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New Synthesis of 3-Substituted 7-Nitro-2H-1,2-benzothiazine-1,1-dioxides—Potential Precursors for Dyestuffs and Optical Whiteners

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ABSTRACT

*New routes to 3-substituted 7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide derivatives from the readily available 4-nitrotoluene-2-sulphonamide as starting material are reported.*

1 INTRODUCTION

Devising newer strategies for the synthesis of heterocyclic compounds of interest in the pharmaceutical and dyestuff field has gained momentum in recent years. The reported[1] biological activity of 1,2-benzothiazines and the commercialisation of drugs such as Piroxicam and Sudoxicam has generated much activity in this area.

Studies on new heterocyclic precursors for dyes and optical whiteners have led to new synthetic routes to 1,2-benzothiazine derivatives, and to the synthetic utility of some of these derivatives as heterocyclic diazo compounds has been reported.[2,3]

This paper reports novel synthetic pathways to 3-amino-, 3-oxo-, 3-aryl- and 3-hetaryl-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide derivatives from readily available starting materials such as 4-nitrotoluene-2-sulfonamide.

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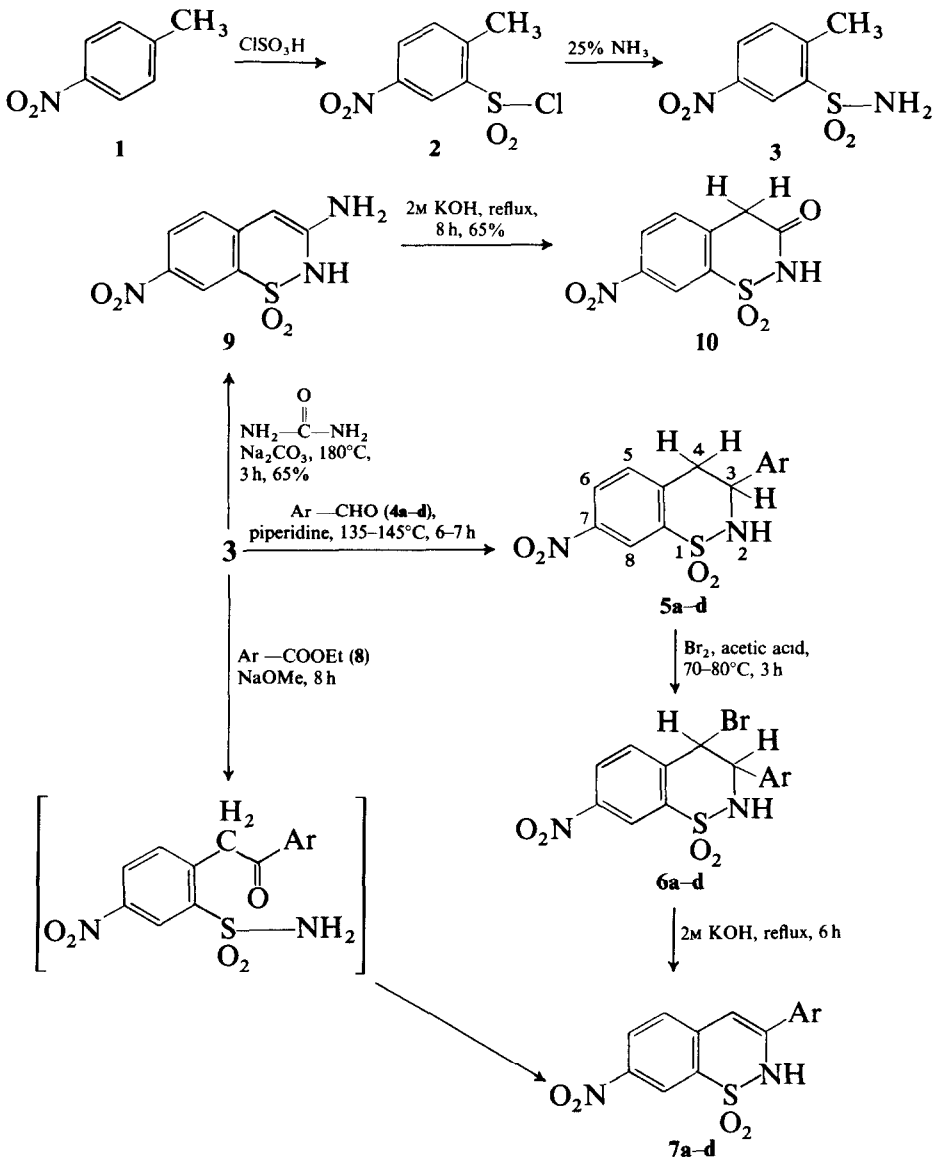


