Pergamon

Tetrahedron 56 (2000) 9669–9674

TETRAHEDRON

Pyridinium *N*-Ylides and (Arylmethylene)azol-5-ones. Reaction Cascade Leading to an Unusual Spiroisoxazolinone Ring

Francesco Risitano,* Giovanni Grassi, Francesco Foti and Cristina Bilardo

Istituto di Chimica dei Composti eterociclici, Università, Vill. S. Agata, I-98166 Messina, Italy

Received 7 July 2000; revised 7 September 2000; accepted 28 September 2000

Abstract—The reaction of a series of (arylmethylene)azol-5-ones with phenacylpyridinium salt **3** in glacial acetic acid/ammonium acetate mixture gives different results depending on the starting azolone. The isoxazol-5-ones **1** give the unusual spirans **6** in a reaction cascade involving Michael- and retro-Michael reactions, *C*-alkylation, aldol addition, and diastereospecific cyclization. The reaction performed with oxazol-5-ones **11** has shown that a literature report has to be corrected since no oxazolopyridines **12** but rather arylideneimidazol-5-ones **13** are produced. In the case of pyrazolin-5-ones **14**, the unavoidable formation of bis-adducts **15** always prevents any other type of reaction.

Introduction

4-(Arylmethylene)isoxazol-5-ones **1** remarkably show heterodienic behaviour towards Diels–Alder reactions with a variety of electron-rich dienophiles and can be considered as a useful means for the preparation of fused heterocycles.[1] On the other hand the exocyclic double bond of these arylmethylene derivatives **1** can also work perfectly well as an electrophilic or dipolarophilic unit. Nevertheless, while it is recognised that it can easily undergo addition reactions of primary and secondary amines[2] and with C-nucleophiles[3] to give open-chain adducts, its dipolarophilic reactivity with 1,3-dipoles has successfully been tested in only a few cases and is limited to nitrile oxides,[4] munchnones[5] and benzonitrilium *N*-phenylimides.[6]

Some of our recent work on the reactivity of the above-mentioned arylidene derivatives **1** towards the easily accessible dipole-like **2** has demonstrated that these intermediates readily react with **1**, but only as C-nucleophiles, producing high yields of stable betaines **4**.[7] Although these zwitterions have shown no tendency to rearrange into fused 5.5 or 5.6 heterocycles, similar non-isolated intermediates have nevertheless been thought to have been successfully converted into carbocyclic aromatic systems or substituted and annelated pyridines.[8] Generally the latter transformation is achieved by getting α,β-unsaturated carbonylic compounds, sometimes incorporated in rings, to react with pyridinium salts **3** in a mixture of glacial acetic acid and ammonium acetate which may liberate in situ the appropriate ylide **2** and provide the nitrogen of the final heterocycle. This result has suggested that similar treatment with $AcOH/AcONH_4$ of arylidene derivatives **1** and ylides **2** or of betaines **4** would be an attractive and versatile route to known isoxazolo-[5,4-*b*]pyridine systems **5**.[9]

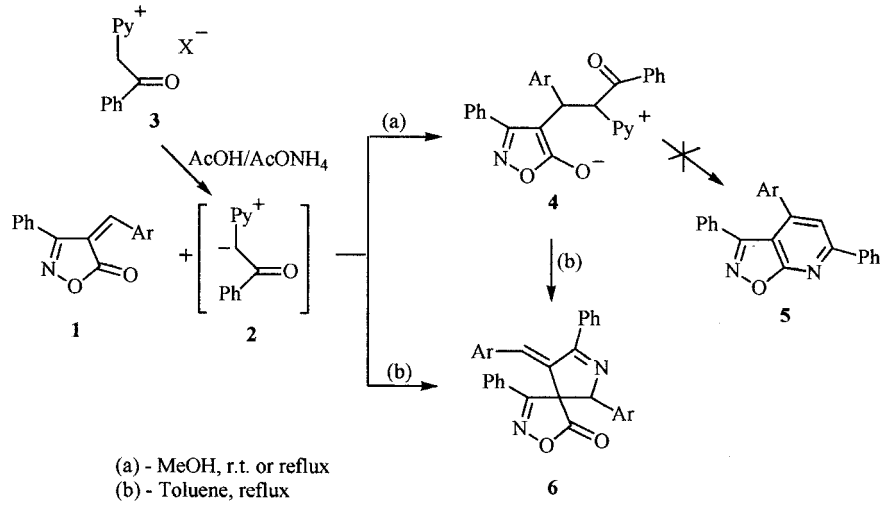
In practice, this reaction has led to a variety of products, depending on the conditions used, which have, however, never included the desired isoxazolopyridines **5**. Here we report the results obtained and the action of the ylides **2** is extended both to arylmethylene-pyrazolin-5-ones **14** and to arylmethylene-oxazol-5-ones **11**. With the latter, the correct course of a previously studied reaction is clarified.[10]

