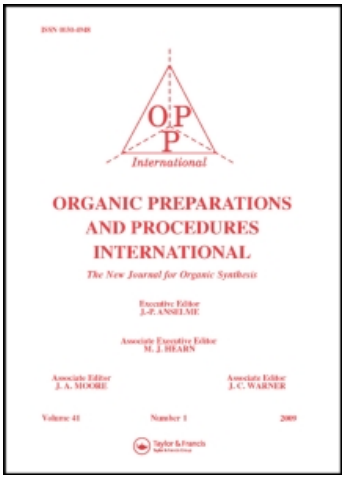


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

REGIOSELECTIVITY OF THE METHYL-TOSMIC REACTION WITH SUBSTITUTED ETHYL CINNAMATES

Roberto Di Santo[a]; Roberta Costi[a]; Carlo Galeffi[a]; Michela Forte[a]
[a] "Istituto Pasteur-Fondazione Cenci Bolognetti"-Dipartimento di Studi Farmaceutici, Università di Roma "La Sapienza", Roma, ITALY

To cite this Article Santo, Roberto Di , Costi, Roberta , Galeffi, Carlo and Forte, Michela(2005) 'REGIOSELECTIVITY OF THE METHYL-TOSMIC REACTION WITH SUBSTITUTED ETHYL CINNAMATES', Organic Preparations and Procedures International, 37: 2, 178 — 183
To link to this Article: DOI: 10.1080/00304940509354884
URL: http://dx.doi.org/10.1080/00304940509354884

REGIOSELECTIVITY OF THE METHYL-TOSMIC REACTION WITH SUBSTITUTED ETHYL CINNAMATES

Submitted by (12/13/04)

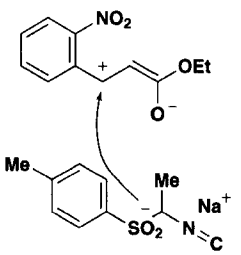
Roberto Di Santo*, Roberta Costi, Carlo Galeffi, and Michela Forte

"Istituto Pasteur-Fondazione Cenci Bolognetti"-Dipartimento di Studi Farmaceutici, Università di Roma "La Sapienza" Piazzale Aldo Moro 5, I-00185 Roma, ITALY
e-mail: roberto.disanto@uniroma1.it
Telephone & Fax: +39-06-49913150

Tosylmethyl isocyanide (TosMIC) is an attractive building block useful in the synthesis of cyclic ketones, nitriles, amines, and expecially in heterocyclic synthesis.[1] Substances with carbon-carbon double bond conjugated to electron-withdrawing groups, such as carbonyl, nitrile and nitro groups, have been widely employed in the synthesis of 3,4-disubstituted pyrroles, using α- metalated tosylmethyl isocyanide.[1-4] Moreover, 2,3,4-trisubstituted pyrroles were obtained by reaction of α-monosubstituted TosMIC with the above mentioned olefin derivatives.[3,5-7]

Our decade-long interest in the chemistry of pyrrole annulated heterocyclic systems led us to explore new routes to synthesize 2*H*-pyrrolo[3,4-*c*]quinoline derivatives, with the aim to obtain new potential ligands of the 5-HT receptors. A recent paper[8] reported the synthesis of 1-substituted 2*H*-pyrrolo[3,4-*c*]quinolines *via* the Me-TosMIC reaction with ethyl cinnamates. Surprisingly, the reaction of ethyl 2-nitrocinnamate with Me-TosMIC with the intention of obtaining the key intermediate ethyl 2-methyl-3-(2-nitrophenyl)-1*H*-pyrrole-4-carboxylate (**2a**), gave both the expected **2a** and its isomer ethyl 2-methyl-4-(2-nitrophenyl)-1*H*-pyrrole-3-carboxylate (**3a**); it is well known that the same reaction with similar Michael acceptors such as methyl cinnamate or 1,3-diphenylpropenone gave 5-methyl derivatives as the sole products.[9,10] Our hypothesis was that the nitro substituent at the 2-position of the phenyl ring altered the polarization of the cinnamate double bond, making possible the competitive attack of Me-TosMIC at the 2- or 3-position of the acrylate moiety (*Fig. 1*).