	a	b	c	d
4	Ar ≠ Ph	—NMe2	—OCH3	—NHCOCH3
8	Ar ≠ Ph			

Scheme 1

2 DISCUSSION OF RESULTS

Reaction of 4-nitrotoluene-2-sulphonamide (**3**) with aromatic aldehydes (**4a–d**) in the presence of a basic catalyst such as piperidine yielded the 3-aryl-7-nitro-3,4-dihydro-2*H*-1,2-benzothiazine-1,1-dioxide derivatives, (**5a–d**) (Scheme 1). The 3,4-dihydro compounds (**5a–d**), on treatment with bromine at 70–80°C, gave the 4-bromo derivatives, (**6a–d**) which were immediately dehydrobrominated with potassium hydroxide to the 3-aryl-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide derivatives, **7a–d**. Characterisation data for the compounds are shown in Table 1.

An alternate synthesis of the 3-aryl-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide derivative, **7a**, was also successfully carried out by reacting **3** with an aromatic carboxylic ester (**8**) in the presence of sodium methoxide. The compound obtained by this route was identical in all physical and spectral characteristics with that prepared by the aldehyde condensation method. Thus, the reactions with aromatic aldehydes or with aromatic carboxylic esters can be selectively adopted, depending on the availability of starting materials. These 3-aryl derivatives are being studied for their utility as useful precursors for dyestuffs.

The utility of **3** to generate intermediates for dyestuff synthesis has been highlighted by a high temperature urea fusion reaction, followed by alkaline hydrolysis. Reaction of **3** with urea in the presence of a basic catalyst such as sodium carbonate yielded 3-amino-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide (**9**), the use of which as a diazo compound has been reported earlier.[2,3] It was hydrolysed using 2M KOH to give 3-oxo-7-nitro-3,4-dihydro-2*H*-1,2-benzothiazine-1,1-dioxide (**10**). The products of these reactions are characterised by their ease of formation compared with the more tedious preparation from *o*-aminophenylacetonitrile as reported by Sianesi *et al.*[4]

Reaction of **3** with diethyl oxalate (**11**) in the presence of sodium ethoxide yielded the 3-carbethoxy derivative, (**12**), which acts as a precursor to 3-hetaryl derivatives (Scheme 2). Reaction of **12** with bifunctional compounds such as *o*-aminophenol (**13b**) or *o*-phenylenediamine (**13a**) yielded the 3-benzoxazolo and 3-benzimidazolo derivatives, **14b** and **14a**, respectively. Reaction of (**12**) with benzoylhydrazide (**15**) yielded the 3-oxadiazolyl derivative (**16**). Characterisation data for these compounds are given in Table 2.

The amino derivative (**9**) was diazotised and coupled with 2-naphthylamine-1-sulphonic acid (**17**, Tobias acid). A substitution reaction occurs, with elimination of the sulphonic acid group, to give the azo dye (**18**), which was treated with copper (II) acetate in dimethylformamide under oxidising conditions to effect an oxidative triazolisation to the 3-naphthotriazole derivative (**19**). This compound had no colour value, as shown by its

