Advances in Colour Science and Technology
Volume 6 Number 4 October 2003

Indigo revisited

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The synthesis of indigo and five derivatives containing electron-donating groups by the Baeyer-Drewsen method is described. An indigoid product containing ester groups was prepared *via* the corresponding 3-formylindole by a Dakin reaction. The blue dyes were characterised by their absorption (UV-Vis and IR) and NMR spectra, and either elemental analysis or mass spectrometry. The objective of this study was to prepare and fully characterise indigo derivatives with electron-donating groups and to obtain and characterise a carboxylated indigo derivative.

Keywords: dyes, dimethylindigo, tetramethoxyindigo, Baeyer-Drewsen method

INTRODUCTION

Indigo, one of the earliest known colorants, initially extracted from plants and later marketed as a synthetic product, is now produced at the rate of around 20,000 tons *per annum* and is used mainly for dyeing blue jeans [1].

The versatility of indigo is demonstrated by its application in fields other than the textile industry, for example as a traditional medicine, in cosmetics, in hair dyeing and as a paint pigment.

Although it is often suggested that India is the "home" of indigo, it may have seen earlier use in the Mediterranean region. A historical description of the application of indigo in the Arab world is given by Balfour-Paul [2].

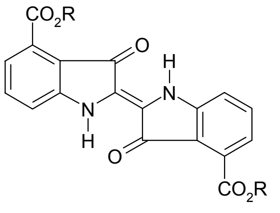
Archaeological findings in Egypt [3a], China and Peru demonstrated an extensive knowledge of textile technology, thousands of years before Christ. Methyl, methoxy and hydroxyindigos were known [3b] and indigo 4,4'-dicarboxylic acid **1** was made from isatin 4-carboxylic acid [4], their preparations being quite ancient. However, there are relatively few accounts of the complete characterisation of indigo derivatives, hence the investigation reported here.

The insolubility of indigo derivatives gives them excellent properties of washfastness, but it may also be the reason why little analytical data, particularly nuclear magnetic resonance spectra, is available.

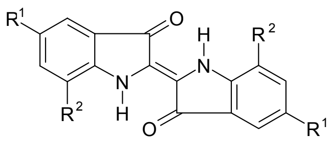
Recently ^{1}H and ^{13}C NMR spectroscopic data of indigoid dyes, as their leuco forms, have been described [5].

An excellent review of Tyrian Purple, the main component of which is 6,6´-dibromoindigo, was published by Cooksey [6].

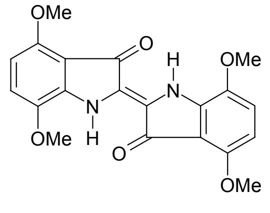
In this paper the synthesis and analytical data of the dimethyl ester **2** of indigo derivative **1**, five indigo derivatives **3**-**7** and unsubstituted indigo **8** will be described. The Baeyer-Drewsen method [3b], starting from *ortho*-nitrobenzaldehyde, was used to prepare most of these products.



1 R = H
2 R = Me



3 R^1 = Me, R^2 = H
4 R^1 = H, R^2 = Me
8 R^1 = R^2 = H



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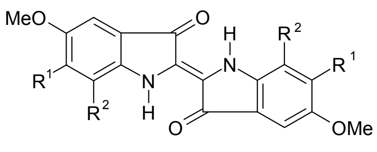
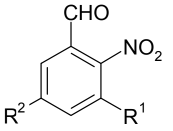


6 R^1 = H, R^2 = OMe
7 R^1 = OMe, R^2 = H

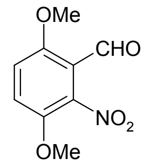
RESULTS AND DISCUSSION

The starting materials for indigos **3**, **4** were the corresponding *ortho*-nitrobenzaldehydes **9a** [7a] and **9b** [7b] obtained by nitration of the 3-methylbenzaldehyde at 0-5 °C in yields 40 and 30% respectively.

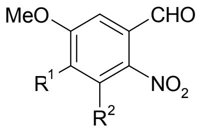


9a R^1 = Me, R^2 = H
9b R^1 = H, R^2 = Me

3,6-Dimethoxy-2-nitrobenzaldehyde [7b] **10**, the starting material for the synthesis of **5**, was prepared in 74% yield and nitrobenzaldehydes **11a** [8] and **11b** [7b] were obtained in 21 and 87% yield by nitration of the corresponding benzaldehydes.