Nucleophilic attack on C3



Nucleophilic attack on C2

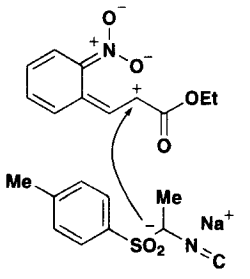
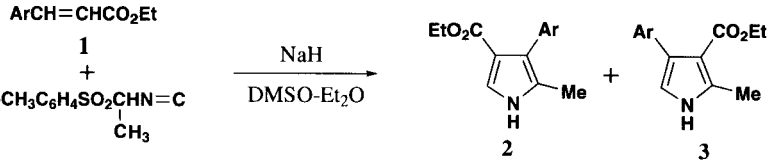


Fig. 1

These results prompted us to study the regioselectivity of the Me-TosMIC reaction with ethyl cinnamates substituted on the phenyl ring.



a) Ar = 2-$NO_2C_6H_4$; b) Ar = 4-$NO_2C_6H_4$; c) Ar = 2-CNC_6H_4; d) Ar = 5-Cl-2-$NO_2C_6H_3$; e) Ar = 2,4-$(NO_2)_2C_6H_3$; f) Ar = 3-$NO_2C_6H_4$; g) Ar = 3-CNC_6H_4; h) Ar = 4-CNC_6H_4; i) Ar = 2-$CO_2EtC_6H_4$; j) Ar = 3-$CO_2EtC_6H_4$; k) Ar = 4-$CO_2EtC_6H_4$; l) Ar = 2-ClC_6H_4; m) Ar = 3-ClC_6H_4; n) Ar = 4-ClC_6H_4; o) Ar = 4-MeC_6H_4; p) Ar = 2-$MeOC_6H_4$; q) Ar = 3-$MeOC_6H_4$; r) Ar = 4-$MeOC_6H_4$

Scheme 1

Thus ethyl cinnamates **1a-r** (obtained from the appropriate aldehydes by the Wittig-Horner reaction) were treated with Me-TosMIC, in the presence of NaH as the base, under typical conditions used to obtain 2,3,4-trisubstituted pyrroles (anhydrous DMSO/Et_2O mixture). The substituents were chosen among electron-withdrawing (Cl, NO_2, CN, COOEt) and electron-donating groups (Me, OMe) and the substitutions in 2-, 3- or 4-position of the phenyl ring were investigated.

As expected from the rationale discussed above, the reaction furnished the 5-methyl derivatives **2**, and in some cases 2-methyl derivatives **3a-e** depending upon the substituents and their location on the phenyl ring (*Table 1*).

Table 1. Yields, mps, Physical Data and Elemental Analyses of Compounds **2** and **3**

Cmpd	Yield (%)	mp.[a] (°C)	Color	Elemental Analyses Calcd (Found) C	H	N
2a[8]	20	----	Yellow oil	61.31 (61.29)	5.14 (5.15)	10.22 (10.17)
3a[8]	20	152-154	Yellow solid	61.31 (61.30)	5.14 (5.26)	10.22 (10.40)
2b	9	----	Dark oil	61.31 (61.41)	5.14 (5.08)	10.22 (10.23)
3b	30	----	Brown oil	61.31 (61.46)	5.14 (5.04)	10.22 (10.17)
2c	30	153-156	Yellow solid	70.85 (70.69)	5.55 (5.66)	11.02 (11.10)
3c	3	----	Yellow oil	70.85 (70.91)	5.55 (5.62)	11.02 (11.03)
2d[b,8]	8	129-132	Yellow solid	54.47 (54.46)	4.24 (4.11)	9.07 (9.13)
3d[c,8]	42	158-160[d]	Yellow solid	54.47 (54.54)	4.24 (4.25)	9.07 (9.09)
3e	20	168-171[d]	Light brown solid	52.67 (52.78)	4.10 (4.03)	13.16 (13.26)
2f	56	187-190[d]	Yellow-orange solid	61.31 (61.44)	5.14 (5.05)	10.22 (10.15)
2g	36	145-148	Yellow solid	70.85 (70.77)	5.55 (5.62)	11.02 (11.15)
2h	16	150-152[d]	Yellow solid	70.85 (70.80)	5.55 (5.59)	11.02 (11.00)
2i	44	----	Brown oil	67.76 (67.68)	6.36 (6.38)	4.65 (4.71)
2j	23	----	Brown oil	67.76 (67.79)	6.36 (6.27)	4.65 (4.62)

Table 1. Continued...