TABLE 1
Physical and Spectral Data of Compounds **5a–d** and **7a–d**

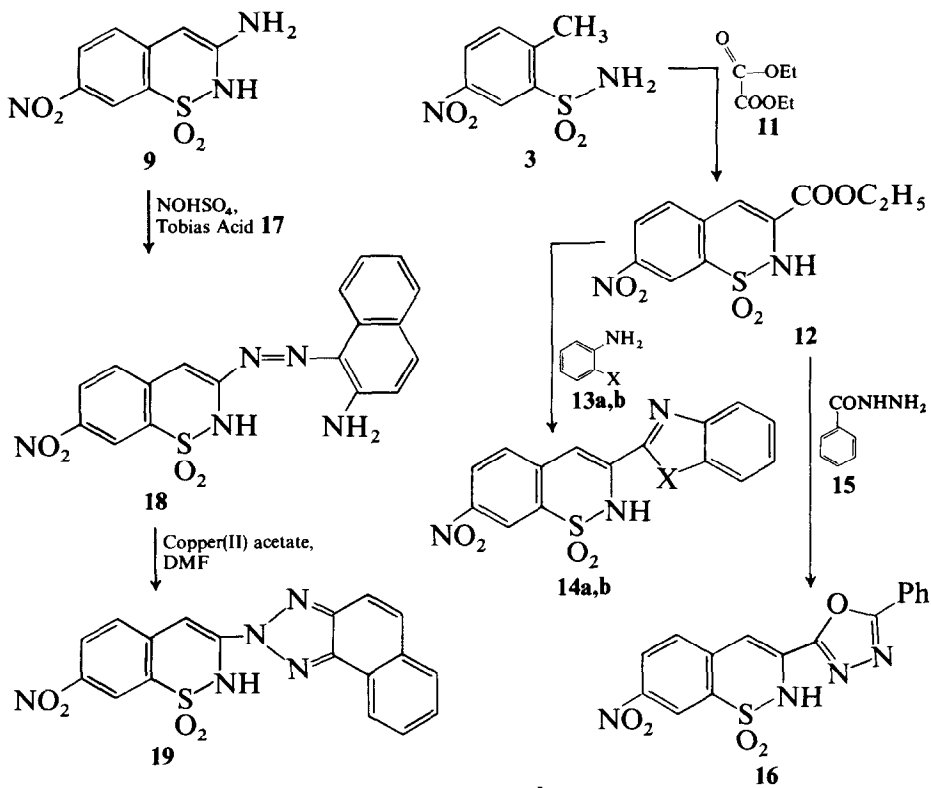
Compound	*Reaction time (h)*	*Yield*[a] *(%)*	*Melting point (°C)*	*Molecular formula (m⁺/e)*	*IR (cm⁻¹)*	*UV (methanol)*		*¹H-NMR (TFA) J, J Hz, δ*
						λ_{max}	*log ε*	
5a	6	75	152[b]	$C_{14}H_{12}N_2O_4S$ (304·0)	3 150 (—NH)	380	4·2	—
5b	6	80	174[b]	$C_{16}H_{17}N_3O_4S$ (346.0)	3 150 (—NH)	390	4·3	3·3[d,8H,—$N(CH_3)_2$] and [2H,—CH_2 at C-4]; 4·8[t,1H,C-3]; 7·2–7·7 [m,6H, and five aromatic protons of phenyl ring at C-3, 1H at C-5 of —NH]; 8·2 [d,1H, C-6]; 8·6 [s, 1H, C-8]
5c	7	70	138[c]	$C_{15}H_{14}N_2O_3S$ (334·0)	3 150 (—NH)	385	4·2	3·2[d,2H,C-4]; 3·8[s,3H,—OCH_3]; 4·9[t,1H, C-3]; 7·0[d,2H,3′,5′ of phenyl ring at C-3]; 7·8[d,1H,C-5]; 8·2[a,1H,—NH]; 8·5[s,2H,C-6 and C-8]
5d	6	70	137[b]	$C_{16}H_{15}N_3O_5S$ (361·0)	1 690 (CO) 3 150 (—NH)	385	4·2	—
7a	9	75	308[d]	$C_{14}H_{10}N_2O_4S$ (302·0)	3 150 (—NH)	420	4·3	—
7b	9	75	310[e]	$C_{16}H_{15}N_3O_4S$ (341·0)	3 150 (—NH)	485	4·6	3·3[s,6H,—NMe_2]; 7·2–8·5(m,9H,) aromatic protons and 1 —NH proton)
7c	10	68	>310[d]	$C_{15}H_{12}N_2O_5S$ (331·0)	3 150 (—NH)	425	4·5	
7d	9	70	293[ae]	$C_{16}H_{13}N_3O_5S$ (359·0)	1 690 (CO) 3 150 (—NH)	470	4·5	—

[a] Yield based on **3**. [b] Recrystallisation solvent: chlorobenzene. [c] Recrystallisation solvent: ethanol.
[d] Recrystallisation solvent: dimethylformamide. [e] Recrystallisation solvent: acetic acid.
All the compounds showed satisfactory elemental analysis.