10

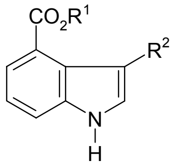


11a R^1 = H, R^2 = OMe
11b R^1 = OMe, R^2 = H

Methylated indigos **3** and **4** were obtained in 54 and 79% yields respectively. Lower yields were obtained for methoxylated indigos, 38% for indigo **6**, 31% for product **5** and 19% for indigo **7**.

When the preparation of 5,5',6,6'-tetramethoxy-indigo **7** was attempted by the Harley-Mason method [9] the yield was substantially lower (4%).

Indigo 4,4'-dicarboxylic acid dimethyl ester **2** was prepared in low yield (9%) by a Dakin reaction [10] from 3-formyl-1*H*-indole-4-carboxylic acid methyl ester **12b** [11]. This starting material was made by Vilsmeier formylation [12a] (73%) of the corresponding indole which was prepared, in 36% overall yield, from ethyl 2-methyl-3-nitrobenzoate by a published route [12b]. A more convenient method of preparation of **12b**, by metallation, has been described [13].



12a R^1 = Me, R^2 = H
12b R^1 = Me, R^2 = CHO
12c R^1 = H, R^2 = CHO

The yield for the preparation of indigo **2** was not reproducible, and subsequently lower yields were obtained or in some cases no product was formed. During chromatographic purification of this compound, extensive decolouration was observed possibly due to decomposition by sunlight [14].

The compounds were characterised by the usual analytical techniques (Tables 1-3). They did not melt below 330 °C and indigo **3** evolved violet vapours above 300 °C. A similar observation was recorded for indigo itself. This compound did not melt [20] below 320 °C but sublimed above 300 °C evolving violet vapours.

In view of the limited number of indigo derivatives prepared in this paper it was decided to add other literature data that might be useful for a better understanding of the relationship between the substituents and the resulting spectroscopic properties (Table 4).

For 4,4'-dimethoxycarbonyl-indigo **2** the C=O ester groups show their stretching vibrations at 1721 cm^{-1} and a signal at 188.8 ppm on the ^{13}C NMR spectrum.

Regarding the indigo chromophore, in general terms, any substituent that strengthens (or shortens) the C=O bond will increase its stretching frequency, and substituents that weaken (or elongate) that bond will decrease its stretching frequency. When compared to indigo itself, examples of indigos in which the C=O bond is strengthened are indigos **6**, and entries 9, 10, 11, 12 (Table 4) and Se, S, and O analogues; examples in which the C=O bond is weakened are compounds **2**, **7** and entry 5 (Table 4).

From the examples displayed in both tables the lowest wavenumber (1600 cm^{-1}) is observed with compound **2** and the highest (1689 cm^{-1}) with *N,N'*-diacetylindigo, and oxi-indigos (1692 cm^{-1}), where no intramolecular hydrogen bond is possible.

Absorption spectral data of indigo derivatives were thoroughly described and explained in terms of electron distributions [19].

The well known solvatochromism of indigo (mainly due to hydrogen bonding) is shown in the first entry in Table 4, where a bathochromic shift of the visible absorption band, is observed with an increase in solvent polarity.

In general, any substituent that reinforces the donor or acceptor characteristics of NH and C=O groups, respectively, will produce a bathochromic shift in the indigo absorption spectra. Opposite effects induce a hypsochromic deviation.

The hypsochromic effect due to the absence of intramolecular hydrogen bonds and to the electronegativity of the heteroatom present is patent in entry 12 (Table 4).

The effect of an N substituent on the availability of its lone pair is evident in the values shown by both compounds in entry 11.

