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Michael addition–electrophilic quenching chemistry of maleimides using dialkylzinc reagents

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Abstract—Michael addition–electrophilic quench reactions of *N*-alkyl maleimides are possible using dialkylzincs in combination with a copper catalyst and a phosphoramidite ligand. Up to 55% ee has been achieved for one example (E = H) using a chiral ligand.

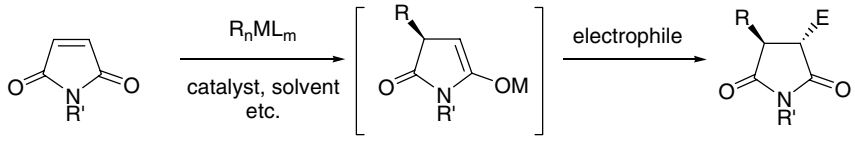
Although catalytic asymmetric addition of organometallics, such as Grignard reagents, organocopper species, organozincs and boronic acid derivatives, to α,β-unsaturated ketones is quite well established,[1] this type of reaction has not been extensively explored with other types of carbonyl-containing Michael acceptors. Recently, several groups have disclosed extensions of this chemistry to asymmetric Michael addition of unsaturated esters, lactones, amides, lactams and related systems with promising levels of selectivity.[2]

In connection with a proposed novel entry to erythrinan alkaloid natural products, we became interested in the asymmetric Michael addition reactions of *maleimides*, including the possibility of achieving selective addition–electrophilic quench sequences, for example, conversion of **1** into **3** via a metal enolate **2**, Scheme 1.

Again this type of 'vicinal dialkylation' is well-known in the realms of enone additions,[3] but we have been unable to locate a single example for maleimides—even to give racemic products. Indeed, only recently has the area of asymmetric addition to maleimides attracted significant attention, the Hayashi group having described highly selective addition of aryl groups by rhodium catalysed reaction of aromatic boronic acids ($ArB(OH)_2$), using chiral dienes, bis-phosphines or hybrid alkene–phosphine ligands.[4] This method, although effective, has to date been carried out under aqueous conditions that make the development of an addition–electrophilic quench sequence like that shown in Scheme 1 problematic.

The lack of an existing solution to the problem outlined in Scheme 1, combined with the fact that variously substituted succinimide systems **3** are the component parts of significant natural products prompted us to explore this issue.[5]

Herein, we describe the use of a Feringa-type system, composed of dialkylzinc reagent (R_2Zn), $Cu(OTf)_2$ and a phosphoramidite ligand, to accomplish the type of



1 **2** **3**

Scheme 1. Addition of a generic organometallic to a maleimide followed by electrophilic quench.

Keywords: Imide; Michael addition; Dialkylzinc; Phosphoramidite; Asymmetric catalysis.
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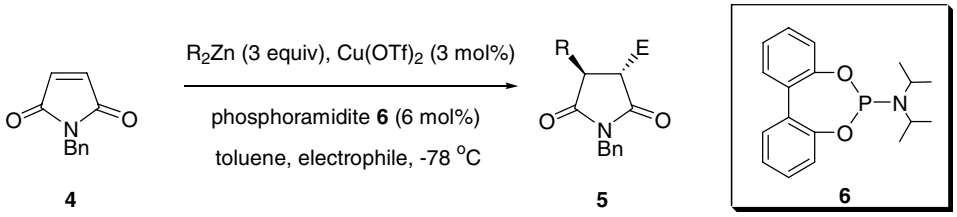
Table 1. Addition–quench reactions of maleimide **4**



R	Electrophile	E	Product/yield (%)	Diast. ratio
Et	MeCOMe	$C(OH)Me_2$	**5a** 86	—
Et	PhCHO	CH(OH)Ph	**5b** 99	60:40
Et	*i*-BuCHO	CH(OH)*i*-Pr	**5c** 96	80:20
Et	MeCHO	CH(OH)Me	**5d** 93	50:50
Et	CyclohexylCHO	CH(OH)cyclohexyl	**5e** 62	80:20
Et	MeOC(O)CN	CO_2Me	**5f** 75	—
Et	MeCOCl	COMe	**5g** 92	—
Et	PhCOCl	COPh	**5h** 85	—
Et	Ac_2O	COMe	**5g** 76	—
i-Pr[a]	PhCHO	CH(OH)Ph	**5i** 88	60:40

[a] Reaction carried out at 0 °C.

overall transformation shown in Scheme 1, including preliminary enantioselective variants.