TABLE 2
Physical and Spectral Data of 3-Hetaryl Derivatives

Compound	*Reaction time (h)*	*Yield*[a] *(%)*	*Melting point (°C)*	*Molecular formula m⁺/e*	*IR (cm^{-1})*	*UV (methanol)*	
						λ_{max}	*log ε*
14a	2	60	310	$C_{15}H_{10}N_4O_4S$ (342·0)	3 150 (—NH)	360 380	4·1 (absorption) (emission)
14b	2	60	315	$C_{15}H_9N_3O_5S$ (343·0)	3 150 (—NH)	350 400	4·2 (absorption) (emission)
16	3	60	>310	$C_{16}H_{10}N_4O_5S$ (370·0)	3 150 (—NH)	360	4·2 (absorption)

[a] Yield based on **3**.



	a	b
13 X	NH_2	OH
14 X	NH	O

Scheme 2

λ_{max} value of 360 nm compared with the azo precursor's (λ_{max}—500 nm); this is attributable to the disruption of the azo chromophore in the triazolisation reaction. The 3-triazolyl derivative, 19, showed no —NH bonds in its IR spectrum, indicating that the triazolisation reaction involving the amino and azo groups had occurred.

3 EXPERIMENTAL PROCEDURES

3.1 General

All melting points were recorded on a Metler apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer, ^{1}H-NMR spectra on a Varian EM-360L spectrophotometer and mass spectra on a Varian CH7 spectrophotometer. 4-Nitrotoluene-2-sulphonamide (**3**),[5] 4-nitrotoluene-2-sulphonylchloride (**2**),[6] *N*,*N*-dimethylaminobenzaldehyde

(**4b**),[7] 4-acetamidobenzaldehyde (**4d**)[8] and benzoylhydrazide (**15**)[9] were prepared according to reported methods. *p*-Nitrotoluene (**1**), *p*-anisaldehyde (**4c**), benzaldehyde (**4a**) ethyl benzoate (**8**), *o*-phenylenediamine (**13a**), *o*-aminophenol (**13b**) and Tobias acid (**17**) were commercial samples.

3.2 Synthesis of 3-aryl-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide derivatives (7a–d)

3.2.1 From aromatic aldehydes

A mixture of the appropriate aldehyde (**4a–d**, 12·5 mmol) and **3** (1·76 g, 10 mmol) was heated in the presence of piperidine (0·3 ml) at 135–145°C for 6–7 h. The molten mass was slowly added to ice-cold methanol (15 ml) with stirring. The product was filtered, and purified by crystallisation. The reaction conditions, yields, physical and spectroscopic data of the resultant 3-aryl-7-nitro-3,4-dihydro-2*H*-1,2-benzothiazine-1,1-dioxides (**5a–d**) are given in Table 1.

A mixture of the appropriate 3,4-dihydro compound (**5a–d**, 12·5 mmol) and bromine (0·20 g, 12·5 mmol) was heated in acetic acid (10 ml) at 70–80°C for 3 h. The clear solution was then poured into water (50 ml) and the bromo compound filtered, washed and dried. It was then refluxed in 2M KOH solution (10 ml) for 6 h, the solution cooled and poured into ice-cold hydrochloric acid (15 ml, 15%). The products were filtered and crystallised. Reaction conditions, yields, physical and spectroscopic data of the resultant compounds (**7a–d**) are given in Table 1.

3.2.2 From aromatic carboxylic esters

For the synthesis of 3-aryl-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide (**7a**) a mixture of **3** (1·76 g, 10 mmol), **8** (0·15 g, 10·1 mmol) and sodium methoxide (1·5 g) was heated for 8 h. The brown reaction mass was run into ice-cold water (15 ml) and then neutralised with dilute hydrochloric acid. The product was crystallised from dimethylformamide. Reaction conditions, yields, physical and spectroscopic data are given in Table 1.