Results and Discussion

Our initial attempt to obtain fused heterocycles **5** involved reacting equimolecular quantities of pyridinium salt **3** and **1** in MeOH in the presence of glacial acetic acid-ammonium acetate at room temperature or under reflux. Under these conditions, the reactions stopped with high yields of **4**, as already described using triethylamine.[7] Further experiments carried out using a mixture of pyridinium salt **3** and **1**, or the monocyclic compounds **4**, using $AcOH/AcONH_4$ in refluxing benzene or toluene,[8] proved unsuccessful in the formation of the desired compounds **5**. Surprisingly, spirans **6** were isolated from the reaction in moderate yields (35%) as single diastereomers (Scheme 1). All attempts to obtain these spirans **6** without the arylidene group, for example by conducting the reaction under strictly anhydrous conditions, were unsuccessful, giving always the same compounds **6**. The structure of the spirans indicates that in the presence of $AcOH/AcONH_4$ one molecule of arylaldehyde is further required to react with stochiometric quantities of **4** or **1**

Keywords: pyridinium *N*-ylides; (arylmethylene)azol-5-ones; spirans; cascade reactions; cleavage reactions.
* Corresponding author. Tel.: +390-90-393-897; fax: +390-90-398-892; e-mail: frisitan@isengard.unime.it

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00921-2



Ar	Ph	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	*o*-MeC_6H_4	*o*-$MeOC_6H_4$	*m*-MeC_6H_4	*m*-$MeOC_6H_4$
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**

Scheme 1.

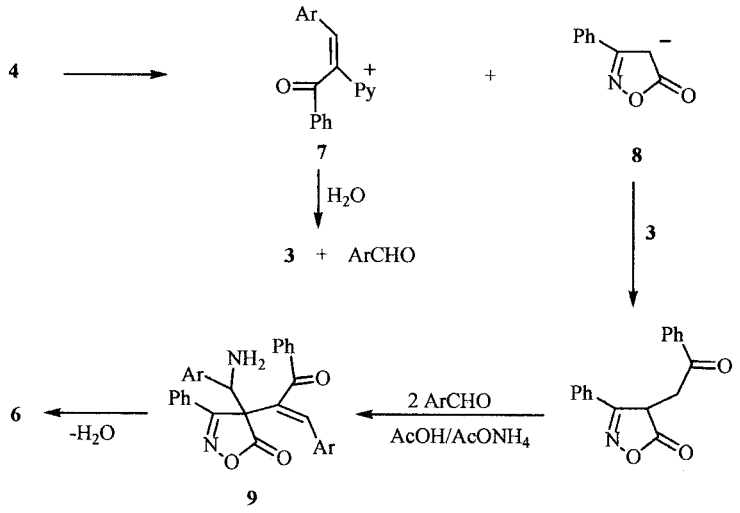
with **2**. Therefore, when a 1:1 molar ratio of betaine/aldehyde (or 1:1:1 of arylidene/aldehyde/ylide) was used, yields of spirans **6** were increased (Table 1).

