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Highly-substituted pyrazoles and pyridazines by MIRC reactions of hydrazone anions and nitrobutadienic fragments

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ABSTRACT

In prosecution of the synthetic exploitation of nitrobutadienes deriving from the initial ring-opening of nitrothiophenes, their multifaceted behavior finds a further clear-cut example in their Michael-type acceptor reactivity toward the anions of α-oxohydrazones. Thus, depending on the starting diene, new poly-functionalized pyrazoles are obtained. Furthermore, most interestingly, in one occasion a dichotomy has been observed, depending on the nature of the Michael-type donor, leading with complete selectivity to either 5-member or 6-member *N*-heterocycles. The outcome encompasses motifs for both mechanistic and synthetic interest, for example, in the field of heterocycles endowed with possible pharmacological/biological activity.

The ring-opening of 3,4-dinitrothiophene,[1] 2-nitrothiophene,[2] and variously functionalized 3-nitrothiophenes[3] has been for our research group a valuable source of a pool of nitrobutadienic building-blocks which, differing by typology, number and/or position of the substituents, exhibit a multi-faceted set of properties,[4] not always predictable on the grounds of the well-known and much more exploited behavior of the isolated nitrovinyl moiety.[5]

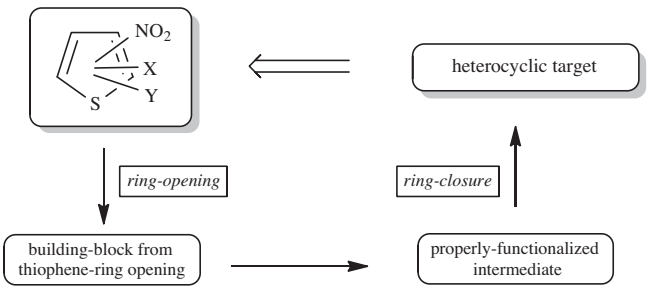
As an example, the concurrence of an arylnitroethenyl moiety and a conjugated double bond has led to promising pharmacological results regarding 2-nitro-1,3-dienes in the field of cancer therapy.[6]

In particular, one rewarding application of such building-blocks hinges upon the possibility to assemble heterocyclic structures in a highly atom-economic way: thus, starting from a substituted thiophene, the whole process can be envisaged as a ring-opening/ring-closing protocol, sometimes involving a ring expansion, which preserves all of the four original thiophenic carbons (Scheme 1).[7]

For such a goal, we became more recently interested in reactions that allow the construction of the final heterocycle after an initial intermolecular Michael-type addition on the nitrovinylic moiety of our nitrobutadienes, a synthetic approach sometimes indicated as a MIRC process.[8]

In the vast field of heterocycles, one surely appealing target is the construction of the pyrazole nucleus, whose outstanding interest is testified by the impressive number of publications on the subject;[9] this is because pyrazole derivatives exhibit a wide range of biological properties, as represented, for instance, by anti-hyperglycemic, anti-inflammatory, anti-obesity, or antitumor activities.[10]

Among the plethora of more or less classic synthetic methods,[11] the addition of hydrazones or hydrazone anions to nitrovinylic systems has been recently described as an initial intermolecular Michael-type process eventually providing a useful regioselective access to 1,3,4- or 1,3,5-substituted pyrazoles.[12] With the aim of exploring and broadening the utility of this kind of approach, also by decorating the heterocycle with functional groups which could be of value in the perspective of further elaboration, we decided to apply to different nitrobutadienic systems (**1–4**, Chart 1)[13] the



Scheme 1. Ring-opening/ring-closing protocol for heterocyclic synthesis from nitrothiophenes.

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reaction with the α-COZ-substituted hydrazones **5a–d** (Z = NMe_2,[16] OBu^t,[16] Ph,[17] and Me,[17] respectively), easily obtainable by a methodology developed some years ago by some of us. The coupling, whose expected outcome is depicted in Scheme 2, should allow the synthesis of polysubstituted pyrazoles bearing, in particular, a versatile 3-COZ functionality.[18]

The preliminary results herein (synthetically collected in the Table at the end of the discussion for an easy, overall view) enlighten the general fulfillment of our expectations, guaranteeing for the success of a synthetic approach which is furthermore accompanied by some unexpected, likewise rewarding, outcomes: the latter surely contribute in turn to further enlarge the range of heterocycles accessible from our building-blocks.

Typically,[19] a THF solution of the nitrobutadiene was added to a molar equivalent of the preformed (Bu^tOK) hydrazone anion in THF at −78 °C. After disappearance of the diene (TLC), trifluoroacetic acid (TFA, 5 mol equiv) was added and the system left to react for some time before allowing to reach room temperature for final work-up.

The relevant results described below are strongly dependent on the nitrobutadiene and, in some measure, on the hydrazone.

Nitrobutadiene **1**, which was tested first, behaves, in the initial step of the proposed mechanism (Scheme 3), as a plain nitrovinylic Michael-type acceptor, and the conjugate addition of the hydrazone anion (step i) is followed by cyclization of the resulting nitronate onto the electrophilic nitrogen of the diazo group (step ii). After the acidic quenching (step iii),[12a] the elimination of nitrous acid (step iv) followed by an oxidative aromatization (step v) (the oxidizing agent being most likely represented by the just eliminated nitrous acid) eventually lead to the expected[12] pyrazoles **6a–d**.

As reported in Scheme 3, the yield is satisfactory when Z = NMe_2 and OBu^t, still acceptable in the case of Z = Ph, but unfortunately drops to a disappointing value when Z = Me.

