Pergamon

Tetrahedron 57 (2001) 8159–8165

TETRAHEDRON

Ring opening of 2-substituted 4-nitrothiophenes with pyrrolidine. Access to new functionalized nitro-unsaturated building blocks

Carlo Dell'Erba,[a] Antonella Gabellini,[a] Marino Novi,[a,*] Giovanni Petrillo,[a] Cinzia Tavani,[a] Barbara Cosimelli[b] and Domenico Spinelli[b]

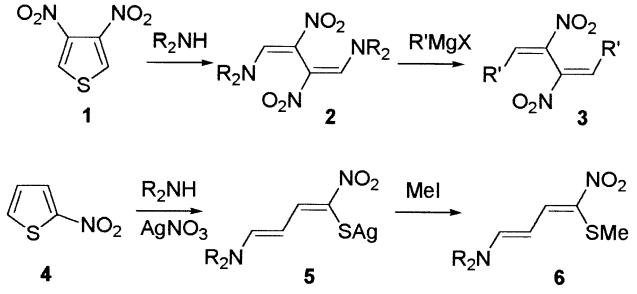
[a]*Dipartimento di Chimica e Chimica Industriale, Via Dodecaneso 31, 16146 Genova, Italy*
[b]*Dipartimento di Chimica Organica 'A. Mangini', Via S. Donato 15, 40127 Bologna, Italy*

Received 4 April 2001; revised 26 June 2001; accepted 19 July 2001

Abstract—The reaction conditions of the ring-opening processes of 3-nitrothiophene **7a** and of 3-nitrobenzo[*b*]thiophene **7b** with pyrrolidine and silver nitrate were optimized as well as those of the subsequent *S*-methylation of the ensuing silver enethiolates **8a** and **8b** to 4-methylthio-2-nitro-1-pyrrolidino-1,3-butadiene **9a** and 1-(2-methylthiophenyl)-1-nitro-2-pyrrolidinoethylene **9b**. Under such conditions 2-X-substituted 4-nitrothiophenes **7c–i** consistently gave good yields of the corresponding 4-methylthio-2-nitro-1-pyrrolidino-4-X-1,3-butadienes **9c–i**. The nitroenamine derivatives **9a–i** were then reacted with *p*-tolylmagnesium bromide to furnish moderate to good yields of 4-methylthio-2-nitro-1-(*p*-tolyl)-4-X-1,3-butadienes **10a,c–i** and 1-(2-methylthiophenyl)-1-nitro-2-(*p*-tolyl)ethylene **10b**. Stereochemistry of the interesting building blocks **9a–i** and **10a–i** was assigned on the grounds of ^{1}H NMR data and NOE experiments.

1. Introduction

The reactions of 3,4-dinitrothiophene **1** with secondary aliphatic amines in ethanol afford 1,4-bis(dialkylamino)-2,3-dinitro-1,3-butadienes **2** via a ring-opening process with extrusion of hydrogen sulphide.[1,2] Employing the diethylamino derivative (Scheme 1, in **2**: R=Et) we have shown that, by reaction with Grignard reagents, it is possible to replace the two amino groups with the residue (alkyl, aryl, vinyl) of the organometallic reagent.[2–5] The ensuing 1,4-disubstituted 2,3-dinitro-1,3-butadienes **3** have proved to be interesting building blocks allowing the attainment of a variety of target molecules, both in the aliphatic and in the heteroaromatic series.[6]



Scheme 1.

Related ring-opening processes of the nitrothiophene moiety include the reactions of 2-nitrothiophene (**4**) that undergoes ring opening by treatment with amines and silver nitrate in ethanol (Scheme 1).[7] Unlike the case of dinitrothiophene **1**, in the reaction with **4** a carbon–sulphur bond is retained in the ring-opened product and the resulting silver butadienethiolates (**5**) can be *S*-methylated with excess methyl iodide to afford the interestingly functionalized butadienes **6**.

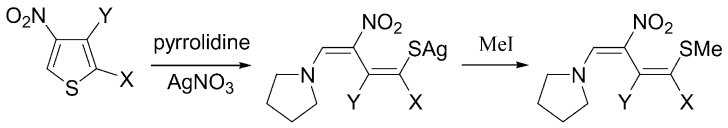
Under the same conditions employed for **4**, also 3-nitrothiophene **7a**[8] and 3-nitrobenzo[*b*]thiophene **7b**[9] have been shown to consistently react, e.g. with pyrrolidine and silver nitrate (Scheme 2), to eventually afford the corresponding ring-opening *S*-methylated products **9a** and **9b**.

In spite of the demonstrated substantial utility of the products arising from the initial ring opening of **1**, the processes on nitrothiophenes above have surprizingly received little attention with regard to the possible synthetic exploitation of the ensuing derivatives. In our opinion this may be also due to not fully satisfactory yields of the processes leading to the potential building blocks of structure related to **6** and **9**.