The identification of **6** was based on their spectral and analytical data, and confirmed by X-ray crystallographic analyses carried out on **6b** and **6f**.[11] The IR spectra showed a strong absorption at ν 1780–1799 cm^{-1}, indicating a 4,4-disubstituted isoxazol-5-one ring,[12] while the absorption band at about 1670 cm^{-1} of the benzoyl group originally present in the betaines **4** disappeared. The ^1H NMR spectra are also consistent with the spiro-structure. A singlet always appears at δ 5.88–6.35 and this can be assigned to the H_6 protons; the presence of the two aryls, both derived from the arylmethylene group of the starting product **1**, was, however, evidenced by the fact that in cases **b**, **c**, **e**, **f**, **g**

Table 1. Analytical and spectroscopic data of the spirans **6** and **10**

Compound (Formula)	Mp (°C)	Yield (%)	Found (Calcd) C	H	N	IR[a]	^1H NMR[b]
6a	180	65	81.93	4.90	6.07	1795	5.95[c]; 6.89–7.99[d]
($C_{31}H_{22}N_2O_2$)			(81.92)	(4.88)	(6.16)		
6b	230	70	82.01	5.35	5.98	1792	5.88[c]; 2.25[e]; 2.33[e]; 6.80–7.93[f]
($C_{33}H_{26}N_2O_2$)			(82.13)	(5.43)	(5.81)		
6c	210	71	77.14	5.15	5.55	17.83	5.87[c]; 3.75[e]; 3.80[e]; 6.69–7.92[f]
($C_{33}H_{26}N_2O_4$)			(77.02)	(5.09)	(5.44)		
6d	231	57	71.09	3.80	5.46	1791	5.90[c]; 6.89–7.99[f]
($C_{31}H_{20}N_2O_2Cl_2$)			(71.14)	(3.82)	(5.35)		
6e	194	65	82.03	5.39	5.79	1799	6.34[c]; 1.68[e]; 2.10[e]; 6.87–7.96[f]
($C_{33}H_{26}N_2O_2$)			(82.13)	(5.43)	(5.81)		
6f	196	66	77.10	5.02	5.24	1796	6.30[c]; 3.37[e]; 3.49[e]; 6.57–7.97[f]
($C_{33}H_{26}N_2O_4$)			(77.02)	(5.09)	(5.44)		
6g	176	50	82.05	5.38	5.96	1789	6.35[c]; 2.10[e]; 2.18[e]; 6.87–7.97[f]
($C_{33}H_{26}N_2O_2$)			(82.13)	(5.43)	(5.81)		
6h	178	51	77.11	5.13	5.60	1786	6.30[c]; 3.38[e]; 3.49[e]; 6.50–7.97[f]
($C_{33}H_{26}N_2O_4$)			(77.02)	(5.09)	(5.44)		
10i	207	18	79.39	5.21	5.76	1780	5.87[c]; 2.25[e]; 3.79[e]; 6.79–7.92[f]
($C_{33}H_{26}N_2O_3$)			(79.50)	(5.30)	(5.70)		
10l	202	18	79.41	5.28	5.84	1784	5.80[c]; 2.33[e]; 3.74[e]; 6.82–7.92[f]
($C_{33}H_{26}N_2O_3$)			(79.50)	(5.30)	(5.70)		

[a] Nujol ($\nu_{C=O}$/cm^{-1}).
[b] $CDCl_3$ (δ/ppm).
[c] (s, 1H, C–H).
[d] (20H, m, ArH).
[e] (s, 3H, Me).
[f] (18H, m, ArH).



Scheme 2.

and **h** there are two separate methyl resonance singlets, one at lower field assigned to the aryl methyl bonded at C-sp^2 and the other, therefore, the aryl methyl on C-sp^3.

We believe that betaines **4** are the starting products of these reactions, and the formation of spirans **6** depends on the facility to cleave the C_4–C_{Ar} bond under the reaction conditions.