The postulated pyrazolidinic intermediate **8** was actually isolated in a few cases,[20] confirming the occurrence of an apparently unfavored 5-*endo-trig* reversible cyclization process, which is effectively driven ahead by the strong acidic quencher (step iii).

For the anionic Michael adduct **7** it cannot be in principle excluded the concurrence of a charge-transfer equilibration between the NO_2-bound and the COZ-bound carbons (cf. the equilibration between **13** and **13′** or **13″** further in the text), that could assume more importance depending on the acidity of the proton α to COZ. Actually, yield-reducing competitive pathways could well play a role, contributing to explain the less satisfactory results observed when Z is phenyl or methyl.

For nitrobutadiene **2**, where a much more electron-withdrawing sulfonyl group replaces the sulfanyl one, strongly increasing the electrophilicity of the nitrovinyl moiety, a preliminary test with hydrazone **5a** disappointingly led to a rather complex mixture of products, from which only the (*E*)-*N*,*N*-dimethyl-4-(4-methylstyryl)-1-*p*-tolyl-1*H*-pyrazole-3-carboxamide (**9a**, Scheme 4) could be isolated and identified, although in very modest yields (13%). A search for more suitable experimental conditions is under way. It seems anyway remarkable that **9a** presents only three ring substituents: as a matter of fact, two successive β-elimination processes

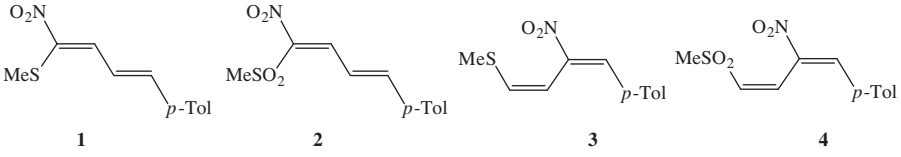
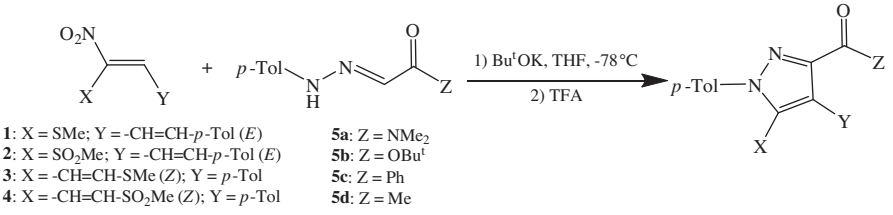
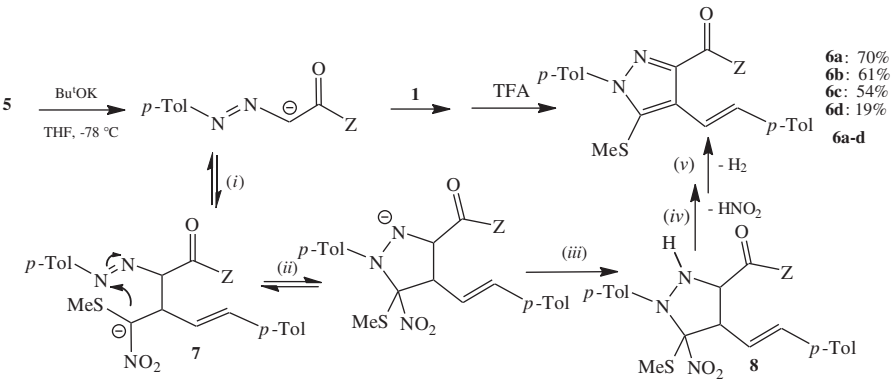


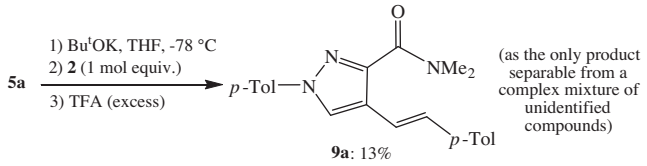
Chart 1. Nitrobutadienes employed in the reaction of Scheme 2.



Scheme 2. Pyrazoles expected from the reactions between nitrobutadienes **1–4** and α-oxo-hydrazones **5a–d** under basic conditions, followed by acidic quenching.[12]



Scheme 3. Formation of pyrazoles **6a–d**, according to the mechanistic rationalization advanced in ref. 12a.



Scheme 4. Trisubstituted pyrazole **9a** from the reaction of **5a**-anion and nitrobutadiene **2**.

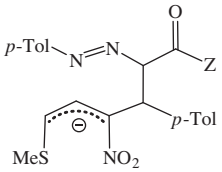


Chart 2. Charge delocalization in the intermediate nitronate from the reaction between **3** and **5**.

most likely occur, the loss of methanesulfinic acid ($MeSO_2H$) formally 'replacing' the final oxidative step of Scheme 3.

The expected cyclization to pyrazoles is smoothly obtained, instead, with nitrobutadiene **3**, whereby two main products (**10** and **10′**: Scheme 5) can be isolated from the final mixture, as a result of a partial *cis* to *trans* isomerization at the remaining double bond of the original nitrodiene array, the presumably more stable *trans* isomer **10′** generally overcoming the *cis*-isomer **10**.

A possible rationale for such a configurational scrambling may be searched in the involvement of the double bond undergoing isomerization in the delocalization of the negative charge of the intermediate nitronate (Chart 2), although its timing is presently under closer investigation.