While similar researches are in progress on α-nitrothiophene systems, we report herein on our optimization of

Keywords: nitrothiophenes; ring-opening reactions; functionalized nitrobutadienes.
* Corresponding author. Address: C.N.R. Centro di Studio per la Chimica dei Composti Cicloalifatici e Aromatici, Via Dodecaneso 31, 16146 Genova, Italy. Tel.: +39-010-353-6103; fax: +39-010-362-4337; e-mail: novi@chimica.unige.it

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00765-7



7 8 9

Scheme 2. **a**: X=Y=H; **b**: X,Y=  ; **c**: X=PhS, Y=H; **d**: X=$PhSO_2$, Y=H; **e**: X=MeS, Y=H; **f**: X=$MeSO_2$, Y=H; **g**: X=MeCO, Y=H; **h**: X=COOMe, Y=H; **i**: X=CN, Y=H.

the ring-opening reaction of **7a** with pyrrolidine and silver nitrate and on the extension of such conditions to **7b** and to 2-substituted 4-nitrothiophenes (**7c–i**). The ensuing nitroenamines (**9a–i**) have been successively reacted with *p*-tolylmagnesium bromide as a first example of their, hitherto-unknown and expectedly wide, utilization as synthetic building blocks.

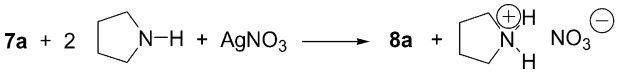
2. Results and discussion

2.1. Ring-opening reactions of nitrothiophenes 7a–i with pyrrolidine and silver nitrate

The reaction of 3-nitrothiophene **7a** with pyrrolidine (9 mol equiv.) and silver nitrate (1.1 mol equiv.) was first carried out as reported in the literature.[8] After 30 h at room temperature, the resulting silver butadienethiolate **8a** was filtered, washed with ethanol, ether, dried and reacted with excess methyl iodide. Through the described workup (1*E*,3*Z*)-4-methylthio-2-nitro-1-pyrrolidino-1,3-butadiene **9a** was isolated in a yield (30%) in good agreement with the reported one (24%).

In order to test whether the yield of **9a** could be improved by a proper choice of the experimental conditions, we carried out several successive experiments on the above reaction on **7a** with modifications both of the reaction (solvent, time and, in particular, the **7a**–amine–$AgNO_3$ molar ratio) and the operative variables (use of sonication, purification of the intermediate **8a**). The best conditions eventually found required the treatment of **7a** and $AgNO_3$ (2.0 mol equiv.) in absolute ethanol with 2.2 mol equiv. of pyrrolidine at room temperature. The use of sonication in an ultrasonic cleaner during the first 30 min of reaction generally assured precipitation of a crystalline silver butadienethiolate. After standing overnight in the dark, from the reaction mixture most of the ethanol was evaporated under vacuum and excess methyl iodide added to the crude still-wet residue. After the standard workup, column chromatography allowed isolation of 11% of unreacted **7a** and 64% of the ring-opened product **9a**, a value corresponding to a 72% yield based on the reacted nitrothiophene.

It is noteworthy that the employment of two moles of amine per mole of **7a** perfectly matches the stoichiometric amount required by Eq. (1). However, while such stoichiometry requires one mole of $AgNO_3$, the use of two moles of it in our best conditions was dictated by the fact that an experiment, carried out with a **7a**–amine–$AgNO_3$ molar ratio of 1:2.2:1, furnished, at the same time of the standard reaction, a significantly lower yield of **9a** based on the reacted **7a** (48%, to be compared with the 72% value reported above).



(1)

As a further check of the above standard procedure, the 3-nitrobenzo[*b*]thiophene **7b** gave, in front of a reported 35% yield,[9] 62% yield of the ring-opened product **9b**, along with 21% of unreacted **7b**: a substantial increase in yield which, while supporting the previous results, has encouraged further researches on the use of the ring-opening reactions of the β-nitrothiophene system with pyrrolidine as a source of interesting unsaturated building blocks.

Our ring-opening procedure with pyrrolidine and silver nitrate was extended to nitrothiophenes **7c–i** and the results obtained are collected in Table 1 together with those relevant to the above mentioned reactions on **7a** and **7b**. Inspection of such results suggests that the procedure may be of quite general applicability since satisfactory yields of the expected nitrobutadienes **9c–i** were obtained. The data of Table 1 also suggest that the conversion of **7** into **9** could possibly be further optimized since variable amounts of unreacted nitrothiophene were recovered.

In this regard, it is necessary to stress that during the ring-opening step, the unreacted **7** cannot be detected by TLC and that only after the methylation of the intermediate silver enethiolate **8** the thiophene substrate can be recovered by chromatography. In our opinion, the incomplete conversion of some experiments is due to the fact that in the first step of

Table 1. Results of the ring-opening reactions of nitrothiophene derivatives **7a–i** with pyrrolidine and silver nitrate and of the subsequent methylation step

Entry	Substrate	Product	Yield (%)[a]	Recovd. **7** (%)
1	**7a**	**9a**	64 (72)	11
2	**7b**	**9b**	62 (78)	21
3	**7c**	**9c**	59 (79)	25
4	**7d**	**9d**	79 (88)	10
5	**7e**	**9e**	52 (70)	26
6	**7f**	**9f**	54 (89)	39
7	**7g**	**9g**	45 (89)	49
8	**7h**	**9h**	48 (89)	46
9	**7i**	**9i**	58 (67)	13

Ring-opening reaction: [**7**]=0.17 M; [$AgNO_3$]≈0.34 M (satd. solution); [pyrrolidine]=0.37 M in absolute ethanol, room temperature, overnight. Methylation step: on crude silver enethiolate **8** with excess MeI, room temperature, 2 h.

[a] Isolated yields, average values of at least two independent reactions. Yields calculated on the amount of **7** consumed are reported in parenthesis.