Cmpd	Yield (%)	mp.[a] (°C)	Color	Elemental Analyses Calcd (Found) C	H	N
2k	48	----	Brown oil	67.76 (67.64)	6.36 (6.44)	4.65 (4.78)
2l[e]	52	132-135	Yellow solid	63.76 (63.71)	5.35 (5.44)	5.31 (5.42)
2m[f]	55	118-121	Pale yellow solid	63.76 (63.77)	5.35 (5.30)	5.31 (5.45)
2n[g]	49	142-145	White solid	63.76 (63.74)	5.35 (5.35)	5.31 (5.34)
2o	42	164-167	Pale yellow solid	74.05 (74.17)	7.04 (7.10)	5.76 (5.82)
2p	36	107-110	Brown solid	69.48 (69.60)	6.61 (6.68)	5.40 (5.29)
2q	45	110-114	Yellow solid	69.48 (69.53)	6.61 (6.64)	5.40 (5.37)
2r	26	116-119	Yellow solid	69.48 (69.55)	6.61 (6.63)	5.40 (5.32)

a) Solid recrystallized from benzene-cyclohexane unless otherwise indicated. b) Cl Analysis: Cl: 11.48. Found: 11.39. c) Cl Analysis: Cl: 11.48. Found: 11.35. d) Recrystallized from benzene. e) Cl Analysis: Cl: 13.44. Found: 13.48. f) Cl Analysis: Cl: 13.44. Found: 13.40. g) Cl Analysis: Cl: 13.44. Found: 13.45.

As reported above, the first clear formation of two isomers was observed when Me-TosMIC was reacted with ethyl 2-nitrocinnamate, these two compounds were isolated in similar yields (20%). The ^{1}H NMR spectrum of the first product showed two signals at δ 7.30 (d) and 2.10 (s), which were respectively assigned to pyrrole C2-H and to the methyl group on pyrrole C5 of **2a**, while the ^{1}H NMR spectrum of the second product showed two signals at δ 6.60 (d) and 2.48 (s), which were assigned to pyrrole C5-H and to the methyl group on pyrrole C2 of isomer **3a**.[8] The presence of the carbethoxy group accounts for the deshielding of the adjacent pyrrole hydrogen at C2 of **2a** and of the methyl group at C2 of **3a** (*Table 2*).

Table 2. IR and ^{1}H NMR Spectra of Compounds **2** and **3**

Cmpd	IR (cm^{-1})	^{1}H NMR (δ, $CDCl_3$)
2a	3310 (NH) 1685 (C=O)	1.10 (t, 3H, CH_2CH_3), 2.10 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 7.30-7.36 (m, 2H, pyrrole C2-H and benzene C6-H), 7.45 and 7.58 (2m, 2H, benzene C4-H and C5-H), 8.00 (dd, 1H, benzene C3-H), 8.85 (broad s, 1H, NH)
3a	3310 (NH) 1680 (C=O)	0.98 (t, 3H, CH_2CH_3), 2.48 (s, 3H, CH_3), 3.97 (q, 2H, CH_2), 6.65 (d, 1H, pyrrole C5-H), 7.37 (dd, 1H, benzene C6-H), 7.42 and 7.54 (2m, 2H, benzene C4-H and C5-H), 7.98 (dd, 1H, benzene C3-H), 8.30 (broad s, 1H, NH)
2b	3307 (NH) 1697 (C=O)	1.21 (t, 3H, CH_2CH_3), 2.16 (s, 3H, CH_3), 4.16 (q, 2H, CH_2), 7.42 (d, 1H, pyrrole C2-H), 7.48 (d, 2H, benzene C2-H and C6-H), 8.22 (d, 2H, benzene C3-H and C5-H), 8.35 (broad s, 1H, NH)
3b	3306 (NH) 1664 (C=O)	1.20 (t, 3H, CH_2CH_3), 2.55 (s, 3H, CH_3), 4.20 (q, 2H, CH_2), 6.67 (d, 1H, pyrrole C5-H), 7.54 (d, 2H, benzene C2-H and C6H), 8.19 (d, 2H, benzene C3-H and C5-H), 8.63 (broad s, 1H, NH)

Table 2. Continued...