The isolation of much unreacted materials (ca. 44% of both diene and hydrazone) from the reaction with α-hydrazonoketone **5c** under the usual conditions, prompted us to perform preliminary attempts in search for optimization. While the increase of the reaction time led to only minor variations in the overall outcome, it was found that the rising of the temperature of steps 2 and 3 (Scheme 5) to -30 °C almost doubles the yield (50% for the *cis*/*trans* mixture; 60% with respect to the reacted diene). Interestingly enough, the diastereomeric ratio is, in this case, significantly in favor of the *cis* isomer (ca. 70:30): a result which surely hinges on the timing of the isomerization.

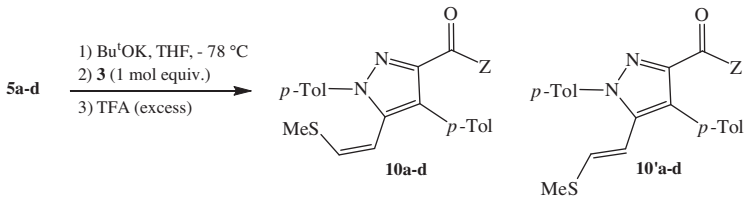
To our surprise, the sulfonyl-activated nitrobutadiene **4** exhibits a much more interesting dichotomic behavior (Scheme 6), depending on the nature of Z in the COZ moiety of the hydrazone. As a matter of fact, with the anions of α-hydrazonoamide **5a** and of α-hydrazonoester **5b**, pyrazoles (**11a** and **11b**, respectively) are obtained in good yields, herein characterized by a complete inversion of the exocyclic C=C double-bond configuration; on the other hand, quite unexpectedly, from the reactions with the anions of α-hydrazonoketones **5c**,**d** tetrahydropyridazines (**12c** and **12d**, respectively) are formed (Scheme 6), almost exclusively as single diastereoisomers out of the three possible ones, whose configuration has not been defined yet. Interestingly enough, the chemoselectivity is complete, no significant amounts of **12a**,**b** or of **11c**,**d** having been detected under the conditions employed.

In order to understand the rationale of such a dichotomy, we should consider the fate of the nitronate **13** (Scheme 7) deriving from the attack of the hydrazone anion onto the nitrovinylic moiety of **4**. First of all, such a carbanion appears more stabilized than in all of the previous cases examined, as it effectively delocalizes its charge not only on the nitrogroup, but also on the sulfonyl vinyl moiety. Such an occurrence reasonably allows to the anion a lifetime long enough so that, as an alternative to the expected unfavored 5-*endo*-*trig* cyclization to pyrazole, it could also equilibrate with **13′** or **13″** (Scheme 7) by transfer of the negative charge to the position adjacent to the COZ moiety. The new anion (**13′** should be the preferred structure, on the grounds of the alleged[7b,d,e] higher stability of a nitrovinyl with respect to a sulfonylvinyl moiety, although **13″** cannot be excluded) seems to have definitely more chance to exist when the carbonyl involved is that of a ketone, rather than that of an amide or of an ester, due to the higher ability of the former to contribute to the stabilization of an adjacent negative charge.

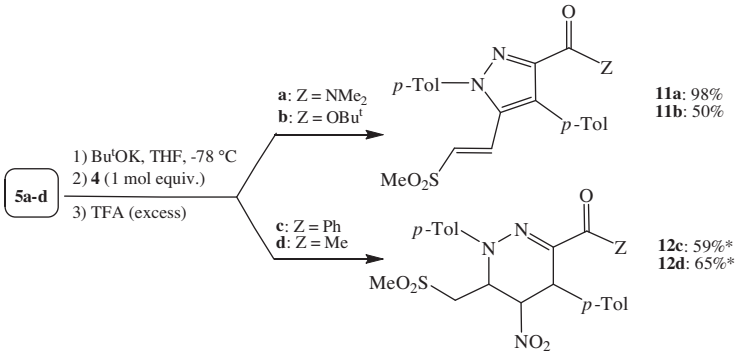
On the **13′** (or **13″**) anion, an electronically-inverted cyclization process becomes possible, whereby a nucleophilic hydrazone anion couples with an electrophilic nitrovinyl (or sulfonylvinyl) moiety, easily providing a six-membered ring: thus, a 6-*endo* or, possibly, a 6-*exo* intramolecular cyclization ways are in principle recognizable, leading to the same final outcome.

A goal of undeniable significance from a preparative point of view is represented by the almost quantitative formation of **12c**,**d** when performing the whole process at 0 °C, under otherwise identical experimental conditions (see Scheme 6): a result which can be tentatively attributed to a more effective completion of the overall process, with concurrent depletion of unidentified side materials. It is worth mentioning that, as experimentally verified, within the dichotomy of Scheme 6, a temperature increase does not seem to either influence the dichotomy itself, or favor the formation of for example, pyrazole **11b**.