3.3 Synthesis of 3-amino-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide (9)

A mixture of **3** (1·76 g, 10 mmol) and urea (3·6 g, 60 mmol) was heated in the presence of sodium carbonate (0·26 g, 2·5 mmol) at 180°C for 3 h. The melt was cooled to 80°C and ethyl alcohol (50 ml) added. On cooling, a solid product separated; this was filtered, washed with water and recrystallised with isopropanol. Yield, 1·6 g (65%, based on **3**); m.p., 228°C (Ref. 4, 227·8°C). $C_8H_7N_3O_4S$ requires C 39·9, H 2·9, N, 17·4 and S 13·2%; found values were C 39·7, H 2·8, N 17·5 and S 13·1%. IR (Nujol) ν: 3340–3330 cm^{-1}

(—NH_2), 3150 cm^{-1} (–NH). ^{1}H-NMR (DMSO-d_6) δ: 3·4 [s, 2H, —CH_2, D_2O exchangeable]; 7·2 [d, 1H, C-5, $J_{5,6} = 10$ Hz]; 7·6 [s, 1H, —NH, D_2O exchangeable]; 8·1 [s, 1H, C-6, $J_{6,8} = 2$ Hz, $J_{5,6} = 10$ Hz]; 8·6 [s, 1H, C-8, $J_{8,6} = 2$ Hz]. (In DMSO-d_6 the compound exists in the tautomeric imino form, hence the signal corresponding to —CH_2.)

3.4 Synthesis of 3-oxo-7-nitro-3,4,dihydro-2*H*-1,2-benzothiazine-1,1-dioxide (10)

A mixture of the 3-amino derivative (**9**) (1·205 g, 5 mmol), and 2M KOH solution (6·5 ml) was refluxed for 8 h. To the hot reaction mixture, charcoal (3 g) was added and heating continued for 0·5 h. The reaction mixture was then filtered hot, and the filtrate cooled to room temperature and neutralised with 2M HCl (6·5 ml). The product was filtered, washed with water and recrystallised from isopropanol. Yield, 0·8 g (65%, based on **9**); m.p., 217°C (Ref. 4, 217–18°C). $C_8H_6N_2O_5S$ requires C 39·6, H 2·4, N 11·5 and S 13·2%; found values were C 39·4, H 2·2, N 11·3 and S 13·4%. IR (Nujol) ν: 1690 cm^{-1} (—CO), 3150 cm^{-1} (—NH). ^{1}H-NMR (DMSO-d_6) δ: 3·4 [s, 1H, —CH_2, D_2O exchangeable]; 7·2 [d, 1H, C-5, $J_{5,6} = 10$ Hz]; 7·6 [s, 1H, —NH, D_2O exchangeable]; 8·1 [s, 1H, C-6, $J_{6,8} = 2$ Hz, $J_{5,6} = 10$ Hz]; 8·6 [s, 1H, C-8, $J_{8,6} = 2$ Hz].

3.5 Synthesis of 3-carbethoxy-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide (12)

3 (4·42 g, 20 mmol) was added in small portions to sodium ethoxide (3·0 g, 44 mmol) in absolute ethanol (30 ml) at 0–5°C. The reaction mixture was stirred at 0–5°C for 0·5 h and diethyl oxalate (**11**) (3·3 g, 22 mmol) added dropwise over 15 min. The mixture was then slowly heated to 75–80°C and maintained at this temperature for 6 h. After cooling, the mixture was poured into ice-cold hydrochloric acid (15 ml, 20%), with stirring, to give a brown-coloured poduct. This was filtered, washed repeatedly with aqueous sodium bicarbonate and recrystallised from ethanol. Yield, 3·0 g (50%, based on **1**); m.p., 302°C. $C_{11}H_{10}N_2O_6S$ requires C 44·2, H 3·3, N 9·3 and S 10·7%; found values were C 44·4, H 3·1, N 9·1 and S 10·9. IR (Nujol) ν: 1690 cm^{-1} (—C=O), 3150 cm^{-1} (—NH). ^{1}H-NMR (DMSO-d_6) δ: 1·2 [t, 3H, CH_3 of COO–C_2H_5]; 4·0 [q, 2H, —CH_2 of COO—C_2H_5]; 7·0 [s, 1H, —NH, D_2O exchangeable]; 7·8 [d, 2H, C-4, C-5]; 8·4 [d, 2H, C-6, C-8].