Table 1: ^{1}H NMR data for compounds 2-8 and 12

	^{1}**H NMR**
2	δ_H (CDCl$_3$) 4.0 (6H, s, 2xCH$_3$), 7.16 (2H, d J 7.6 Hz, 7 and 7'-H), 7.34 (2H, d J 7.6 Hz, 5 and 5'-H), 7.52 (2H, t J 7,6 Hz, 6 and 6'-H), 9.20 (2H, br s, 2xNH)
3	δ_H (300 MHz, DMSO-d$_6$) 2.30 (6H, s, CH$_3$), 7.23 (2H, d J 7.7 Hz, 7 and 7'-H), 7.32 - 7.36 (2H, m, 6 and 6'-H), 7.41 (2H, br s , 4 and 4'-H), 10.35 (2H, s, N-H)
4	δ_H (300 MHz, CDCl$_3$) 2.37 (6H, s, 2x CH$_3$), 6.93 (2H, t J 7.9 Hz, 5 and 5'-H), 7.32 (2H, d J 7.9 Hz, 6 and 6'-H), 7.60 (2H, d J 7.9Hz, 4 and 4'-H), 8.80 (2H, br s, 2xNH)
5	δ_H (300 MHz, DMSO) 3.85 (6H, s, 2xOMe), 3.95 (6H, s, 2xOMe), 7.47 (2H, d J 9.47 Hz, 5 and 5´-H), 7.69 (2H, d J 8.95 Hz, 6 and 6´-H)
6	δ_H (CDCl$_3$, 300 MHz), 3.74 (6H, s, 2xOMe), 3.83 (6H, s, 2xOMe), 6.94 (2H, s, 6 and 6' -H), 7.00 (2H, s, 4 and 4'-H), 9.99 (2H, s, 2xNH)
7	δ_H (DMSO-d$_6$) 3.74 (6H, s, 2x OMe), 3.83 (6H, s, 2xOMe), 6.94 (2H, s, 7 and 7'-H), 7.00 (2H, s, 4 and 4'-H), 9.99 (2H, br s, 2x NH)
8	δ_H (DMSO-d$_6$) 6.92-6.98 (2H, m, 5 and 5'-H), 7.33 (2H, d br J 8.3 Hz, 7 and 7'-H), 7.49 - 7.55 (2H, m, 6 and 6'-H), 7.62 (2H, br d J 7.5 Hz, 4 and 4'-H), 10.5 (2H, s, 2xNH)
12a	δ_H (CDCl$_3$) 4.00 (3H, s, OCH$_3$) 7.18-7.22 (1H, m, 3-H), 7.24 (1-H, t J 7.7 Hz, 6-H), 7.35 (1H, tap J 2.6 Hz, 2-H), 7.60 (1H, dtap J 7.7 and 1 Hz, 7-H), 7.93 (1H, dd J 7.7 and 1Hz, 5-H), 8.58 (1H, br s, NH)
12b	δ_H (CDCl$_3$) 4.0 (3H, s, OCH$_3$), 7.32 (1H, t J 7.9 Hz, 6-H), 7.64 (1H, dd J7.9 and 1 Hz, 7-H), 7.84 (1H, dd J 7.9 and 1 Hz, 5-H), 8.07 (1H, d J 3.4 Hz, 2-H), 9.76 (1H, br s, NH), 10.50 (1H, s, CHO)
12c	δ_H (DMSO-d$_6$) 7.34 (1H, t J 6.9 Hz, 6-H), 7.72 (1H, dap J 6.9, 5 and 7-H), 8.26 (1H, s, 2-H), 10.46 (1H, s, CHO), 12.5 (1H, br s, NH) (OH not observed)

Table 2: Synthesis of indigo derivatives **2-8**

	Method	**Yield (%)**	**Appearance**	**υ [cm^{-1}] / (KBr)**	**λ_{max} [nm] (log ε)**
2	C	9	blue solid	3383, 1721, 1600	233 (3.77) 314 (3.27) 612 (3.17) 311 (4.1), 612 (3.72) (ethanol)
3	A	54	dark blue solid	3297, 1633	291 (4.50), 342 (4.09), 617 (4.22)
4^a	A	79	blue solid with red lustre	3414, 1633	288 (4.57), 342 (4.08), 429 (3.47), 611 (4.30)
5	A	31	dark blue solid	3422, 1643	256 (4.46), 295 (4.20), 395 (3.41), 644 (4.36)
6	A	38	dark blue solid	3472, 1631	226 (4.55), 309 (4.40), 358 (4.07), 665 (4.11)
7	A	19	dark blue solid with green lustre	3423, 1617	296 (4.41), 316 (4.22), 398 (4.37), 592 (3.98)
8^b	A	61	dark blue crystals	3244, 1626	285 (4.42), 603 (4.22)

All the UV/Vis spectra were run in CHCl$_3$ except for **2** where ethanol was also used
[a] Colour Index 73090 [b] Colour Index 73000