A different attempt to drive the system toward the 6-member heterocycle hinges upon the possibility to affect the competition set up at the level of the intermediate anion in Scheme 7 by accelerating the proton transfer from **13** to **13′** (or **13″**), for example in a protic solvent. As a matter of fact, the treatment of an equimolar **4** + **5** mixture with DBU (1 mol equiv) in refluxing ethanol[21] effectively leads to the 2,3-dihydropyridazino moiety **14**, independently on the nature of **5** (Scheme 8 and Table 1). The corresponding tetrahydropyridazines **12** seem the most likely precursors, which

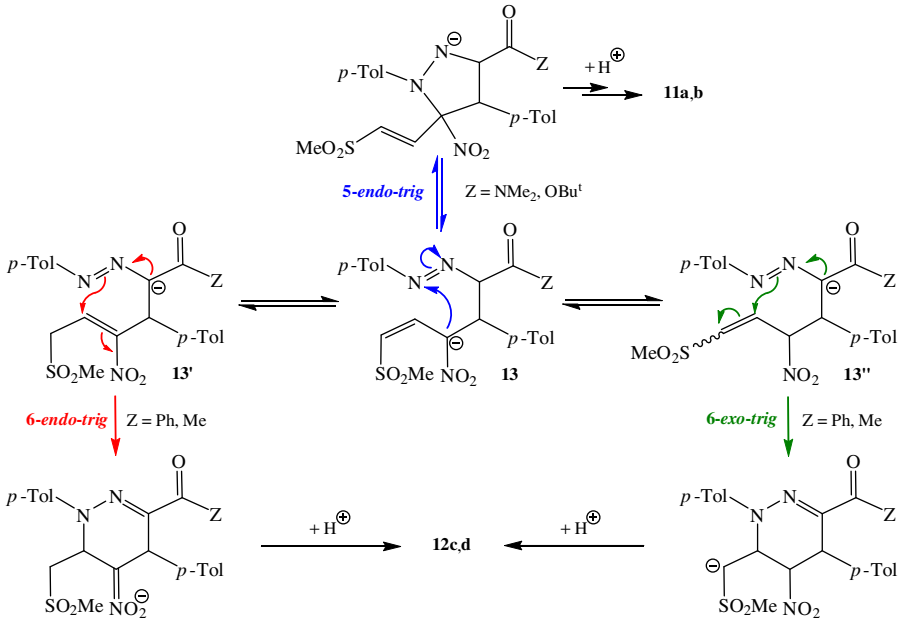


Scheme 5. Results obtained in the reactions of **5a–d** anions with nitrobutadiene **3**.

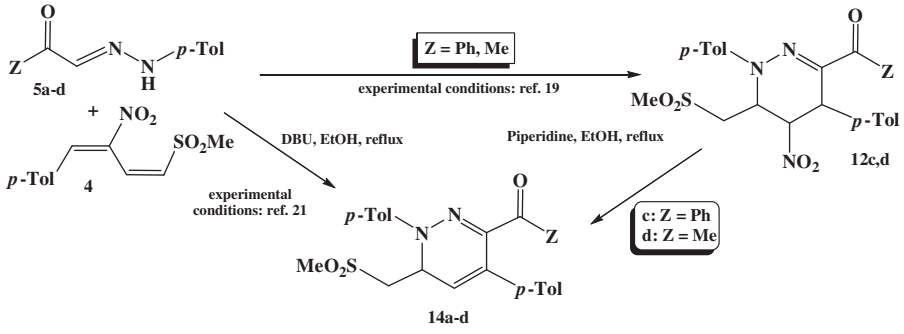


* A quite rewarding quantitative yield is obtained when salification (step1), coupling (step 2), and quenching (step 3) are carried out at 0 °C, under otherwise identical experimental conditions.

Scheme 6. Dichotomy in the reaction between **4** and **5**, sharply dependent on the structure of **5**.



Scheme 7. A proposed rationale behind the observed dichotomic behavior of nitrobutadiene **4**.



Scheme 8. Dihydro- and tetrahydropyridazines from reactions of **5** and **4**.

would undergo β-elimination of HNO_2 in the basic medium to afford the final conjugated azadiene. To confirm this very last point, we have also successfully verified the feasibility of HNO_2 elimination from **12c**,**d** to obtain **14c**,**d** with an alternative two-step route: the use of piperidine in refluxing ethanol leading to an almost quantitative smooth conversion in both cases (see Scheme 8).

In conclusion we feel that the preliminary results reported herein represent a further significant example of the very interesting behavior, from the standpoint of both synthetic and mechanistic aspects, of the nitrosubstituted conjugated butadienic building-blocks of Chart 1. Once again,[7] their synthetic versatility is mirrored by the dependence of the final outcome on structural

Table 1
Overview of the main results obtained from the reactions of nitrobutadienes **1**, **3**, and **4** with hydrazones **5a–d** under the conditions of ref.19, if not differently specified

Michael Acceptor \ Hydrazone	**5a**	**5b**	**5c**	**5d**
1	**6a**: 70%	**6b**: 61%	**6c**: 54%	**6d**: 19%
3	**10a+10'a**: 66%	**10b+10'b**: 52%	**10c+10'c**: 50% (60%)[a]	**10d+10'd**: 74%
4	**11a**: 98%	**11b**: 50%	**12c**: 98%[b]	**12d**: 98%[b]
	14a:71%[c]	**14b**: 80%[c]	**14c**: 72%[c]	**14d**: 81%[c]

[a]Reaction carried out at −30 °C (see text); the yield in parentheses refers to the reacted substrate.
[b]Reaction carried out at 0 °C (see Scheme 6).
[c]Experimental conditions: see ref. 21.

and/or electronic factors. Herein, an additional variable is represented by the Michael-type donors, whose carbonyl (COZ) moiety causes in turn, at least in one case (cf. Scheme 6), an appealing dichotomic behavior, definitely enriching the pool of heterocycles which can be assembled via the overall ring-opening/ring-closing protocol of Scheme 1. Finally, the same COZ functionality characterizes all of the heterocycles formed as a potentially powerful tool for further manipulation.[18]