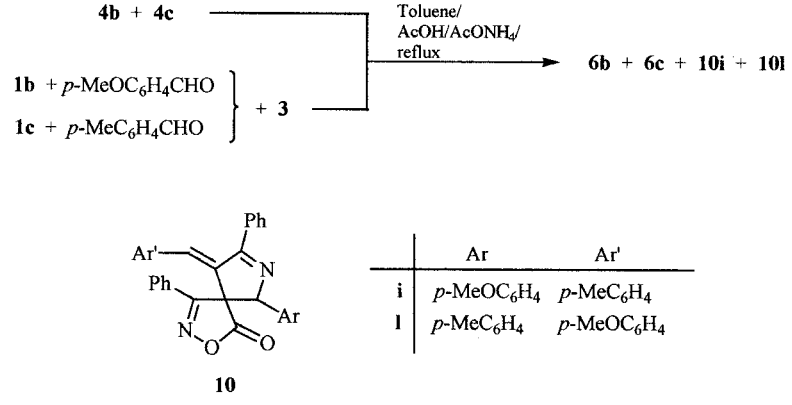
The released chalcone **7** can then hydrolyze to salt **3** and the corresponding aldehyde; these are immediately intercepted by the anion **8** to form the disubstituted isoxazolone **9** which finally evolves stereospecifically to spiro compound **6** according to a 5-*exo*-trig cyclization (Scheme 2).[13]

As proof of this behaviour, besides the observation that the addition of arylaldehyde always increased yields, it can be shown (Scheme 3) that, starting both from **4b** and **4c** and from the reaction between **1b** and *p*-anisaldehyde or between **1c** with *p*-tolylaldehyde and *N*-phenacyl pyridinium **3**, under the usual conditions, we have obtained all four possible spirans **6b** and **6c**, **10i** and **10l**, rather than a single mixed spiran. As further confirmation, the reaction of **4a** with the hindered mesitaldehyde and AcOH/$AcONH_4$ gives the spiran **6a** and, in addition, 4-(2,4,6-trimethylphenyl)methylene-3-phenylisoxazol-5-one **1** (Ar=mesityl).[14]

The attempted unsuccessful synthesis of fused heterocycles **5** from all these reactions can therefore be considered as confirmation that betaines **4** cannot rearrange to fused heterocycles. Moreover, in agreement with previous observations,[15] such a heteroaromatic system with both *peri*-positions occupied by bulky groups would be unlikely to form.

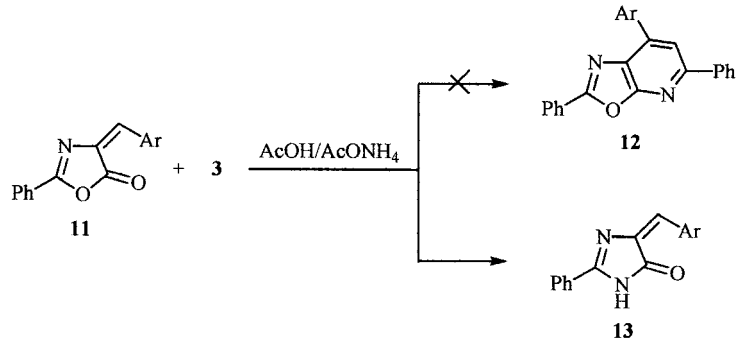
Nevertheless, in contrast to our results, arylmethyleneoxazol-5-ones **15** (Scheme 4) have, under the same conditions, been reported to give fused 2,4,6-triaryloxazolo[5,4-b]pyridine **12**[10] and, although the aforementioned structures were subsequently disproved,[16] no alternative was advanced.