Table 3a: Mass spectrometry data for compounds **2-8**

	Mass spect. m/z (%) (IE)
2	381 (M$^+$+3, 10), 380 (M$^+$+2, 44), 379 (M$^+$+1, 22), 378 (M$^+$, 100), 347 (24), 346 (50), 292 (15), 288 (48), 288 (48), 232 (10), 184 (13)
3	291 (M$^+$+1, 31), 290 (M$^+$, 100), 261 (17), 233 (7), 145 (17)
4	291 (M$^+$+1, 47), 290 (M$^+$, 100) 261 (34) 233 (28), 145 (14)
5	383 (M$^+$+1, 37), 382 (M$^+$, 88), 367 (32), 203 (28), 71 (69), 69 (100), 57 (50), 55 (74)
6	382 (M$^+$, 100)
7	382 (M$^+$, 38), 93 (78), 91 (75), 84 (100), 79 (71), 67 (98), 62 (40)
8	263 (M$^+$ +1, 30), 262 (M$^+$, 100), 234 (16), 205 (27)

Table 3b: Elemental analysis for compounds **3-7**

	Found			**Required**		
	C	**H**	**N**	**C**	**H**	**N**
3	74.40	4.88	9.52	74.46	4.86	9.65
4	74.84	4.78	9.94	74.46	4.86	9.65
5	62.68	5.02	7.27	62.83	4.71	7.33
6	60.70	5.08	6.93	60.00	5.00	7.00
7	62.43	4.78	7.17	62.83	4.71	7.33

Table 4: Spectral data of indigo derivatives

Entry	**Compound**	**υ [cm^{-1}]**	**λ_{max} [nm]**	**Ref**
1	Indigo (CCl$_4$ / xylene / EtOH / DMSO)	----------	588/591/ 606/642	15
2	Indigo	3246 (NH), 1626 (C=O)	610	16
3	Indigo **8**	----------	613	1
4	6,6´-Dimethyl-indigo (xylene)	----------	588	17
5	4,4´,5,5´,6,6´-Hexamethoxy-indigo	3300 (NH) 1610	593	18
6	4,4´-Dichloro-indigo	3295 (NH) 1634	612	16
7	5,5´-Dichloro / dibromo-indigo	3285/3285 (NH) 1629/1639	615/616	16
8	6-Bromo / 6,6´-dibromo-indigo	3271/ 3300 (NH) 1610/1630	606/600	1, 6
9	6,6´/7,7´-Dichloro-indigo	3276/3389 (NH) 1631/1653	570/590	16
10	5,5´,7,7´-Tetrachloro / tetrabromo-indigo	3385/3372 (NH) 1650/1661	616/620	16
11	N,N´-Dimethyl / diacetyl-indigo	1639/1689 (C=O)	656/557	16
12	Seleno/thio/ox-indigo	1642/1656/ 1692 (C=O)	562/543/ 432	16
13	5-Ethoxy,5´-methoxy-indigo (CCl$_4$)	----------	645	19
14	6-Ethoxy,6´-methoxy-indigo (CCl$_4$)	----------	570	19

Note: All the UV/Vis spectra were run in EtOH except when stated otherwise.

A substituent (CO_2Me or Cl) in positions 4,4' does not significantly affect the λ_{max} position. Similarly, halogen or methyl groups in 5,5' have a weak influence on λ_{max}, but alkoxy groups do induce a significant bathochromic shift, possibly as a consequence of their donating resonance effect. Chlorine atoms or alkoxy groups at 6,6' induce a large hypsochromic shift (entries 9 and 14, Table 4).

In tetramethoxy indigo derivatives **6** and **7**, changing an OMe group from position 6 to 7 induces a large bathochromic deviation (73 nm). In compound **6** both OMe groups contribute to an increase in the availability of the N lone pair electrons and the resulting effect is comparable to *N,N'*-dimethylindigo.

Compound **6** showed the highest λ_{max} in the visible region of all the derivatives described in this paper. This would be expected since, as previously indicated [15] electrondonating groups in positions 5,5',7,7' will stabilise the first excited state, and therefore a lower energy is needed for excitation.

EXPERIMENTAL

Synthesis of indigo derivatives 3-6 and 8 (Method A (Baeyer-Drewsen) [3b])

The corresponding 2-nitrobenzaldehyde (7.11 mmol) was dissolved in acetone (20 ml), diluted with water (38 ml), a 2 N NaOH (5.5 ml) solution was added and the mixture was left stirring for five minutes. The dark blue solid was filtered, washed with water and ethanol and dried.