3.6 Synthesis of 3-hetaryl-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide derivatives (14a,b and 16)

Orthophosphoric acid (10 ml, 90%) was added to phosphorus pentoxide (10·0 g) with vigorous stirring and the mixture was heated to 180° for 0·5 h. It

was then cooled to 100°C, and a mixture of **12** (3·6 g, 12 mmol) and **13a** (1·1 g, 10 mmol), **13b** (1·1 g, 10 mmol) or **15** (1·59 g, 12 mmol) was added to the melt. The temperature was raised to 160°C and maintained for 1·5 h. The melt was then cooled, poured into ice-cold water (100 ml) with stirring, and neutralised with aqueous ammonia to pH 6. The solid was filtered, dried and recrystallised from a suitable solvent. Reaction conditions, yield, physical and spectral data are given in Table 2.

3.7 Synthesis of 3-naphtho-triazolyl-7-nitro-2*H*-1,2-benzothiazine-1,1-dioxide (19)

3.7.1 Preparation of the azo derivative, ***18***

9 (2·41 g, 10 mmol) was diazotised with nitrosyl sulphuric acid (prepared from sulphuric acid (5 ml) and sodium nitrite (0·75 g, 11 mmol)) at 10–15°C for 2 h. The diazonium solution was then run into ice-cold acetic acid (10 ml) and the resulting solution added slowly to a solution of 2-naphthylamine-1-sulphonic acid (**17**) (2·24 g, 11 mmol) at 10–15°C over 0·5 h. The coupling mixture was stirred at pH 4–5 for 4 h and the azo dye was then filtered, washed with water, dried and recrystallised from dimethylformamide. Yield, 2·0 g (50%, based on **9**); m.p., 250°C. Absorption: λ_{max}, 500 nm; log ε, 4·9 (in methanol). $C_{18}H_{13}N_5SO_4$ requires C 54·6, H 3·2, N 27·7 and S 8·7%; found values were C 54·5, H 3·4, N 27·5 and S 9·0%. IR (Nujol) *v*: 3340–3330 cm^{-1} (—NH_2), 3150 cm^{-1} (NH).

3.7.2 Triazolisation of the azo derivative (18) to 3-naphtho-triazolyl-7-nitro-2H-1,2-benzothiazine-1,1-dioxide (19)

A mixture of **18** (0·395 g, 1 mmol) and copper (II) acetate (0·199 g, 1 mmol) was refluxed for 5 h in dimethylformamide (10 ml) with continuous passage of air. The reaction mixture was then poured into ice-water (20 ml) containing hydrochloric acid (5 ml) and the mixture stirred at 60° for 1 h. The product was filtered, washed with alcohol and recrystallised from dimethylformamide. Yield, 0·3 g (80%), m.p., 278°C. Absorption: λ_{max}, 360 nm; log ε, 4·1. Emission: λ_{max}, 408 nm. $C_{18}H_{13}N_5SO_4$ requires C 54·6, H 3·2, N 27·7 and S 8·7%; found values were C 54·4, H 3·4, N 27·5 and S 9·0%. IR (Nujol) *v*: 3150 cm^{-1} (—NH).

4 CONCLUSIONS

The present work has highlighted some novel methodologies in designing newer routes to complex heterocyclic derivatives. Further work is in

progress to study the efficacy of the 3-amino-, 3-oxo-, 3-aryl- and 3-hetaryl-7-nitro-2*H*-1,2,benzothiazine-1,1-dioxide derivatives in dyestuff chemistry.

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REFERENCES

1. Lombardino, J. G. & Kuhla, E. D. *Adv. Heterocycl. Chem.*, **28** (1981) 73.
2. Rajagopal, R. & Seshadri, S. *Dyes and Pigments*, **13** (1990) 93.
3. Rajagopal, R. & Seshadri, S. *Dyes and Pigments*, **13** (1990) 161.
4. Sianesi, E., Radaelli, R., Bertani, M. & Dare, P. *Chem. Ber.*, **103** (1970) 1992.
5. Jennsen, F. *Liebigs Annalen*, **172** (1884) 233.
6. Elsager, E. F., Maienthal, M. & Smith, D. P. *J. Org. Chem.*, **21** (1951) 1528.
7. Campaigne, E. & Archer, W. L., *Organic Synthesis Collective Volume 4*, ed. N. Rabjohn. John Wiley, New York, 1962, p. 331.
8. Campaigne, E., Budde, W. M. & Schaefer, G. F., *Organic Synthesis Collective Volume 4*, ed. N. Rabjohn. John Wiley, New York, 1962, p. 31.
9. Stolle, J. *J. Prakt, Chem.*, **64** (1904) 145.