We repeated the reaction of 4-benzylidene-2-phenyloxazol-5-one **11** (Ar=Ph) with phenacylpyridinium salt **3** by refluxing both in AcOH/$AcONH_4$, according to Bansal and Jain,[10] and also in chloroform containing triethylamine under the conditions used for isoxazolones **1**[7] or under reflux. Whereas with triethylamine no reaction was observed,

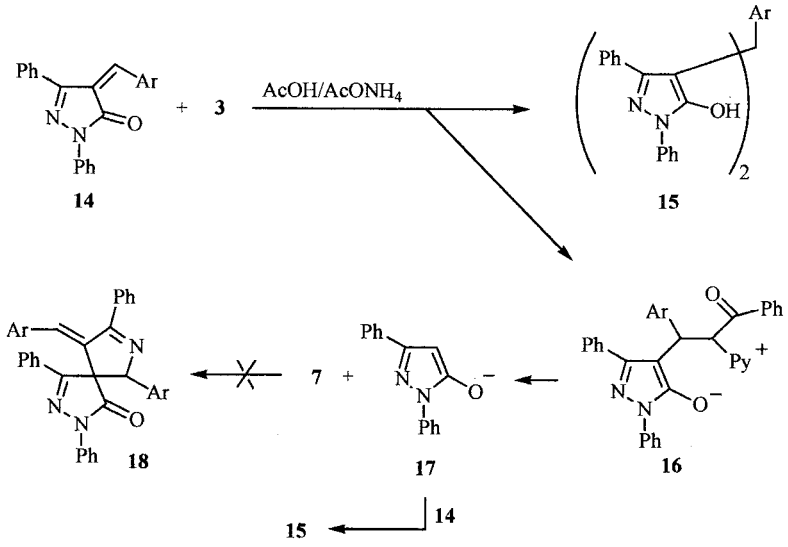


	Ar	Ar'
i	*p*-$MeOC_6H_4$	*p*-MeC_6H_4
l	*p*-MeC_6H_4	*p*-$MeOC_6H_4$

Scheme 3.



Scheme 4.



Scheme 5.

Table 2. Analytical and spectroscopic data of the bis-derivatives **15**

Compound (Formula)	Mp (°C)	Yield (%)	Found (Calcd) C	H	N	IR[a]	^{1}H NMR[b]
a	220	55	79.15	4.99	10.11	1596	5.44[c] 7.17–7.83[d]
($C_{37}H_{28}N_4O_2$)			(79.26)	(5.03)	(9.99)		
b	166	46	79.52	5.32	9.89	1600	5.05[c]; 2.30[e]; 6.81–7.58[f]
($C_{38}H_{30}N_2O_2$)			(79.42)	(5.26)	(9.75)		
c	156	47	77.44	5.26	9.61	1602	5.13[c]; 3.72[e]; 6.75–7.65[f]
($C_{38}H_{30}N_4O_3$)			(77.27)	(5.12)	(9.49)		
d	174	45	79.69	5.10	10.16	1600	5.03[c]; 6.86–7.99[f]
($C_{37}H_{27}N_4O_2Cl$)			(79.55)	(4.96)	(10.03)		
e	216	49	79.39	5.29	9.87	1602	5.24[c]; 2.30[e]; 7.40–7.99[f]
($C_{38}H_{30}N_4O_2$)			(79.42)	(5.26)	(9.75)		
f	215	37	77.45	5.22	9.31	1604	5.38[c]; 3.50[e]; 6.75–7.65[f]
($C_{38}H_{30}N_4O_3$)			(77.27)	(5.12)	(9.49)		
g	170	43	79.61	5.39	9.90	1598	5.12[c]; 2.25[e]; 6.80–7.64[f]
($C_{38}H_{30}N_4O_2$)			(79.42)	(5.26)	(9.75)		
h	160	43	77.35	5.09	9.61	1605	5.32[c]; 3.72[e]; 7.11–7.79[f]
($C_{38}H_{30}N_4O_3$)			(77.27)	(5.12)	(9.49)		

[a] Nujol (ν_{max}/cm^{-1}).
[b] $CDCl_3$ (δ/ppm).
[c] (s, 1H, C–H).
[d] (25H, m, ArH).
[e] (s, 3H, Me).
[f] (24H, m, ArH).

under Bansal's conditions we obtained 4-benzylidene-2-phenylimidazolin-5-one **13** (Ar=Ph).[17] This compound showed a melting point and spectroscopic characteristics very similar to those of the earlier claimed **12** (Ar=Ph), so it seems probable that, in general, the oxazolopyridines of Bansal and Jain are in fact arylideneimidazolin-5-ones **13**.