Initially, we attempted Michael addition of commercially available Et_2Zn to an N-substituted maleimide, using a number of $Cu(OTf)_2$–ligand combinations, and observed mainly polymerisation and some evidence of condensation products of the putative intermediate metal enolate **2**. Indeed, it is well established that dialkylzinc reagents are effective in forming polymers from maleimides, with apparent asymmetric induction if chiral additives are present.[6]

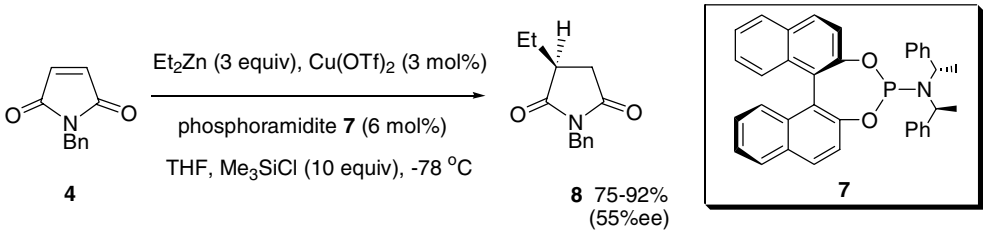
In their studies of dialkylzinc additions to unsaturated lactones, Hoveyda and co-workers had experienced similar difficulties and had solved them by including benzaldehyde as a suitable in situ electrophilic quench.[2c] Pleasingly, this type of protocol also worked in the case of *N*-benzyl maleimide **4**, but with a wider range of aldehydes, and also typical acylating agents, Table 1.[7]

Aldol reactions proceeded in high yield to give products as the expected trans-isomers with respect to the five-membered imide ring, but as mixtures of diastereomers at any newly formed off-template carbinol centre. In the reactions involving acylation, the products were isolated as mixtures of carbonyl and enol forms. Most of our chemistry was conducted using Et_2Zn but the more bulky $^iPr_2Zn$ also participated in the reaction, albeit at 0 °C. Attempts to use Ph_2Zn were not successful.

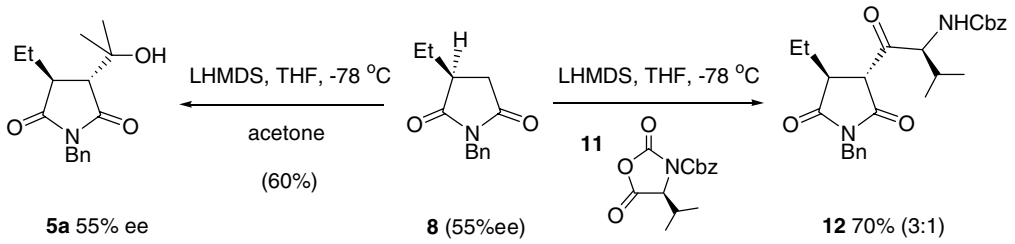
At this point the stage seemed set for us to develop an asymmetric version of this reaction by using a chiral phosphoramidite such as **7**.[8] Using this ligand in place of **6** gave a number of products **5** as before—but no asymmetric induction was observed. We also established that, somewhat surprisingly, the reaction did not proceed at all when we used THF as the solvent—a finding that seems to parallel similar observations by Hoveyda in the lactone series.[2c]

After considerable experimentation, we discovered that the addition of trimethylsilyl chloride to the reaction mixture, in place of the aldehyde or acylating agent, enabled conjugate addition of Et_2Zn to occur in THF. Furthermore, the use of phosphoramidate **7** enabled the isolation of the Michael addition product **8** in good yield and in moderate ee, Scheme 2.[9]

To our knowledge this is the first example of asymmetric addition of an alkyl group (in contrast to the aryl additions cited above) to a maleimide. Somewhat disappointingly, we were unable to fine-tune the selectivity of the process by either (i) changing the maleimide N-substituent to methyl, cyclohexyl, phenyl, 2-naphthylmethyl, or phenylethyl; (ii) changing the solvent to

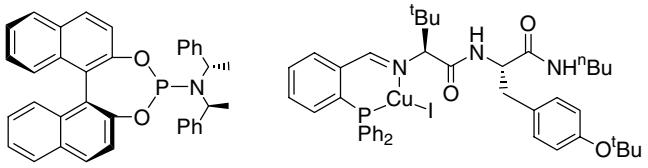


Scheme 2. Asymmetric addition to maleimide **4**.



Scheme 3. Regioselective and stereoselective substitution of imide **8**.

various THF–toluene mixtures, or Et_2O or CH_2Cl_2; (iii) using alternative chiral ligands, including **9** and **10**.[8,2c]



9 **10**

Although the range of racemic adducts **5** available directly from the reactions in toluene (Table 1) could not be formed enantioselectively this way, it proved possible to regenerate a lithium enolate from non-racemic **8** (55% ee) and quench with electrophiles to give the same products by a two-step process, for example, **5a**, Scheme 3.