Acknowledgments

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13. Methyl[(1*Z*,3*E*)-1-nitro-4-(*p*-tolyl)buta-1,3-dienyl]sulfide (**1**) derives from the initial ring-opening of 2-nitrothiophene;[2] (1*E*,3*Z*)-4-(methylsulfanyl)-2-nitro-1-(*p*-tolyl)-1,3-butadiene (**3**) derives from the initial ring-opening of 3-nitrothiophene;[3] methyl[(1*Z*,3*E*)-1-nitro-4-(*p*-tolyl)buta-1,3-dienyl]sulfone (**2**)[14] and (1*E*,3*Z*)-4-(methylsulfonyl)-2-nitro-1-(*p*-tolyl)-1,3-butadiene (**4**)[15] have been obtained by oxidation with MCPBA of **1** and **3**, 'respectively'.
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19. *Typical procedure for the reaction of the nitrobutadienes* ***1-4*** *with the anions of α-oxohydrazones* ***5a-d*** *in THF*. In a flask, the appropriate hydrazone (**5**, 0.2 mmol) was dissolved in THF (2.2 mL) under Argon at −78 °C, and Bu^{t}OK (0.022 g, 0.2 mmol) was added as a solid. After 30 min under magnetic stirring, a solution of the nitrobutadiene (0.2 mmol) in THF (2.2 mL) was added, and the reaction mixture kept at −78 °C for 1–2 h. The reaction was then quenched with TFA (0.114 g, 0.074 mL, 1 mmol), maintained at −78 °C for additional 2 h, and finally allowed to reach room temperature. The mixture was then poured into water, extracted with ethyl acetate, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography using hexane/ethyl acetate mixtures.

*(E)-N,N-Dimethyl-4-(4-methylstyryl)-5-(methylthio)-1-p-tolyl-1H-pyrazole-3-carboxamide (**6a**).* Yellow solid, mp 138–139 °C (light petroleum); ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s), 2.36 (3H, s), 2.43 (3H, s), 3.04 (3H, s), 3.16 (3H, s), 7.13–7.18 (4H, m), 7.29 (2H, d, *J* 8.1 Hz), 7.41 (2H, d, *J* 8.1 Hz), 7.48 (2H, d, *J* 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 18.89, 21.22, 21.25, 35.16, 38.63, 116.58, 122.73, 125.45, 126.36, 129.33, 129.46, 130.46, 133.76, 134.88, 136.64, 137.54, 138.53, 144.77, 165.51. GC–MS: R_t 19.19, *m/z* 391(100)[M$^+$], 344(11), 331(23), 273(12), 154(15), 105(19), 91(12), 72(31), 65(11), 32(13).

*(E)-tert-Butyl 4-(4-methylstyryl)-5-(methylthio)-1-p-tolyl-1H-pyrazole-3-carboxylate (**6b**).* Yellow solid, mp 130–131 °C (light petroleum); ^{1}H NMR ($CDCl_3$) δ 1.64 (9H, s), 2.11 (3H, s), 2.37 (3H, s), 2.43 (3H, s), 7.18 (2H, d, *J* 9.0 Hz), 7.29 (2H, d, *J* 9.0 Hz), 7.46 (4H, two overlapped d, *J* 9.0 Hz), 7.52 (2H, AB system, *J* 18.6 Hz); ^{13}C NMR ($CDCl_3$) δ 18.37, 21.29 (two isochronous carbons), 28.33, 82.06, 117.36, 125.01, 126.02, 126.36, 129.37 (two couples of isochronous carbons), 131.99, 133.89, 135.02, 136.65, 137.55, 138.93, 142.46, 161.96. MS (ESI): *m/z* 421 [M+H]$^+$, 443 [M+Na]$^+$, 459 [M+K]$^+$.

*(E)-3-Benzoyl-(4-methylstyryl)-5-(methylthio)-1-p-tolyl-1H-pyrazole (**6c**).* Yellow solid, mp 121–122 °C (light petroleum); ^{1}H NMR ($CDCl_3$) δ 2.18 (3H, s), 2.36 (3H, s), 2.44 (3H, s), 7.17 (2H, d, *J* 9.0 Hz), 7.32 (2H, d, *J* 9.0 Hz), 7.42–7.59 (9H, m), 8.13–8.19 (2H, m); ^{13}C NMR ($CDCl_3$) δ 18.43, 21.29 (two isochronous carbons), 117.07, 125.80, 126.10, 126.52, 128.14, 129.30, 129.53, 130.73, 132.34, 132.79, 134.29, 134.95, 136.66, 137.59, 137.71, 139.03, 147.35, 189.75. GC–MS: R_t 13.48, *m/z* 424(79) [M$^+$], 105(100), 77(55).

*(E)-3-Acetyl-4-(4-methylstyryl)-5-(methylthio)-1-p-tolyl-1H-pyrazole (**6d**).* Yellow solid, mp 132–133 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s), 2.37 (3H, s), 2.46 (3H, s), 2.65 (3H, s), 7.18 (2H, d, *J* 7.8 Hz), 7.34 (2H, d, *J* 8.1 Hz), 7.45–7.51 (4H, two partly overlapped d, *J* 8.1 and 8.4 Hz), 7.67 (2H, AB system, *J* 17.1 Hz); ^{13}C NMR ($CDCl_3$) δ 18.36, 21.30 (two isochronous carbons), 27.70, 117.27, 124.79, 125.82, 126.58, 129.31, 129.60, 132.66, 134.58, 135.04, 136.66, 137.60, 139.18, 147.48, 195.50. GC–MS: R_t 6.60, *m/z* 362(100) [M$^+$], 305(28), 272(19), 154(11), 91(16), 65(17), 43(44).