In confirmation, the 4-arylmethylene-2-phenyloxazol-5-ones **11** used by Bansal and Jain[10] were treated with $AcOH/AcONH_4$ in the presence and in the absence of the salt **3**; in both cases only the corresponding imidazolin-5-ones **13** were obtained, indicating that in our hands these reactions achieved exclusively the transformation of the oxazolone ring into the imidazolinone, consistent with previous results.[18]

Arylmethylenepyrazolin-5-ones **14**, however, showed behaviour different from both isoxazolone **1** and oxazolone **11** derivatives. Indeed, after treatment under the same conditions with ylid **2** generated in situ from salt **3** in the presence of triethylamine or $AcOH/AcONH_4$ and with a significant excess of the arylaldehyde corresponding to the arylmethylene group, these did not give the expected products **16** or **18**, but only the corresponding bis-derivatives **15** (Scheme 5).

The structure of these can easily be deduced from analytical and spectroscopic data (Table 2) and confirmed by the comparison of their IR spectra with that of compound **15a**, already known and prepared by other means.[19] Obviously, in these cases is possible that hydrolytic scission of the arylmethylene bond and subsequent unavoidable formation of bis-adducts **15** take place, preventing any other type of reaction. Otherwise an initial formation of the betaine **16** can also occur, which under the reaction conditions splits into **7** and **17** with the latter immediately forming **15** in the presence of the starting products **14**.

Experimental

Melting points: Reichert–Kofler hot-stage microscope. Microanalyses: Carlo Erba EA 1102. IR: Nicolet FT-IR Impact 400D spectrometer. ^{1}H NMR spectra with a Bruker ARX 300, tetramethylsilane as internal reference, hexadeuterodimethyl sulfoxide as solvent. 4-(arylmethylene)azol-5-ones **1**,[20] **11**[21] and **14**[22] and phenacylpyridinium salt **3**[23] were prepared by standard procedures.

General procedure for the reactions of the 4-(arylmethylene)isoxazol-5-ones (1) with phenacylpyridinium salt (3)

Route (a): A mixture of 4-(arylmethylene)isoxazol-5-ones **1** (5 mmol), salt **3** (5 mmol), ammonium acetate (3.8 g, 50 mmol) and glacial acetic acid (20 mL) in methanol was stirred for 2 h at room temperature or at reflux. The solvent was removed under reduced pressure, and then the residue was allowed to cool and quenched with water to yield the betaines **4**.[7]

Route (b): A mixture of isoxazol-5-ones **1** (5 mmol), salt **3** (5 mmol), ammonium acetate (3.8 g, 50 mmol) and glacial acetic acid (20 mL) and the appropriate aromatic aldehyde (5 mmol) was stirred in refluxing toluene (20 mL). The solution was at first orange but later became green-brown. After 2 h, the reaction mixture was filtered and the solvent evaporated under reduced pressure to give an oily residue which was crystallized from methanol to yield the spirans **6**. According to this procedure, identical results were obtained from betaines **4** as starting material. Yields, analytical and selected spectroscopic data of the new compounds are given in Table 1.

General procedure for the reactions of the 4-(arylmethylene)oxazol-5-ones (11) with phenacylpyridinium salt (3)

4-(Arylmethylene)oxazol-5-ones **11** (2.6 mmol) and salt **3** (2.6 mmol) were refluxed for 3 h in glacial acetic acid (20 mL) containing ammonium acetate (26 mmol).The precipitate which formed on cooling was collected by filtration and recrystallized from methanol to give products **13**. Analytical and spectroscopic data are identical to those reported in Ref. 10.

Reactions of the 4-(arylmethylene)pyrazol-5-ones (14) with phenacylpyridinium salt (3)

The procedure described above (routes a and b) for isoxazol-5-ones **1** was used for pyrazolones **14**. The residues were chomatographed on silica gel (chloroform) to afford **15**. Yields analytical and selected spectroscopic data are given in Table 2.