Cmpd	IR (cm^{-1})	^1H NMR (δ, $CDCl_3$)
2c	3271 (NH) 2225 (CN) 1667 (C=O)	1.16 (t, 3H, CH_2CH_3), 2.13 (s, 3H, CH_3), 4.13 (q, 2H, CH_2), 7.36 (d, 1H, pyrrole 7.42-7.37 (m, 2H, benzene C5-H and C6-H), 7.57 (t, 1H, benzene C4-H), 7.70 (d, 1H, benzene C3-H), 8.59 (broad s, 1H, NH)
3c	3296 (NH) 2225 (CN) 1693 (C=O)	1.09 (t, 3H, CH_2CH_3), 2.58 (s, 3H, CH_3), 4.14 (q, 2H, CH_2), 6.70 (d, 1H, pyrrole C5-H), 7.35 (t, 1H, benzene C5-H), 7.37 (d, 1H, benzene C6-H), 7.51 (t, 1H, benzene C4-H), 7.66 (d, 1H, benzene C3-H), 8.42 (broad s, 1H, NH)
2d	3280 (NH) 1675 (C=O)	1.11 (t, 3H, CH_2CH_3), 2.06 (s, 3H, CH_3), 4.12 (q, 2H, CH_2), 7.25-7.35 (m, 2H, pyrrole C2-H and benzene C6-H), 7.40 (dd, 1H, benzene C4-H), 7.96 (d, 1H, benzene C3-H), 8.48 (broad s, 1H, NH)
3d	3320 (NH) 1665 (C=O)	1.08 (t, 3H, CH_2CH_3), 2.53 (s, 3H, CH_3), 4.07 (q, 2H, CH_2), 6.61 (d, 1H, pyrrole C5-H), 7.36-7.39 (m, 2H, benzene C4-H and C6-H), 7.93 (d, 1H, benzene C3-H), 8.44 (broad s, 1H, NH)
3e	3309 (NH) 1666 (C=O)	1.18 (t, 3H, CH_2CH_3), 2.63 (s, 3H, CH_3), 4.16 (q, 2H, CH_2), 6.77 (d, 1H, pyrrole C5-H), 7.65 (d, 1H, benzene C6-H), 8.43-8.46 (m, 2H, benzene C3-H and C5-H), 8.89 (broad d, 1H, pyrrole N-H)
2f	3283 (NH) 1678 (C=O)	1.10 (t, 3H, CH_2CH_3), 2.15 (s, 3H, CH_3), 4.09 (q, 2H, CH_2), 7.35 (d, 1H, pyrrole C2-H), 7.45 (t, 1H, benzene C5-H), 7.60 (dd, 1H, benzene C6-H), 8.08 (dd, 1H, benzene C4-H), 8.12 (d, 1H, benzene C2-H), 8.27 (broad s, 1H, NH)
2g	3315 (NH) 2228 (CN) 1682 (C=O)	1.11 (t, 3H, CH_2CH_3), 2.12 (s, 3H, CH_3), 4.08 (q, 2H, CH_2), 7.33 (d, 1H, pyrrole C2-H), 7.38 (t, 1H, benzene C5-H), 7.53-7.47 (m, 3H, benzene C2-H, C4-H and C6-H), 8.32 (broad s, 1H, NH)
2h	3295 (NH) 2226 (CN) 1677 (C=O)	1.18 (t, 3H, CH_2CH_3), 2.19 (s, 3H, CH_3), 4.16 (q, 2H, CH_2), 7.39 (d, 1H, pyrrole C2-H), 7.42 (d, 2H, benzene C2-H and C6-H), 7.63 (d, 2H, benzene C3-H and C5-H), 8.44 (broad s, 1H, NH)
2i	3315 (NH) 1687 (C=O)	0.99 (t, 3H, $ArCOOCH_2CH_3$), 1.09 (t, 3H, pyrrolyl-$COOCH_2CH_3$), 1.96 (s, 3H, CH_3), 3.96 (q, 2H, benzene CH_2), 4.07 (q, 2H, pyrrole CH_2),7.16 (d, 1H, benzene C6-H), 7.21 (d, 1H, pyrrole C2-H), 7.27 (t, 1H, benzene C5-H), 7.40 (t, 1H, benzene C4-H), 7.85 (d, 1H; benzene C3-H), 8.74 (broad s, 1H, NH)
2j	3400 (NH) 1708 (C=O)	0.96 (t, 3H, $ArCOOCH_2CH_3$), 1.16 (t, 3H, pyrrolyl-$COOCH_2CH_3$), 1.95 (s, 3H, CH_3), 3.91 (q, 2H, benzene CH_2), 4.17 (q, 2H, pyrrole CH_2), 7.28 (d, 1H, pyrrole C2-H), 7.31 (t, 1H, benzene C6-H), 7.40 (m, 1H, benzene C5-H), 7.85 (dd, 1H, benzene C4-H), 7.88 (d, 1H, benzene C2-H), 9.31 (broad s, 1H, NH)
2k	3310 (NH) 1682 (C=O)	1.17 (t, 3H, $ArCOOCH_2CH_3$), 1.38 (t, 3H, pyrrolyl-$COOCH_2CH_3$), 2.17 (s, 3H, CH_3), 4.15 (q, 2H, benzene CH_2), 4.37 (q, 2H, pyrrole CH_2), 7.36 (d, 1H, pyrrole C2-H), 7.37 (d, 2H, benzene C2-H and C6-H), 8.04 (d, 2H, benzene C3-H and C5-H), 8.54 (broad s, 1H, NH)
2l	3267 (NH) 1671 (C=O)	1.08 (t, 3H, CH_2CH_3), 2.07 (s, 3H, CH_3), 4.09 (q, 2H, CH_2), 7.26-7.20 (m, 3H, benzene C4-H, C5-H and C6-H), 7.37 (d, 1H, pyrrole C2-H), 7.42 (dd, 1H, benzene C3-H), 8.48 (broad s, 1H, NH)
2m	3278 (NH) 1681 (C=O)	1.11 (t, 3H, CH_2CH_3), 2.09 (s, 3H, CH_3), 4.07 (q, 2H, CH_2), 7.23-7.11 (m, 4H, benzene C2-H, C4-H, C5-H and C6-H), 7.29 (d, 1H, pyrrole C2-H), 8.49 (broad s, 1H, NH)