*(E)-N,N-Dimethyl-4-(4-methylstyryl)-1-p-tolyl-1H-pyrazole-3-carboxamide (**9a**).* The compound was obtained in very small quantities and could not be fully characterized;^{1}H NMR ($CDCl_3$) δ 2.34 (3H, s), 2.40 (3H, s), 3.17 (3H, s), 3.22 (3H, s), 6.88 (1H, d, *J* 16.5 Hz), 7.12-7.20 (3H, two partly overlapped d, *J* 8.1 and 16.5 Hz), 7.26 (2H, d, *J* 8.1 Hz), 7.37 (2H, d, *J* 8.1 Hz), 7.59 (2H, d, *J* 8.4 Hz), 8.08 (1H, s).

*(Z)-N,N-Dimethyl-5-(2-(methylthio)vinyl)-1,4-di-p-tolyl-1H-pyrazole-3-carboxamide (**10a**).* White solid, mp 195.6–196.8 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.10 (3H, s), 2.36 (3H, s), 2.40 (3H, s), 2.84 (3H, s), 3.03 (3H, s), 6.25 (1H, d, *J* 10.2 Hz), 6.31 (1H, d, *J* 9.6 Hz), 7.15 (2H, d, *J* 7.9 Hz), 7.23 (2H, d, *J* 8.1 Hz), 7.30 (2H, d, *J* 8.1 Hz), 7.42 (2H, d, *J* 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 17.49, 21.17, 21.30, 34.87, 38.42, 113.58, 121.08, 124.63, 128.37, 129.10, 129.15, 129.36, 135.72, 136.47, 136.90, 137.33, 137.69, 145.73, 165.56. GC-MS: R_t 7.08, *m/z* 391(64) [M$^{+\bullet}$], 334(14), 319(18), 305(27), 299(100), 287(16), 273(32), 256(15), 190(20), 172(19), 164(10), 91(22), 72(29), 65(19).

*(E)-N,N-Dimethyl-5-(2-(methylthio)vinyl)-1,4-di-p-tolyl-1H-pyrazole-3-carboxamide (**10′a**).* The compound was obtained in very small quantities and could not be fully characterized. ^{1}H NMR ($CDCl_3$) δ 2.15 (3H, s), 2.37 (3H, s), 2.42 (3H, s), 2.88 (3H, s), 2.99 (3H, s), 6.02 (1H, d, *J* 15.6 Hz), 6.33 (1H, d, *J* 15.6 Hz), 7.13–7.43 (8H, m).

*(Z)- and (E)-tert-Butyl 5-(2-(methylthio)vinyl)-1,4-di-p-tolyl-1H-pyrazole-3-carboxylate (**10b** and **10′b**, respectively).* The ^{1}H NMR analysis revealed that the crude isolated by chromatography was a 54:46 mixture of *Z*/*E* isomers. All the eluents tried for separation were unsuccessful. ^{1}H NMR ($CDCl_3$) δ 1.34 (9H *E*, s), 1.42 (9H *Z*, s), 2.07 (3H *Z*, s), 2.10 (3H *E*, s), 2.37 (3H *Z*, s), 2.40 (3H *Z* + 3H *E*, s), 2.42 (3H *E*, s), 5.91 (1H *E*, d, *J* 15.6 Hz), 6.13 (1H *Z*, d, *J* 10.2 Hz), 6.16 (1H *E*, d, *J* 15.6 Hz), 6.23 (1H *Z*, d, *J* 10.5 Hz), 7.13–7.30 (6H *E* + 6H *Z*, m), 7.38–7.47 (2H *E* + 2H *Z*, m).

*(Z)- and (E)-(5-(2-(Methylthio)vinyl)-1,4-di-p-tolyl-1H-pyrazol-3-yl)(phenyl) methanone (**10c** and **10′c**, respectively).* The ^{1}H NMR analysis revealed that the crude isolated by chromatography was a 32:68 mixture of *Z*/*E* isomers. All the eluents tried for separation were unsuccessful. ^{1}H NMR ($CDCl_3$) δ 2.10 (3H *Z*, s), 2.12 (3H *E*, s), 2.35 (3H *Z*, s), 2.38 (3H *E*, s), 2.41 (3H *Z*, s), 2.44 (3H *E*, s), 6.01 (1H *E*, d, *J* 15.6 Hz), 6.24 (1H *Z*, d, *J* 10.2 Hz), 6.28 (1H *E*, d, *J* 15.6 Hz), 6.31 (1H *Z*, d, *J* 10.2 Hz), 7.13–7.60 (11H *E* + 11H *Z*, m), 8.12–8.17 (2H *E* + 2H *Z*, m). GC–MS: R_t 9.74, *m/z* 424(5) [M$^+$], 377(7), 299(6), 188(12), 105(100), 91(5), 77(44), 65(5), 51(9) and R_t 9.93, *m/z* 424(4) [M$^{+\bullet}$], 377(4), 299(9), 188(9), 105(100), 91(5), 77(44), 65(8), 51(4).

*(Z)- and (E)-1-(5-(2-(Methylthio)vinyl)-1,4-di-p-tolyl-1H-pyrazol-3-yl)ethanone (**10d** and **10′d**, respectively).* The ^{1}H NMR analysis revealed that the crude isolated by chromatography was a 36:64 mixture of *Z*/*E* isomers. All the eluents tried for separation were unsuccessful. ^{1}H NMR ($CDCl_3$) δ 2.07 (3H *Z*, s), 2.08 (3H *E*, s), 2.37 (3H *Z*, s), 2.39 (3H *E*, s), 2.42 (3H *Z*, s), 2.45 (3H *E*, s), 2.54 (3H *E*, s), 2.60 (3H *Z*, s), 5.92 (1H *E*, d, *J* 15.6 Hz), 6.16 (1H *Z*, d, *J* 10.5 Hz), 6.17 (1H *E*, d, *J* 15.9 Hz), 6.26 (1H *Z*, d, *J* 10.5 Hz), 7.13–7.47 (8H *E* + 8H *Z*, m).

