyrazol-5-yl]-10*H*-phenothiazine (12d). Red plates; (0.545 g, 70%), mp 77–79 °C (from *n*-hexane); (found C 69.4, H 5.6, N 8.1, S 6.3; $C_{30}H_{29}FeN_3S$ requires C 69.4, H 5.6, N 8.1, S 6.2%).

10-Methyl-3-[1-methyl-3-(ferrocen-1-yl)-4,5-dihydropyrazol-5-yl]-10*H*-phenothiazine (13d). This compound was isolated as major product from the reaction of **4d** with methylhydrazine. Purification made by repeated chromatography on silica with hexane–ethylacetate 4 : 1 as eluent afforded orange powder; yield 27%, mp 162–165 °C; (found C 67.7, H 5.3, N 8.8, S 6.7; $C_{27}H_{25}FeN_3S$ requires C 67.6, H 5.3, N 8.8, S 6.7%).

General procedure for the preparation of oxidation products 9a–c, 14b,c, 15b and 16–18

The corresponding precursor (**1**–**3**, **4b**,**c**, **6a**–**c**, or **14b**, 1 mmol) and $Cu(NO_3)_2 \cdot 3H_2O$ (0.726 g, 3 mmol) were dissolved in DCM (20 cm^3). The reaction mixture was sonicated for 1 h (for **1**–**3**, **4b**,**c**, **6a**–**c**) or 10 h (for **14b**) at room temperature. The reaction was monitored by TLC. After completion the reaction medium was filtered and the solid was washed with DCM (2 × 20 cm^3). After evaporation the residue obtained was purified (or after the reaction of **4b** or **14b** the mixture of **14b** and **15b** was separated) by column chromatography on silica using DCM–MeOH (15 : 1) as eluent and re-crystallised from EtOH.

3-[1-Acetyl-3-(3-nitrophenyl)-4,5-dihydropyrazol-5-yl]-10-methyl-10*H*-phenothiazine-5-oxide (9a). Yellow powder; (0.414 g 90%); 159–165 °C; (found C 62.6, H 4.4, N 12.2, S 7.1; $C_{24}H_{20}N_4O_4S$ requires C 62.6, H 4.4, N 12.2, S 7.0%).

3-[1-Acetyl-3-(4-methoxyphenyl)-4,5-dihydropyrazol-5-yl]-10-methyl-10*H*-phenothiazine-5-oxide (9b). White powder; (0.423 g, 95%); 214–217 °C; (found C 67.4, H 5.2, N 9.5, S 7.2; $C_{25}H_{23}N_3O_3S$ requires C 67.4, H 5.2, N 9.4, S 7.2%).

3-[1-Acetyl-3-(2-naphthyl)-4,5-dihydropyrazol-5-yl]-10-methyl-10*H*-phenothiazine-5-oxide (9c). White powder; (0.428 g, 92%); 156–158 °C; (found C 72.3, H 4.9, N 9.05, S 6.8; $C_{28}H_{23}N_3O_2S$ requires C 72.2, H 5.0, N 9.0, S 6.9%).

(*E*)-10-Methyl-3-[1-(3-nitrophenyl)-1-oxo-2-propen-3-yl]-10*H*-phenothiazine-5-oxide (14a). Yellow powder; (0.348 g, 86%); 201–204 °C; (found C 65.2, H 4.1, N 6.8, S 7.9; $C_{22}H_{16}N_2O_4S$ requires C 65.3, H 4.0, N 6.9, S 7.9). MS (electrospray) 405.1 (ESI+).

(*E*)-10-Methyl-3-[1-(4-methoxyphenyl)-1-oxo-2-propen-3-yl]-10*H*-phenothiazine-5-oxide (14b). Yellow powder; (0.272 g, 70%); 237–241 °C; (found C 80.05, H 4.8, N 3.8, S 8.1; $C_{23}H_{19}NO_3S$ requires C 70.9, H 4.9, N 3.6, S 8.2). MS (electrospray) 390.2 (ESI+).

(*E*)-10-Methyl-3[1-(2-naphthyl)-1-oxo-2-propen-3-yl]-10*H*-phenothiazine-5-oxide (14c). White powder; (0.327 g, 80%); 225–226 °C; (found C 76.45, H 4.65, N 3.3, S 7.8; $C_{26}H_{19}NO_2S$ requires C 76.3, H 4.7, N 3.4, S 7.8%).

10-Methyl-3[1-(4-metoxyphenyl)-1-oxo-oxiran-2-yl]-10*H*-phenothiazine-5-oxide (15b). White powder, (0.032 g, 8% obtained by treatment of **4b** for 1 h; 0.345 g, 85% obtained by treatment of **14b** for 10 h), 198–201 °C; found C 68.3, H 4. 6, N 3.35, S 8.05; $C_{23}H_{19}NO_4S$ requires C 68.1, H 4.7, N 3.45, S 7.9%).

10-Methyl-10*H*-phenothiazine-5-oxide (16). White powder; (0.217 g, 95%), mp 187–189 °C [lit.: 185–187 °C, ref. 15*b*]; (found C 67.9, H 5.95, N 6.1, S 14.1; $C_{13}H_{11}NOS$ requires C 68.1, H 4.8, N 6.1, S 14.0%).

3-Formyl-10-methyl-10*H*-phenothiazine-5-oxide (17). Yellow powder; (0.232 g, 90%); mp 205–207 °C; [lit.: 207–208 °C, ref. 15*f*] (found C 65.5, H 4.2, N 5.35, S 12.6; $C_{14}H_{11}NO_2S$ requires C 65.35, H 4.3, N 5.4, S 12.5%).

3,7-Diacetyl-10-ethyl-10*H*-phenothiazine-5-oxide, (18). Yellow powder; (0.278 g, 85%); mp 259–262 °C; (found C 65.8, H 4.2, N 4.5, S 9.95; $C_{18}H_{17}NO_3S$ requires C 66.0, H 4.3, N 4.3, S 9.8%).

Conclusions

Besides affording a series of novel heterocyclic derivatives including sulfoxides with potential pharmacophoric units the simple reactions described and theoretically modelled in this paper may contribute to a better understanding of general substituent-dependent reactivity of enones and pyrazolines in cyclisations and redox reactions. The energetic data and reactivity indices obtained by high-level DFT calculations using adequate solvent model, can be taken into account to set up procedures for analogous transformations of aromatic enones. Finally, the new compounds described in this contribution deserve a multilateral investigation, both as biologically active substances, and as potential scintillators in radiation-detecting devices.

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