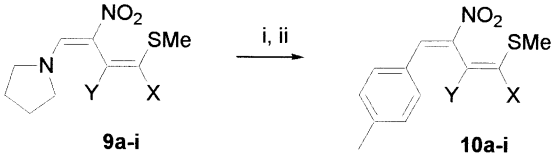
the procedure some thiophene **7** remains adsorbed on the precipitated enethiolate **8**. On the other hand, it should be recalled that in control experiments the use of longer times of sonication and/or of reaction in the first (ring opening) step resulted in a substantial decrease in the absolute and relative yields of **9** with concomitant increase in the amount of tarry material produced.

Finally, it should also be mentioned that the reactions of Table 1 were generally performed starting from 1.4 to 1.5 mmol of **7**. The scale-up of the experiments generally resulted in a decrease in the absolute yield of **9** so that reactions carried out in duplicate or triplicate were to be preferred to a single scaled-up experiment.

2.2. Reactions of the unsaturated derivatives 9a–i with *p*-tolylmagnesium bromide

A common feature of the unsaturated building blocks **9a–i** is the presence of a *tert*-nitroenamine function whose potentiality in synthesis is well known.[10–12] A particularly interesting aspect of the latter are the reactions with organometallic reagents which, after acidic quenching, result in an overall substitution of the dialkylamino group with the residue of the employed organometal.[2–5,13]

Because of the importance of C–C bond forming processes, as a first approach to the study of the behavior of the polyfunctionalized derivatives **9a–i**, we investigated on their reactions with *p*-tolylmagnesium bromide. The results obtained from the reactions of **9a–i** with 1.1 mol equiv. of *p*-tolylmagnesium bromide in THF at −78°C (Scheme 3, Table 2) show that it is possible to approach the new nitrovinyl derivatives **10a–i** where the tolyl replaces the parent pyrrolidine moiety of **9a–i**. The yields of **10a–i** were from



9a-i **10a-i**

Scheme 3. (i) *p*-MeC_6H_4MgBr, THF, −78°C; (ii) H_3O^+ quenching.

Table 2. Yields of **10a–i** from the reactions of the unsaturated derivatives **9a–i** with *p*-tolylmagnesium bromide in THF at −78°C

Entry	Substrate	Product	Yield (%)[a]
1	**9a**	**10a**	84[b]
2	**9b**	**10b**	94
3	**9c**	**10c**	78
4	**9d**	**10d**	66
5	**9e**	**10e**	86
6	**9f**	**10f**	85
7	**9g**	**10g**	39
8	**9h**	**10h**	57
9	**9i**	**10i**	60

[**9**]≈[*p*-TolylMgBr]≈0.08 M; quenching into ice–CH_2Cl_2 with HCl equimolar with Grignard.

[a] Isolated yields: average values of at least two independent reactions.

[b] Depending on workup conditions, in some cases traces of the isomer (1*E*,3*E*)-**10a** have been detected (^{1}H NMR, Ref. 14) in mixed chromatographic fractions.

moderate to good in dependence of the nature of the functionalized vinyl bonded at C(2) of the 2-nitroenamine system of **9a–i**.

The regioselectivity of the reaction leading to **10a–i** from **9a–i** proved to be satisfactory when considering the presence in the latter substrates of groups which can potentially react with the Grignard reagent[15,16] in competition with the nitroenamine system. Actually, the lower yields of entries 7–9 suggest the intervention of competitive processes whose exact nature is at the moment unclear since not well defined by-products could be isolated from the somewhat complex final reaction mixtures. Studies aimed at the optimization of the yields of the above cited reactions, in particular that with **9g**, are planned.

2.3. Stereochemical assignments

As regard the stereochemistry of the nitrovinyl system of compounds **9** and **10** an (*E*)-configuration can be confidently assigned on the grounds of the marked deshielding of the nitrovinylic protons *cis* to the nitrogroup[2–4] (average values: δ 8.5 and 8.1 ppm for compounds **9** and **10**, respectively). The preferential (*E*)-configuration of *tert*-nitroenamines is well documented[10,12] and, consistently, compounds **9b–i** show chemical shift values, for the nitrovinylic protons, in good agreement with the H–C(1) proton of 1-pyrrolidino-2-nitro-4-methylthio-1,3-butadiene **9a**, to which a (1*E*)-configuration has been attributed.[8] On the basis of the ^{1}H NMR data of nitrobutadiene systems structurally related to **9** and **10**,[17] moreover, a moderate upfield shift (ca. 0.2–0.3 ppm) is expected for H–C(1) protons on going from an (*E*)-1-pyrrolidino-2-nitro- to an (*E*)-1-(*p*-tolyl)-2-nitrovinyl system. Consistently enough, compounds **10** show signals for the nitrovinyl protons with an average shielding of 0.4 ppm with respect to the corresponding pyrrolidino derivative **9**. The preference for (*E*)-configuration in 1-aryl-2-nitrovinyl systems arising from substitution by Grignard reagents of the dialkylamino group of nitroenamines is, on the other hand, well assessed.[2–4]