*(E)-N,N-Dimethyl-5-[2-(methylsulfonyl)vinyl]-1,4-di-p-tolyl-1H-pyrazole-3-carboxamide (**11a**).* Beige solid, mp 193–194 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.39 (3H, s), 2.44 (3H, s), 2.80 (3H, s), 2.90 (3H, s), 2.99 (3H, s), 6.31 (1 H, d, *J* 15.6 Hz), 7.22–7.30 (4H, m), 7.34 (4H, app. s), 7.43 (1H, d, *J* 15.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.19, 21.28, 34.92, 38.44, 42.79, 124.75, 125.71, 127.35, 128.75, 129.23, 129.27, 129.80, 130.22, 132.36, 135.93, 138.34, 139.75, 146.59, 164.05. GC-MS: R_t 9.24, *m/z* 423(34) [M$^+$], 366(21), 344(19), 299(99), 287(24), 273(100), 256(36), 242(16), 212(10), 164(10), 142(30), 128(21), 115(14), 106(12), 91(51), 77(16), 72(71), 65(52).

*(E)-tert-Butyl 5-[2-(methylsulfonyl)vinyl]-1,4-di-p-tolyl-1H-pyrazole-3-carboxylate (**11b**).* Orange solid, mp 144–145 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.34 (9H, s), 2.42 (3H, s), 2.44 (3H, s), 2.75 (3H, s), 6.12 (1H, d, *J* 15.9 Hz), 7.18 (2H, d, *J* 8.4 Hz), 7.26 (2H, d, *J* 7.8 Hz), 7.29–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.50, 21.60, 28.06, 43.02, 82.15, 126.11, 127.46, 128.83, 129.51, 129.61, 129.82, 130.45, 134.14, 136.02, 138.34, 140.24, 143.93, 161.13 (two carbons are accidentally isochronous). MS (ESI): *m/z* 475 $[M+Na]^+$, 491 $[M+K]^+$.

*3-Benzoyl-6-(methylsulfonylmethyl)-5-nitro-1,4-di-p-tolyl-1,4,5,6-tetrahydropyridazine (**12c**).* Yellow solid, mp 121–123 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.26 (3H, s), 2.34 (3H, s), 2.73 (3H, s), 3.30–3.44 (2H, two partly overlapped dd, *J* 5.1, 5.7 and 15.0 Hz), 4.96 (1H, d, *J* 9.9 Hz), 5.35 (1H, dd, *J* 3.9 and 9.9 Hz), 5.45 (1H, app. q), 7.10 (2H, d, *J* 8.1 Hz), 7.17 (2H, d, *J* 8.1 Hz), 7.21 (2H, d, *J* 8.7 Hz), 7.31 (2H, d, *J* 8.7 Hz), 7.37–7.47 (2H, m), 7.50–7.56 (1H, m), 7.93–7.97 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.72, 21.07, 40.16, 42.42, 49.81, 51.95, 86.06, 117.94, 127.81, 128.02, 130.20, 130.32, 130.38, 132.57, 132.75, 134.45, 136.25, 138.32, 141.16, 142.70, 188.91. MS (ESI): *m/z* 506 $[M+H]^+$.

*3-Acetyl-6-(methylsulfonylmethyl)-5-nitro-1,4-di-p-tolyl-1,4,5,6-tetrahydropyridazine (**12d**).* Yellow solid, mp 79–80 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s), 2.38 (6H, s), 2.77 (3H, s), 3.28 (1H, dd, *J* 6.0 and 14.7 Hz), 3.39 (1H, dd, *J* 5.1 and 14.7 Hz), 4.73 (1H, d, *J* 7.7 Hz), 5.14 (1H, app. q), 5.28 (1H, dd, *J* 3.9 and 7.7 Hz), 7.02 (2H, d, *J* 8.1 Hz), 7.13 (2H, d, *J* 7.8 Hz), 7.26 (2H, d, *J* 8.1 Hz), 7.37 (2H, d, *J* 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.86, 21.11, 24.90, 39.39, 42.44, 49.15, 51.66, 85.39, 119.85, 127.50, 130.15, 130.28, 133.69, 135.45, 138.15, 141.12, 141.99, 195.06. MS (ESI): *m/z* 444 $[M+H]^+$.