References

1. De Simoni, G.; Gamba, A.; Righetti, P. P.; Tacconi, G. *Gazz. Chim. Ital.* **1971**, 899–922; De Simoni, G.; Tacconi, G. *Gazz. Chim. Ital.* **1968**, 1329–1342.
2. Knowles, A. M.; Lawson, A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1240–1243.
3. Pastour, P. *Comp. Rend.* **1957**, *244*, 2243–2248; Mustafà, A.; Asker, W.; Harhash, A. H.; Kassab, N. A. L. *Tetrahedron* **1963**, *52*, 1577–1585; Lo Vecchio, G.; Caruso, F.; Foti, F.; Grassi, G.; Risitano, F. *Atti Accademia Peloritana dei Pericolanti* **1974**, 303–310; Cook, D. C.; Lawson, A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1112–1116.
4. Lo Vecchio, G.; Grassi, G.; Risitano, F.; Foti, F. *Tetrahedron Lett.* **1973**, *39*, 3777–3780.
5. Clerici, F.; Erba, E.; Mornatti, P.; Trimarco, P. *Chem. Ber.* **1989**, *122*, 295–300; Grassi, G.; Risitano, F.; Caruso, F.; Foti, F. presented in part at the Euchem Conference, Vulcano (Italy), June, 1995.
6. Abbass, J. M.; Mosselhi, M. A. N.; Abdallah, M. A.; Shawali, A. S. *J. Chem. Research (Synopsis)* **1995**, 190–191.
7. Risitano, F.; Grassi, G.; Bruno, G.; Nicolò, F. *Liebigs Ann.* **1997**, *2*, 441–445.
8. Kröhnke, F.; Zecher, W.; Curtze, J.; Drechsler, D.; Pfleghar, K.; Schnalke, K. E.; Eis, W. W. *Angew. Chem.* **1962**, *74*, 811–817; Kröhnke, F.; Zecher, W. *Angew. Chem., Int. Ed. Engl.* **1962**, *12*, 626–639.
9. Adembri, G.; Campanini, A.; Ponticelli, F.; Tedeschi, P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2190–2194.

10. Bansal, R. K.; Jain, J. K. *Synthesis* **1986**, 840–842.
11. Bruno, G.; Nicolò, F.; Risitano, F.; Grassi, G.; Foti, F. *Acta Crystallogr., Sect. C*, submitted for publication.
12. Boulton, A. J.; Katritzky, A. R. *Tetrahedron* **1961**, 41–50.
13. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–741.
14. Lo Vecchio, G.; Risitano, F.; Grassi, G.; Foti, F.; Caruso, F. *Atti Accademia Peloritana dei Pericolanti* **1974**, 297–302.
15. Skotsch, S.; Kohl Meyer, I.; Breitmaier, E. *Synthesis* **1979**, 449–452.
16. Gelmi, M. L.; Pocar, D.; Viziano, M.; Destro, R.; Merati, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 701–705.
17. Erlenmeyer, E. *Ber.* **1900**, *33*, 2036–2041.
18. Williams, D. L.; Ronzio, A. R. *J. Am. Chem. Soc.* **1946**, 647–649.
19. Knorr, L.; Klozt, C. *Ber.* **1887**, *20*, 2545–2548; Ehsan, A.; Ali, S.; Ahmed, I.; Karimullah, G. *Pakistan J. Sci. Ind. Res.* **1967**, *10*, 228–229.
20. Quilico, A. *The Chemistry of Heterocyclic Compounds*; Wiley-Interscience: New York, 1962; pp 117–124.
21. Rao, Y. S. *J. Org. Chem.* **1976**, *41*, 722–725; Carter, H. E. *Org. React.* **1974**, *3*, 199–201.
22. Risitano, F.; Grassi, G.; Caruso, F.; Foti, F. *Tetrahedron* **1996**, 1443–1450.
23. Henrick, C. A.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 2441–2453.