In the 1-pyrrolidino-**9** and in the 1-(*p*-tolyl)-2-nitro-4-methylthio-4-X-1,3-butadienes **10** the configuration at the remaining C(3)–C(4) double bonds of **9a**, **9c**,**d**,**f–i**, **10a** and **10c**,**d**,**f–i** had to be assigned. As far as **9a** and **10a** (X=H) are concerned, the $J_{H-C(3),H-C(4)}$ values of 9.8 and 10.5 Hz (for **9a** and **10a**, respectively) proved that the two protons are *cis* related. Such a result, while confirming the (1*E*,3*E*) configuration of **9a** already reported,[8] suggests no significant inversion of configuration at the C(3)–C(4) double bond during the transformation of **9a** into **10a** by action of the Grignard reagent. The fact that the *cis*-relation between H–C(3) and X–C(4) of the parent thiophenes **7c**,**d**,**f–i** is retained both in the ring-opening products **9c**,**d**,**f–i** and in their derivatives **10c**,**d**,**f–i** is in agreement with the absence of NOE between the H–C(3) and the MeSC(4), as ascertained by NOEDIF experiments. The only NOE's observed were in the experiments performed on **9e** and on **10e** showing NOE between H–C(3) and one MeS group (*cis*-relation) while the effect on the second MeS (*trans*-relation) was, as expected, negligible.

3. Conclusion

In conclusion, the ring-opening reactions of 2-substituted 4-nitrothiophenes with pyrrolidine and silver nitrate and the subsequent treatment of the ensuing nitroenamines **9** with Grignard reagents to afford nitrovinyl derivatives **10** represent a convenient access to polyfunctionalized building blocks of possibly wide potentiality in synthesis, as highlighted by the presence of groups whose interesting reactivity is well known: the nitroenamine,[2–5,10–13] nitrovinyl,[18–24] ketene *S*,*S*- and *S*,SO_2-acetal moieties[15,25–29] as well as the captodative[30–32] vinyl systems of α-methylthio-α,β-unsaturated ketones, esters and nitriles.[16,33,34]

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer with TMS as internal reference; chemical shifts are expressed as δ ppm. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Silica gel 230–400 mesh was used for column chromatography. Sonication was performed at room temperature with a Bransonic Ultrasonic Cleaner Model 2510. All solvents were distilled before use; petroleum ether and light petroleum refer, respectively, to the fraction with bp 40–60 and 80–100°C. Tetrahydrofuran (THF) was purified by standard methods and distilled over potassium benzophenone ketyl before use. Pyrrolidine was dried and distilled over potassium hydroxide before use. The thiophene derivatives **7a**,[35] **7b**,[36] **7c**,[37] **7d**,[37] **7f**,[38,39] **7g**,[40] **7h**,[41] and **7i**,[42] were synthesized according to known procedures. *p*-Tolylmagnesium bromide (ca. 1 M in THF) was prepared using standard procedures and titrated just before use.[43] All other commercially available reagents were used as-received.

4.1.1. 2-Methylthio-4-nitrothiophene (7e). To a solution of 3,4-dinitrothiophene[44] (1.24 g, 7.1 mmol) in methanol (25 ml) was added, under magnetic stirring and cooling with an external ice bath, commercial sodium methanethiolate (1.0 g, 14.3 mmol). The reaction was kept at room temperature until TLC revealed disappearance of the parent substrate (ca. 2 h). The reaction mixture was poured into ice/water and extracted with dichloromethane. The combined extracts were washed with water, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The oily residue was chromatographed on a silica gel column using a gradient of petroleum ether and diethyl ether as eluant. The 2-methylthio-4-nitrothiophene was thus obtained in 45% yield as an oil which solidified in the refrigerator: mp 24.0–25.0°C (lit.[45] 21–22°C); ^{1}H NMR ($CDCl_3$) δ 2.55 (3H, s), 7.55 (1H, d, *J*=1.6 Hz), 8.20 (1H, d, *J*=1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.17, 124.05, 128.38, 140.82, 148.01.

4.2. Ring opening of β-nitrothiophenes 7a–i and access to nitrovinylpyrrolidines 9a–i

The ring opening of the β-nitrothiophenes **7** and the subsequent methylation reactions of the intermediates **8** were performed according to the following general procedure.

A mixture of β-nitrothiophene derivative **7** (1.4 mmol) and silver nitrate (0.48 g, 2.8 mmol) in absolute ethanol (8.5 ml) was sonicated under argon until complete dissolution of **7** (ca. 10 min; some silver nitrate remained undissolved). The flask was disaerated with argon and pyrrolidine (0.26 ml, 3.1 mmol) was added by syringe, cooling with an external ice bath. After further 30 min of sonication, the reaction mixture was left to stand overnight at room temperature in the dark. Most of the solvent was evaporated under reduced pressure to leave a dark yellowish still-wet precipitate. The reaction was cooled to 0°C and excess methyl iodide (5 ml) was added by syringe and the reaction mixture allowed to reach room temperature. After 2 h, the reaction was diluted with acetone and filtered from a grey precipitate, which was washed with acetone. The clear filtrate was evaporated under reduced pressure to leave a residue that was dissolved in dichloromethane and chromatographed on a silica gel column (dichloromethane and then a gradient of the latter with ethyl acetate). Some unreacted β-nitrothiophene derivative **7** was eluted first followed by the nitrovinylpyrrolidine **9**.

4.2.1. (1*E*,3*Z*)-4-Methylthio-2-nitro-1-pyrrolidino-1,3-butadiene (9a). Yellow solid, mp 79.2–80.3°C (petroleum ether–dichloromethane) (lit.[8] 24% yield, mp 80–81°C); ^{1}H NMR ($CDCl_3$) δ 1.98 (4H, m), 2.31 (3H, s), 3.18 (2H, m), 3.72 (2H, m), 6.26 (1H, d, *J*=9.8 Hz), 6.36 (1H, d, *J*=9.8 Hz), 8.41 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.16, 24.89, 25.62, 49.14, 54.68, 116.82, 120.60, 132.13, 145.56.