Synthesis of 5, 5´, 6, 6´-tetramethoxyindigo 7 (Method B (Harley-Mason) [9])

4,5-Dimethoxy-2-nitrobenzaldehyde **11b** (3 g, 16 mmol) and nitromethane (1.15 g, 19 mmol) in methanol (12 ml) were treated slowly at 0 °C with a solution (4 ml) of sodium methoxide in methanol (0.9 g of Na in 10 ml of methanol). After 12 hours at 4 °C, a yellow solid was collected, washed with ether and dissolved in water (25 ml). 2 N NaOH (7.5 ml) was added, and sodium dithionite (3.25 g) was then added slowly with stirring. Air was drawn through the solution for two hours and the indigo (230 mg, 4%) was obtained as a dark-blue greenish solid. δ(DMSO-d_6) 3.74 (6H, s, 2x OMe), 3.83 (6H, s, 2xOMe), 6.94 (2H, s, 7 and 7'-H), 7.00 (2H, s, 4 and 4'-H), 9.99 (2H, broad s, 2x NH). Part of this solid (60 mg) was submitted to chromatography and the indigo **7** was obtained in 3% yield.

Synthesis of indigo-4,4'-dicarboxylic acid dimethyl ester 2 (Method C Dakin reaction [10])

Synthesis of 1H-indole-4-carboxylic acid methyl ester 12a:

Reaction [21] of 2-methyl-3-nitrobenzoic acid with $SOCl_2$, in methanol, gave ethyl 2-methyl-3-nitrobenzoate in 97% yield as a white solid, m.p. 66-67 °C (lit.[22] m.p. 66 °C). From the above ester, *N,N'*-dimethylformamide dimethylacetal and pyrrolidine were obtained in 80% yield (slightly contaminated with the starting ester) and methyl *E*-2-β-pyrrolidinitrostyrene-3-nitrobenzoate, as a reddish oil [12b]. The above styrene was treated with hydrazine and Raney Ni and gave the 1*H*-indole-4-carboxylic acid methyl ester **12a** (63%) [20] as an oil that solidified m.p. 64-64.8 °C (lit.[23a] 63 °C, [23b] 64 °C).

Synthesis of 3-formyl-1H-indole-4-carboxylic acid methyl ester 12b:

The above indole was formylated [12a] in DMF/$POCl_3$ and the 3-formyl-1*H*-indole-4-carboxylic acid methyl ester **12b** was obtained as a beige solid (73%), m.p. 130.2-131.4 °C (lit. 134–135 °C [11]).

In another preparation using the same experimental conditions compound **12b** was obtained in a lower yield (21%). Acidification of the aqueous extracts to neutral pH gave the 3-formyl-1*H*-indole-4-carboxylic acid **12c** as a light pink solid (13%) mp 211-218 °C. ν_{max} (Nujol)/cm^{-1} 3200-2500 (OH), 1687, 1632, 1573, 1497, 1314, 1259, 1198, 1145, 1051, 1021, 920, 898, 888, 736, 664; m/z (%) 203 (M^+, 72), 188 (100), 172 (28), 143 (62), 116 (65), 89 (78). Found: C, 63.40; H, 3.80; N, 7.49 %. $C_{10}H_7NO_3$ requires: C, 63.49; H, 3.73; N, 7.40 %.

Synthesis of indigo-4,4'-dicarboxylic acid dimethyl ester 2:

To a solution of 3-formyl-1*H*-indole-4-carboxylic acid methyl ester **12b** (97 mg, 0.48 mmol) in a 1 N NaOH aqueous solution (1 ml), a 1% H_2O_2 solution (0.6 ml) was added and the mixture was left stirring, at room temperature, for 3 hours. A blue solid precipitated which was filtered, washed with water, dried and submitted to preparative chromatography (silica, chloroform). The main product (R_f 0.45) was obtained as an oily blue solid and identified as indigo-4,4'-dicarboxylic acid dimethyl ester **2** (17 mg, 9%). δ_C ($CDCl_3$) 52.3 (2xOMe), 116.4 (2xCH), 119.6, 122.9 (2xCH), 124.4, 125.1 (2xCH), 133.7, 137.7, 168.9 (2 x C=O), 188.8 (2 x CO_2Me). Found (HRMS) 378.0843; required for $C_{20}H_{14}N_2O_6$ 378.0852.