Table 2. Continued...

Cmpd	IR (cm^{-1})	^1H NMR (δ, $CDCl_3$)
2n	3299 (NH) 1682 (C=O)	0.89 (t, 3H, CH_2CH_3), 2.16 (s, 3H, CH_3), 3.89 (q, 2H, CH_2), 7.30 (d, 1H, C2-H), pyrrole C2-H), 7.34 (d, 2H, benzene C2-H and C6-H), 7.81 (d, 2H, benzene C3-H and C5-H), 8.46 (broad s, 1H, NH)
2o	3285 (NH) 1673 (C=O)	1.20 (t, 3H, CH_2CH_3), 2.15 (s, 3H, CH_3), 2.36 (s, 3H, pyrrole CH_3), 4.17 (q, 2H, CH_2), 7.15 (d, 2H, benzene C2-H and C6-H), 7.22 (d, 2H, benzene C3-H and C5-H), 7.30 (d, 1H, pyrrole C2-H), 8.46 (broad s, 1H, NH)
2p	3291 (NH) 1678 (C=O)	1.04 (t, 3H, CH_2CH_3), 2.01 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.07 (q, 2H, CH_2), 6.85 (t, 1H, benzene C5-H), 6.90 (t, 1H, benzene C4-H), 7.10 (dd, 1H, benzene C6-H), 7.19 (d, 1H, benzene C3-H), 7.23 (d, 1H, pyrrole C2-H), 8.49 (broad s, 1H, NH)
2q	3309 (NH) 1686 (C=O)	1.11 (t, 3H, CH_2CH_3), 2.10 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.08 (q, 2H, CH_2), 6-85-6.74 (m, 3H, benzene C4-H, C5-H and C6-H), 7.20 (t, 1H, benzene C2-H), 7.28 (d, 1H, pyrrole C2-H), 8.33 (broad s, 1H, NH)
2r	3312 (NH) 1682 (C=O)	1.12 (t, 3H, CH_2CH_3), 2.10 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.09 (q, 2H, CH_2), 6.85 (d, 2H, benzene C2-H and C6-H), 7.17 (d, 2H, benzene C3-H and C5-H), 7.29 (d, 1H, pyrrole C2-H), 8.18 (broad s, 1H, NH)