4.2.2. (*E*)-1-(2-Methylthiophenyl)-1-nitro-2-pyrrolidinoethylene (9b). Yellow solid, mp 122.5–123.5°C (petroleum ether–dichloromethane) (lit.[9] 35% yield, no physical, spectroscopic or analytical data reported); ν_{max} (Nujol) 1612, 1485, 1395, 1263, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.82 (4H. m), 2.43 (3H, s), 2.70 (2H, m), 3.66 (2H, m), 7.20 (3H, m), 7.38 (1H, m), 8.67 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.00, 24.35, 25.95, 47.85, 55.07, 122.24, 123.94, 124.03, 129.76, 130.00, 133.36, 142.19, 145.90; Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.1; H, 6.1; N, 10.6%. Found: C, 59.3; H, 6.3; N, 10.5%.

4.2.3. (1*E*,3*E*)-4-Methylthio-2-nitro-4-phenylthio-1-pyrrolidino-1,3-butadiene (9c). Yellow solid, mp 132.2–132.8°C (petroleum ether–dichloromethane); ν_{max} (Nujol) 1622, 1580, 1438, 1398, 1274 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.97 (4H, m), 2.23 (3H, s), 3.20 (2H, m), 3.70 (2H, m), 6.70 (1H, s), 7.33 (3H, m), 7.50 (2H, m), 8.42 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.42, 24.55, 25.85, 49.40, 55.36, 120.52, 124.75, 127.73, 129.29, 131.20, 134.01, 136.87, 145.83. Anal. Calcd for $C_{15}H_{18}N_2O_2S_2$: C, 55.9; H, 5.6; N, 8.7%. Found: C, 55.5; H, 5.6; N, 8.6%.

4.2.4. (1*E*,3*E*)-4-Methylthio-2-nitro-4-phenylsulfonyl-1-pyrrolidino-1,3-butadiene (9d). Yellow solid, mp 132.3–133.3°C (petroleum ether–dichloromethane); ν_{max} (Nujol) 1605, 1567, 1413, 1307, 1266, 1084 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (3H, s), 2.00 (4H, m), 2.94 (2H, m), 3.80 (2H, m), 7.57 (3H, m), 8.01 (2H, m), 8.20 (1H, s), 8.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.58, 24.47, 25.84, 51.69, 55.73,

118.68, 128.70, 129.03, 133.46, 136.64, 136.71, 139.48, 147.35. Anal. Calcd for $C_{15}H_{18}N_2O_4S_2$: C, 50.8; H, 5.1; N, 7.9%. Found: C, 50.6; H, 5.3; N, 8.1%.

4.2.5. (1*E*)-4,4-Bis(methylthio)-2-nitro-1-pyrrolidino-1,3-butadiene (9e). Yellow solid, mp 60.9–61.8°C (petroleum ether); ν_{max} (Nujol) 1614, 1566, 1393, 1256, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (4H, m), 2.31 (3H, s), 2.43 (3H, s), 3.17 (2H, m), 3.70 (2H, m), 6.32 (1H, s), 8.47 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.43, 16.96, 24.53, 26.03, 49.25, 54.87, 117.05, 120.26, 139.35, 146.17. Anal. Calcd for $C_{10}H_{16}N_2O_2S_2$: C, 46.1; H, 6.2; N, 10.8%. Found: C, 46.1; H, 6.2; N, 10.8%.

4.2.6. (1*E*,3*E*)-4-Methylsulfonyl-4-methylthio-2-nitro-1-pyrrolidino-1,3-butadiene (9f). Yellow solid, mp 81.5–82.5°C (petroleum ether–diethyl ether); ν_{max} (Nujol) 1610, 1566, 1410, 1260, 1305, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (4H, m), 2.24 (3H, s), 3.09 and 3.16 (5H in all, partly overlapping m and s), 3.84 (2H, m), 7.97 (1H, s), 8.54 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.54, 24.54, 25.88, 40.56, 51.67, 55.87, 118.62, 135.25, 135.71, 147.20. Anal. Calcd for $C_{10}H_{16}N_2O_4S_2$: C, 41.1; H, 5.5; N, 9.6%. Found: C, 40.9; H, 5.6; N, 9.6%.

4.2.7. (3*Z*,5*E*)-3-Methylthio-5-nitro-6-pyrrolidino-3,5-hexadien-2-one (9g). Yellow oil, ν_{max} (Nujol) 1673, 1612, 1560, 1471, 1408, 1275, 1148, 1087, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (4H, m), 2.17 (3H, s), 2.53 (3H, s), 2.98 (2H, m), 3.81 (2H, m), 7.68 (1H, s), 8.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.53, 24.45, 25.77, 27.32, 50.78, 55.29, 119.86, 132.44, 137.02, 148.05, 196.19. Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.5; H, 6.3; N, 10.9%. Found: C, 51.3; H, 6.5; N, 11.0%.