CONCLUSIONS

Six derivatives of indigo were prepared, purified and fully characterised. The product indigo-4,4'-dicarboxylic acid dimethyl ester **2** was found to be difficult to synthesise and unstable during purification.

An attempt was made to relate the structure of the indigo-class dyes to the absorption properties. It is expected that the information described in this paper will be useful to other researchers interested in this class of compounds.

ACKNOWLEDGEMENTS

Thanks are due to Prof. G. Kirsch for helpful suggestions, to FCT-Portugal, for support through IBQF-UM, PRAXIS and FEDER under project PRAXIS XXI/2/2.1/QUI/44/94 and for a scholarship to PCRSS and also to Departamento de Gestão de Recursos Educativos do Ministério de Educação, Portugal, for a Sabatical leave to MIGMGT.

REFERENCES

1. RJH Clark , CJ Cooksey, MAM Daniels and R Withnall, *Educ. Chem,* 16, (1996)
2. J Balfour-Paul in *Indigo in the Arab world*, Curzon Press, Richmond, Surrey (1997)
3. (a) M Sainsbury in *Rodd's Chemistry of Carbon Compounds*, **IVB**, Elsevier, 2nd Ed. Amsterdam, p. 346 (1977); (b) M Sainsbury in *Rodd's Chemistry of Carbon Compounds*, **IVB**, Elsevier, 2nd Ed. Amsterdam, p. 345 and p 353 (1977)
4. P Friedlander and J Weisberg, *Berichte*, 1641, (1895)
5. G Voss, *J Soc Dyers Colour*, **116**, 87 (2000)
6. CJ Cooksey, *Molecules,* **6**, 736, (2001)
7. (a) JRA Pollock and R Stevens in *Dictionary of Organic Compounds*, Eyre & Spottiswoode Pub. Ltd. London, **Vol. 4**, 2515, (1965); (b) *ibid*, **Vol. 2**, 1130, (1965)
8. KV Rao, *J Heterocycl Chem*, **14** (4), 653, (1977)
9. J Harley-Mason, *J Chem Soc*, 2907, (1950)
10. A Chatterjee, GK Biswas and AB Kundu, *J Indian Chem Soc*, **46** (5), 429, (1969)
11. CV Ananthanarayanan, N Rastogi, GK Patnaik and N Anand, *CA*, **88**, 121125v, (1978); *Indian J Chem* , **15 B**, 710, (1977)
12. (a) PN James and HR Snyder in *Organic Syntheses*, Coll. Vol. IV, John Wiley and Sons, Inc., New York, 539, (1963); (b) AD Batcho and W Leimgruber in *Organic Syntheses*, Coll. Vol. VII, John Wiley and Sons, Inc., New York, 34, (1990)
13. F Yamada and M Somei, *Heterocycles*, **26** (5), 1173 (1987)
14. S Sakamura and Y Obata, *CA*, **51**, 11081g (1957).
15. J Shore in *Colorants and Auxiliaries*, **1**, 9-10 and 267-273, (1990)
16. M Luettke and M Klessinger, *Chem Ber*, **97** (8), 2342, (1964)
17. A Martinet, *CR Acad Sc Paris*, **264**, série C 2063-6 (1967)
18. MJS Hewlins, AH Jackson, AMF Oliveira-Campos and PVR Shannon, *J Chem Soc Perkin Trans 1*, 2906, (1981)
19. J Fabian and H Hartman in *Light Absorption of Organic Colorants*, Springer Verlag, Berlin, p. 115-128, (1980).
20. LM Harwood and CJ Moody in *Experimental Organic Chemistry*, Blackwell Scientific Publ., Oxford, 660, (1989)
21. AP Kozikowski, H Ishida and Y-Y Chen, *J Org Chem*, **45**, 3350, (1980)
22. LF Tietze and Th Eicher in *Reactions and Syntheses in Organic Chemistry Laboratory*, University Science Books, Mill Valley, 185, (1989)
23. (a) GS Ponticello and JJ Baldwin, *J Org Chem*, **44**, (22), 4003, (1979); (b) E Hardegger and H Corrodi, *Helv Chim Acta,* **37**, 1826, (1954)