20. Preliminary analytical data for the pyrazolidine **8a**, isolated as a secondary product, after acidic quenching, from the reaction of hydrazone **5a** and nitrobutadiene **1′** (Scheme 2 and 1: Y = CH=CH-p-anisyl):
*(E)-4-(4-Methoxystyryl)-N,N-dimethyl-5-(methylthio)-5-nitro-1-(p-tolyl)pyrazolidine-3-carboxamide (**8a**)*: ^{1}H NMR ($CDCl_3$): δ 2.25 (3H, s), 2.39 (3H, s), 2.93 (3H, s), 3.14 (3H, s), 3.80 (3H, s), 4.58 (1H, t, *J* 9.3 Hz), 5.71 (1H, d, *J* 9.6 Hz), 6.14 (1H, dd, *J* 9.1, 15.8 Hz), 6.62 (1H, d, *J* 15.9 Hz), 6.84 (2H, d, *J* 8.7 Hz), 7.22 (2H, d, *J* 8.1 Hz), 7.31 (2H, d, *J* 8.7 Hz), 7.59 (2H, d, *J* 8.3 Hz). MS (ESI): *m/z* 457 $[M+H]^+$.
21. *Typical procedure for the reaction of nitrobutadiene **4** with the anions of α-oxohydrazones **5a–d** in EtOH.* In a flask, **4** (0.05 g) and the appropriate **5** (1 mol equiv) were dissolved in EtOH (2.5 mL) and DBU (1 mol equiv) was added. The solution was refluxed for 1 h under magnetic stirring, and the end of reaction checked by TLC. The final mixture was diluted with ethyl acetate, washed with water, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude residue was purified by column chromatography using hexane/ethyl acetate mixtures.

*N,N-dimethyl-6-(methylsulfonylmethyl)-1,4-di-p-tolyl-1,6-dihydropyridazine-3-carboxamide (**14a**).* Orange solid, mp 138–139 °C (dichloromethane/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 2.34 (3H, s), 2.95 (3H, s), 2.97 (3H, s), 3.18 (3H, s), 3.23 (1H, dd, *J* 2.6 and 13.4 Hz), 3.66 (1H, dd, *J* 9.8 and 13.4 Hz), 5.72 (1H, ddd, *J* 2.7, 7.2 and 9.9 Hz), 6.24 (1H, d, *J* 6.9 Hz), 7.14 (4H, app. s), 7.18 (2H, d, *J* 8.4 Hz), 7.32 (2H, d, *J* 8.7 Hz). ^{13}C NMR ($CDCl_3$) δ 20.74, 21.38, 35.20, 38.83, 43.24, 47.30, 54.35, 115.63, 120.99, 127.06, 129.48, 130.28, 132.14, 132.71, 133.13, 138.45, 141.51, 141.97, 165.76. MS (ESI): *m/z* 426 $[M+H]^+$.

*tert-Butyl 6-(methylsulfonylmethyl)-1,4-di-p-tolyl-1,6-dihydropyridazine-3-carboxylate (**14b**).* Yellow solid, mp 86–88 °C (diethyl ether/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.30 (9H, s), 2.34 (3H, s), 2.37 (3H, s), 2.99 (3H, s), 3.21 (1H, dd, *J* 2.9 and 13.4 Hz), 3.56 (1H, dd, *J* 9.9 and 13.4 Hz), 5.77 (1H, ddd, *J* 2.9, 7.2 and 9.9 Hz), 6.02 (1H, d, *J* 7.2 Hz), 7.11 (2H, d, *J* 8.3 Hz), 7.15 (2H, d, *J* 8.2 Hz), 7.20 (2H, d, *J* 8.4 Hz), 7.43 (2H, d, *J* 8.6 Hz). ^{13}C NMR ($CDCl_3$) δ 20.89, 21.42, 27.90, 43.30, 47.95, 54.40, 82.03, 116.36, 119.28, 127.63, 129.03, 130.35, 132.90, 133.70, 135.09, 137.90, 139.02, 141.23, 162.64. MS (ESI): *m/z* 477 $[M+Na]^+$, 493 $[M+K]^+$.

*3-Benzoyl-6-(methylsulfonylmethyl)-1,4-di-p-tolyl-1,6-dihydropyridazine (**14c**).* Yellow solid, mp 189–190 °C (EtOH).; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.33 (s, 3H), 2.99 (s, 3H), 3.20 (1H, dd, *J* 2.1 and 13.4 Hz), 3.61 (1H, dd, *J* 10.0 and 13.2 Hz), 5.85 (1H, ddd, *J* 2.1, 7.3 and 10.0 Hz), 6.25 (1H, d, *J* 7.2 Hz), 7.10 (4H, app. s), 7.19 (2H, d, *J* 8.2 Hz), 7.32 (2H, d, *J* 8.7 Hz), 7.46–7.58 (2H, m), 7.60–7.65 (1H, m), 8.10–8.12 (2H, m). ^{13}C NMR ($CDCl_3$) δ 20.66, 21.23, 43.17, 47.46, 54.70, 116.00, 120.35, 127.19, 128.17, 129.16, 130.30, 130.62, 132.70, 133.03, 133.67, 133.70, 136.83, 137.96, 140.81, 143.53, 189.27. MS (ESI): *m/z* 459 $[M+H]^+$.

*3-Acetyl-6-(methylsulfonylmethyl)-1,4-di-p-tolyl-1,6-dihydropyridazine (**14d**).* Yellow solid, mp 136–137 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s), 2.38 (3H, s), 2.55 (3H, s), 2.98 (3H, s), 3.19 (1H, dd, *J* 2.7 and 13.2 Hz), 3.52 (1H, dd, *J* 9.9 and 13.2 Hz), 5.78 (1H, ddd, *J* 2.7, 7.2 and 9.9 Hz), 6.05 (1H, d, *J* 7.2 Hz), 7.03 (2H, d, *J* 8.0 Hz), 7.13 (2H, d, *J* 8.0 Hz), 7.25 (2H, d, *J* 8.4 Hz), 7.45 (2H, d, *J* 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.89, 21.42, 25.97, 43.41, 47.91, 54.58, 116.36, 120.08, 127.47, 128.99, 130.47, 132.69, 134.35, 134.61, 137.78, 140.82, 143.40, 194.88. MS (ESI): *m/z* 397 $[M+H]^+$.