4.2.8. Methyl (2*Z*,4*E*)-2-Methylthio-4-nitro-5-pyrrolidino-2,4-pentadienoate (9h). Waxy yellow solid, ν_{max} (Nujol) 1717, 1621, 1540, 1410, 1273, 1123, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (4H, m), 2.25 (3H, s), 3.02 (2H, m), 3.79 and 3.85 (5H in all, partly overlapping m and s), 7.80 (1H, s), 8.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.94, 24.51, 25.84, 50.70, 52.74, 55.23, 119.85, 128.03, 133.45, 148.03, 165.37. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.5; H, 5.9; N, 10.3%. Found: C, 48.2; H, 6.1; N, 10.1%.

4.2.9. (2*Z*,4*E*)-2-Methylthio-4-nitro-5-pyrrolidino-2,4-pentadienenitrile (9i). Yellow solid, mp 124.0–125.0°C (petroleum ether–dichloromethane); ν_{max} (Nujol) 2216, 1613, 1580, 1397, 1244, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (4H, m), 2.48 (3H, s), 3.04 (2H, m), 3.80 (2H, m), 7.31 (1H, s), 8.44 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.56, 24.55, 25.84, 50.58, 55.27, 109.38, 115.24, 118.82, 132.85 and 147.79. Anal. Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.2; H, 5.5; N, 17.6%. Found: C, 50.4; H, 5.6; N, 17.7%.

4.3. Reactions of nitrovinylpyrrolidines 9a–i with *p*-tolylmagnesium bromide

A solution of nitrovinylpyrrolidines **9** (1 mmol) in THF (12 ml) was cooled to −78°C under magnetic stirring. The calculated amount of a ca. 1 M solution of *p*-tolylmagnesium bromide (1.1 mmol) in THF was slowly added by syringe and the reaction mixture left under stirring at the same temperature until disappearance of the substrate (ca. 15–45 min): the progress of the reaction being monitored by TLC. Quenching of the reactions was performed by pouring the reaction solution, with vigorous shaking, into a mixture of dichloromethane with ice/water containing 1.1 mmol of HCl. After extraction with dichloromethane, the organic phase was washed with water, dried (Na_2SO_4) and concentrated in a rotary evaporator under reduced pressure. The products **10** were usually obtained in quite pure form by chromatography of the residue on a silica gel column eluted with a gradient of dichloromethane and diethyl ether.

4.3.1. (1*E*,3*Z*)-4-Methylthio-2-nitro-1-(*p*-tolyl)-1,3-butadiene (10a). Yellow oil, ν_{max} (Nujol) 1638, 1604, 1550, 1517, 1436, 1316, 1305, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (3H, s), 2.39 (3H, s), 6.46 (1H, d, J=10.5 Hz), 6.60 (1H, d, J=10.5 Hz), 7.21 and 7.47 (2H each, AA′BB′, J=8.2 Hz), 8.05 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.62, 21.66, 114.61, 128.45, 129.56, 130.95, 134.67, 138.66, 141.46, 144.10. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.3; H, 5.6; N, 6.0%. Found: C, 61.1; H, 5.8; N, 6.0%.

4.3.2. (*E*)-1-(2-Methylthiophenyl)-1-nitro-2-(*p*-tolyl)-ethylene (10b). Yellow solid, mp 56.2–57.0°C (petroleum ether); ν_{max} (Nujol) 1636, 1605, 1584, 1515, 1435, 1323, 1310, 1184 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (3H, s), 2.42 (3H, s), 6.98 and 7.06 (2H each, AA′BB′, J=8.5 Hz), 7.25 (2H, m), 7.41 (1H, app d, J=6.8 Hz), 7.52 (1H, m), 8.30 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.90, 21.51, 125.93, 126.91, 128.24, 129.66, 130.34, 130.77, 131.08, 131.16, 136.40, 140.13, 141.86, 147.10. Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.3; H, 5.3; N, 4.9%. Found: C, 67.0; H, 5.1; N, 4.8%.

4.3.3. (1*E*,3*E*)-4-Methylthio-2-nitro-4-phenylthio-1-(*p*-tolyl)-1,3-butadiene (10c). Yellow solid, mp 96.4–97.0°C (petroleum ether–dichloromethane); ν_{max} (Nujol) 1631, 1603, 1547, 1514, 1439, 1316, 1292, 1179 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (3H, s), 2.40 (3H, s), 6.45 (1H, s), 7.22 (2H, half AA′BB′, J=8.0 Hz), 7.40 (5H, m), 7.55 (2H, m), 7.96 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.52, 21.64, 120.21, 128.57, 128.98, 129.47, 129.67, 130.84, 132.50, 132.65, 135.07, 141.63, 144.43, 145.29. Anal. Calcd for $C_{18}H_{17}NO_2S_2$: C, 62.9; H, 5.0; N, 4.1%. Found: C, 62.7; H, 5.0; N, 4.2%.

4.3.4. (1*E*,3*E*)-4-Methylthio-2-nitro-4-phenylsulfonyl-1-(*p*-tolyl)-1,3-butadiene (10d). Yellow solid, mp 81.5–82.5°C (petroleum ether–dichloromethane); ν_{max} (Nujol) 1633, 1608, 1516, 1502, 1322, 1313, 1185, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (3H, s), 2.39 (3H, s), 7.15 and 7.24 (2H each, AA′BB′, J=8.3 Hz), 7.66 (3H, m), 8.01 (3H in all, partly overlapping s and m), 8.15 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.86, 21.68, 127.87, 128.70, 129.23, 129.98, 130.98, 134.04, 134.75, 138.06, 138.46, 141.62, 142.97, 146.27. Anal. Calcd for $C_{18}H_{17}NO_4S_2$: C, 57.6; H, 4.6; N, 3.7%. Found: C, 57.4; H, 4.7%; N, 3.7%.