The effect of the position of the nitro group was investigated further. Interestingly, the reaction of ethyl 2-nitrocinnamate gave a 1:1 ratio of **2a** to **3a** while 4-nitrocinnamate afforded **2b** and **3b** in a ratio of 1:3.3. This result may be rationalized in terms of more efficient conjugation with the 4-nitro group which is not subject to the steric hindrance (to perfect co-planarity) of the 2-nitro substituent. The ethyl 3-nitrocinnamate (**1f**) gave only the 5-methyl derivative **2f**, thus supporting the hypothesis that the inductive effect is marginal at best compared with the mesomeric one. The presence of both a NO_2 group and a chlorine atom (**1d**) furnished a **2d/3d** ratio of 1:5.3, while two NO_2 groups in the 2,4-positions led to 2-methyl derivative **3e** as the sole product, thus completely reversing the reactivity of the acrylate moiety. Among the remaining electron-withdrawing groups (Cl, COOEt, CN), only the nitrile at 2-position afforded both isomers (**2c** and **3c** derivatives, ratio 1:0.1). Lastly, electron-donor groups (Me, OMe) gave exclusively the 5-methyl isomers.

In conclusion, the presence of a NO_2 group on the 2- or 4-position of the phenyl ring causes a competition with the ester function in the polarization of the ethene moiety of the cinnamate, favoring attack of the nucleophile at the 2-position of the carbon chain. This effect is enhanced by the presence of two electron-withdrawing groups (Cl and NO_2), while the 2-CN function exerts only a weak effect. The other electron-withdrawing groups (COOEt, Cl and 3- and 4-CN) are not sufficient to lead to the reversal of polarization discussed above.

EXPERIMENTAL SECTION

Mps were determined on a Buchi 530 melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum-one spectrophotometer. ^1H NMR spectra were recorded at 400 MHz on a Bruker AC 400 Ultrashield spectrophotometer using tetramethylsilane

(Me_4Si) as the internal reference standard. Column chromatographies were performed on aluminum oxide (Merck; 70-230 mesh). All compounds were routinely checked by TLC using aluminum-backed alumina plates (Fluka DC-Alufolien Kieselgel 60 F_{254}). Developed plates were visualized by UV light. Solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of rotary evaporator (Buchi) operating at reduced pressure (ca. 20 Torr). Organic solutions were dried over anhydrous sodium sulfate. Analytical results agreed to within 0.30% of the theoretical values. All compounds were analyzed for C, H, N, and, when present, Cl.

General Procedure for the Preparation of Pyrroles 2 and 3.- A solution of **1** (10 mmol) and Me-TosMIC (10 mmol, 2.1 g) in anhydrous DMSO-Et_2O mixture (13:26 mL) was added dropwise into a well-stirred suspension of sodium hydride (22 mmol, 0.9 g, 60% in mineral oil) in anhydrous Et_2O (26 mL) under an argon atmosphere. Then, the mixture was stirred at room temperature for 15 h, carefully treated with water (30 mL) and extracted with ethyl acetate (3 x 50 mL). The organic extracts were collected, washed with brine (3 x 30 mL), dried, and the solvent was evaporated *in vacuo*. The crude products were separated by chromatography on alumina column (chloroform as eluent) to afford compounds **2** and, when present, **3** (*Tables 1 and 2*).

Acknowledgements.- The authors thank Professor Marino Artico for his helpful comments and the Italian MIUR for financial support.

REFERENCES

1. A. M. van Leusen, *Lect. Heterocyclic Chem.*, **5**, S111 (1980).

2. R. Di Santo, S. Massa and M. Artico, *Farmaco*, **48**, 209 (1993).

3. A. M. van Leusen, H. Siderius, B. E. Hoogenboom and D. van Leusen, *Tetrahedron Lett.*, **52**, 5337 (1972).

4. S. Massa, R. Di Santo, R. Costi, A. Mai, and M. Artico, *Med. Chem. Res.*, **3**, 192 (1993).

5. R. Di Santo, R. Costi, S. Massa and M. Artico, *Synth. Commun.*, **25**, 795 (1995).

6. O. Possel and A. M. van Leusen, *Heterocycles*, **7**, 77 (1977).

7. H. P. Dijkstra, R. ten Have and A. M. van Leusen, *J. Org. Chem.* **63,** 5332 (1998).

8. R. Di Santo, R. Costi, M. Forte and C. Galeffi, *ARKIVOC* (**5**), 181 (2004); *Chem. Abstr.*, **141**, 225282 (2004).

9. A. M. van Leusen, R. J. Bouma and O. Possel, *Tetrahedron Lett.*, **40,** 3487 (1975).

10. R. Baumes, R. Jacquier and G. Tarrago, *Bull. Soc. Chim. Fr.*, 1147 (**1974**).