4.3.5. (1*E*)-4,4-Bis(methylthio)-2-nitro-1-(*p*-tolyl)-1,3-butadiene (10e). Yellow solid, mp 69.5–70.8°C (petroleum ether); ν_{max} (Nujol) 1643, 1605, 1547, 1514, 1506, 1317, 1311, 1185 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (3H, s), 2.39 (3H, s), 2.49 (3H, s), 6.30 (1H, s), 7.22 and 7.43 (2H each, AA′BB′, J=8.2 Hz), 7.95 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.46, 16.85, 21.60, 114.65, 129.14, 129.68, 130.78,

134.65, 141.47, 144.63, 146.83. Anal. Calcd for $C_{13}H_{15}NO_2S_2$: C, 55.5; H, 5.4; N, 5.0%. Found: C, 55.3; H, 5.5; N, 5.0%.

4.3.6. (1*E*,3*E*)-4-Methylsulfonyl-4-methylthio-2-nitro-1-(*p*-tolyl)-1,3-butadiene (10f). Yellowish solid, mp 119.5–121.0°C (petroleum ether–dichloromethane); ν_{max} (Nujol) 1641, 1604, 1519, 1510, 1317, 1295, 1190, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (3H, s), 2.41 (3H, s), 3.16 (3H, s), 7.27 and 7.36 (2H each, AA′BB′, J=8.4 Hz), 7.86 (1H, s), 8.20 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.68, 21.68, 40.44, 127.82, 130.13, 131.15, 134.48, 138.44, 141.57, 143.18, 145.01. Anal. Calcd for $C_{13}H_{15}NO_4S_2$: C, 49.8; H, 4.8; N, 4.5%. Found: C, 49.9; H, 5.0; N, 4.3%.

4.3.7. (3*Z*,5*E*)-3-Methylthio-5-nitro-6-(*p*-tolyl)-3,5-hexadien-2-one (10g). Yellow solid, mp 71.2–71.6°C (petroleum ether); ν_{max} (Nujol) 1660, 1630, 1582, 1480, 1425, 1306, 1260, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (3H, s), 2.40 (3H, s), 2.56 (3H, s), 7.23 (2H, half AA′BB′, J=8.0 Hz), 7.35 (3H in all, s and half AA′BB′ partly overlapping, J=8.0 Hz), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.05, 21.66, 27.63, 127.63, 128.30, 129.92, 130.98, 137.20, 142.46, 143.34, 146.25, 196.48. Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.6; H, 5.5; N, 5.1%. Found: C, 60.2; H, 5.4; N, 5.0%.

4.3.8. Methyl (2*Z*,4*E*)-2-methylthio-4-nitro-5-(*p*-tolyl)-2,4-pentadienoate (10h). Yellow solid, mp 67.1–67.7°C (petroleum ether); ν_{max} (Nujol) 1721, 1640, 1605, 1502, 1434, 1325, 1293, 1246, 1186, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (3H, s), 2.40 (3H, s), 3.91 (3H, s), 7.24 and 7.36 (2H each, AA′BB′, J=8.0 Hz), 7.59 (1H, s), 8.11 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.35, 21.63, 53.08, 128.31, 129.89, 129.98, 130.99, 137.32, 137.77, 142.36, 143.23, 164.43. Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.3; H, 5.2; N, 4.8%. Found: C, 57.1; H, 5.2; N, 4.9%.

4.3.9. (2*Z*,4*E*)-2-Methylthio-4-nitro-5-(*p*-tolyl)-2,4-pentadienenitrile (10i). Yellow solid, mp 118.2–118.7°C (light petroleum); ν_{max} (Nujol) 2227, 1632, 1603, 1499, 1310, 1290, 1213, 1185, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 and 2.42 (3H each, two s partly overlapped), 7.26 (3H in all, s and half AA′BB′ partly overlapping, J=8.4 Hz), 7.35 (2H, half AA′BB′, J=8.4 Hz), 8.22 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.65, 21.76, 114.27, 119.78, 127.66, 129.85, 130.16, 130.96, 139.02, 140.87, 143.13. Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 60.0; H, 4.6; N, 10.8%. Found: C, 60.0; H, 4.7; N, 10.9%.

Acknowledgements

The authors wish to thank the University of Genova, the University of Bologna and C.N.R. for financial support to this research.

References

1. Dell'Erba, C.; Spinelli, D.; Leandri, G. *J. Chem. Soc., Chem. Commun.* **1969**, 549.
2. Dell'Erba, C.; Mele, A.; Novi, M.; Petrillo, G.; Stagnaro, P. *Tetrahedron Lett.* **1990**, *31*, 4933–4936.
3. Dell'Erba, C.; Mele, A.; Novi, M.; Petrillo, G.; Stagnaro, P. *Tetrahedron* **1992**, *48*, 4407–4418.
4. Dell'Erba, C.; Novi, M.; Petrillo, G.; Spinelli, D.; Tavani, C. *Tetrahedron* **1996**, *52*, 3313–3326.
5. Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pertici, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem.* **1999**, 431–435.
6. Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem.* **2000**, 903–912 and previous papers in the series.
7. Guanti, G.; Dell'Erba, C.; Leandri, G.; Thea, S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2357–2360.
8. Surage, S. S.; Kumaran, G.; Rajappa, S.; Rajalakshmi, K.; Pattabhi, V. *Tetrahedron* **1997**, *53*, 8531–8540.
9. Surage, S. S.; Rajappa, S. *Tetrahedron Lett.* **1998**, *39*, 7169–7172.
10. Rajappa, S. *Tetrahedron* **1981**, *37*, 1453–1480.
11. Fuji, K.; Node, M. *Synlett* **1991**, 603–610.
12. Rajappa, S. *Tetrahedron* **1999**, *55*, 7065–7114.
13. Severin, T.; Scheel, D.; Adhikary, P. *Chem. Ber.* **1969**, *102*, 2966–2971.
14. For the (1*E*,3*E*)-**10a** isomer: ^1H NMR ($CDCl_3$) 2.37 and 2.39 (6H in all, two partly overlapping s), 6.16 (1H, d, J=15.5 Hz), 6.98 (1H, d, J=15.5 Hz), 7.22 and 7.43 (2H each, AA′BB′, J=8.1 Hz), 7.68 (1H, s).
15. Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357–402.
16. Kobayashi, K.; Tanaka, H.; Takabatake, H.; Kitamuna, T.; Nakahashi, R.; Morikawa, O.; Hisatoshi, K. *Bull. Chem. Soc. Jpn* **1999**, *72*, 1071–1074.
17. Compare for instance (Ref. 3): (*E*,*E*)-1,4-bis(pyrrolidino)-2,3-dinitro-1,3-butadiene [$\delta_{H-C(1)}=\delta_{H-C(4)}$=8.70 ppm] with (*E*,*E*)-1,4-bis(*p*-tolyl)-2,3-dinitro-1,3-butadiene [$\delta_{H-C(1)}=\delta_{H-C(4)}$= 8.50 ppm].
18. Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. *Nitroalkenes, Conjugated Nitro Compounds*; Wiley: New York, 1994.
19. Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1–18.
20. Barrett, A. G.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751–762.
21. Seebach, D.; Imwinkelried, R.; Weber, T. *EPC syntheses with C,C bond formation via acetals and enamines*. Schefford, R., Ed.; Modern Synthetic Methods; Vol. 4; Springer: Berlin, 1986; pp. 220–240.
22. Kabalka, G. W.; Varma, R. S. *Org. Prep. Proced. Int.* **1987**, *19*, 283–328.
23. Rosini, G.; Ballini, R. *Synthesis* **1988**, 833–847.
24. Pecunioso, A.; Galoppini, E.; Menicagli, R. *Tetrahedron* **1990**, *46*, 7497–7508.
25. Tominaga, Y.; Matsuda, Y. *J. Heterocycl. Chem.* **1985**, *22*, 937–949.
26. Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029–3096.
27. Kolb, M. *Synthesis* **1990**, 171–190.
28. Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423–5506.
29. Braverman, S.; Cherkinsky, M.; Nov, E.; Sprecher, M. *Tetrahedron* **1999**, *55*, 2353–2362 and references therein.
30. Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917–932.
31. Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148–154.
32. Viehe, H. G.; Merényi, R.; Janousek, Z. *Pure Appl. Chem.* **1988**, *60*, 1635–1644.
33. Aggarwal, V. K.; Ali, A.; Coogan, M. P. *Tetrahedron* **1999**, *55*, 293–312.

34. For leading references see: Gonzales-Cameno, A. M.; Mella, M.; Fagnoni, M.; Albini, A. *J. Org. Chem.* **2000**, *65*, 297–303.
35. Blatt, A. H.; Gross, N.; Tristram, E. W. *J. Org. Chem.* **1957**, *22*, 1693–1695.
36. Zahradnik, R.; Parkanyi, C.; Horak, V.; Koutecky, J. *Coll. Czech. Chem. Commun.* **1963**, *28*, 776–778.
37. Dell'Erba, C.; Spinelli, D.; Leandri, G. *Gazz. Chim. Ital.* **1969**, *99*, 535–541.
38. (a) Hurtel, P.; Decroix, B.; Morel, J.; Terrier, F. *J. Chem. Res. (S)* **1983**, 58. (b) Hurtel, P.; Decroix, B.; Morel, J.; Terrier, F. *J. Chem. Res. (M)* **1983**, 725–754.
39. Arnone, C.; Consiglio, G.; Spinelli, D.; Dell'Erba, C.; Sancassan, F.; Terrier, F. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1609–1612.
40. Fournari, P.; Chané, J. P. *Bull. Soc. Chim. Fr.* **1963**, 479–484.
41. Rinkes, I. J. *Recl. Trav. Chim. Pays-Bas* **1933**, *52*, 538–548.
42. Reynaud, P.; Delaby, R. *Bull. Soc. Chim. Fr.* **1955**, 1614–1615.
43. Bergbreit, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219–220.
44. Blatt, A. H.; Gross, N. *J. Org. Chem.* **1957**, *22*, 1588–1590.
45. (a) Belen'kii, L. I.; Ksenzhek, N. S.; Gol'dfarb, Ya. L. *Chem. Heterocycl. Compd. Engl. Transl.* **1972**, *8*, 280. (b) Belen'kii, L. I.; Ksenzhek, N. S.; Gol'dfarb, Ya. L. *Khim. Geterotsikl. Soedin.* **1972**, *8*, 310.