We also used this procedure to acylate the lithium enolate from **8** with the enantiomerically pure valine derived anhydride **11**,[10] thus providing adduct **12** as a diastereoisomeric mixture (ca. 3:1 ratio, major isomer shown) that reflected the initial ee of **8** (55%). Crystallisation of the major isomer from the mixture allowed the assignment of absolute stereochemistry of **12**, and thus **8** as shown, following an X-ray structure determination, Figure 1.[11]

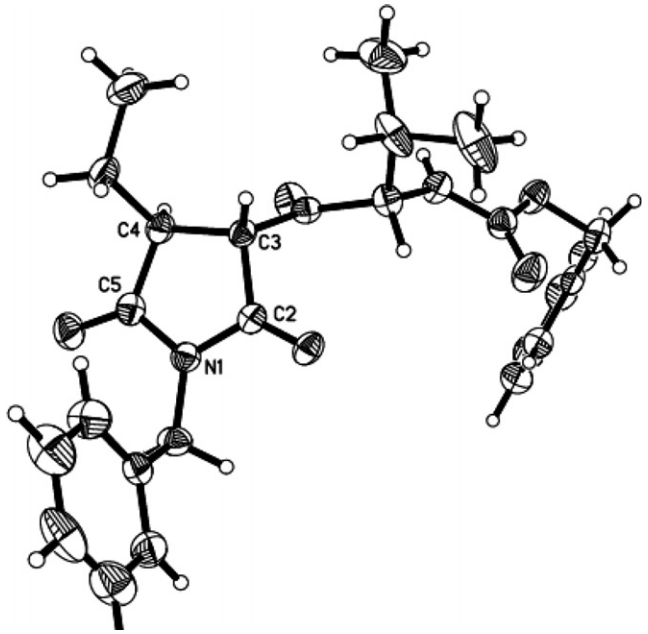


Figure 1. X-ray crystal structure of major diastereomeric product **12**. Ellipsoids are drawn at 30% probability level.

A second correlation was also possible by reduction of **8**, using BH_3–SMe_2, to give the known compound, (3*S*)-1-benzyl-3-ethylpyrrolidine, which supported the assignment from the X-ray structure.[12]

In summary, we have described the first examples of Michael addition–electrophilic quenching of maleimides, using organozinc chemistry, and also the first example of an asymmetric addition of an alkyl group. The chemistry shows promise for the construction of natural product fragments (and their pharmaceutically important counterparts), and should also provide access to reduction products such as lactams and pyrrolidines.

Acknowledgements

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References and notes

1. (a) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179; (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829; (c) Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5560.
2. (a) Itoh, T.; Mase, T.; Nishikata, T.; Iyama, T.; Tachikawa, H.; Kobayashi, Y.; Yamamoto, Y.; Miyaura, N. *Tetrahedron* **2006**, *62*, 9610; (b) Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889; (c) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306; (d) Navarre, L.; Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2005**, *46*, 4247; (e) Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 2433; (f) Pucheault, M.; Michaut, V.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4729.
3. (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (b) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977; (c) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874.
4. (a) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628; (b) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int.*

Ed. **2005**, *44*, 4611; (c) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425; See also: (d) Trenkle, W. C.; Barkin, J. L.; Son, S. U.; Sweigart, D. A. *Organometallics* **2006**, *25*, 3548.

5. For examples, see: (a) Isaka, M.; Prathumpai, W.; Wongsa, P.; Tanticharoen, M. *Org. Lett.* **2006**, *8*, 2815; (b) Lehmann, A.; Brocke, C.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2006**, *3205*, and references cited therein; (c) Fredenhagen, A.; Tamura, S. Y.; Kenny, P. T. M.; Komura, H.; Naya, K.; Nakanishi, K.; Nishiyama, K.; Sugiura, M.; Kita, H. *J. Am. Chem. Soc.* **1987**, *109*, 4409; (d) Needham, J.; Kelly, M. T.; Ishige, M.; Andersen, R. J. *J. Org. Chem.* **1994**, *59*, 2058; See also: (e) Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4966, and references cited therein. See also Ref. 10.
6. Hori, K.; Yoshimura, K.; Ohno, H.; Onimura, K.; Oishi, T. *Tetrahedron* **2003**, *59*, 6301.
7. *Typical procedure for multicomponent 1,4-addition–electrophilic quench (Table 1)*. A solution of copper triflate (6 mg, 16 μmol, 0.03 equiv) and phosphoramidite **6** (0.06 equiv) in toluene (3 ml) was stirred for 1 h at room temperature under argon. To this solution the maleimide **4** (0.53 mmol, 1.0 equiv) was added and the reaction mixture was cooled to −78 °C. The electrophile (10 equiv) was added and then a solution of Et_2Zn in toluene (1.6 mmol of a 1.1 M solution, 3.0 equiv) was added. After 1 h the reaction was quenched by addition of a saturated solution of NH_4Cl(aq) (2 ml), the product extracted into Et_2O (2 × 10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 8:2) to give the products in the yields indicated.
Selected data (Table 1).
Compound (**5a**) as a clear oil (126 mg; 86%); *m*/*z* (ESI) calculated for $C_{16}H_{21}NNaO_3$ 298.1419 found 298.1400; δ_H ($CDCl_3$, 270 MHz) 0.24 (t, 3H, $J = 8.3$, CH_3CH_2), 0.43 (s, 3H, Me), 0.59 (s, 3H, Me), 1.20 (m, 2H, CH_3CH_2), 2.04 (m, 2H, H-3 and H-4), 4.37 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar); δ_C ($CDCl_3$, 67 MHz) 178.9 (C=O), 178.7 (C=O), 135.6 (C), 128.6 (CH), 128.5 (CH), 128.0 (CH), 72.0 (COH), 54.8 (C3), 44.2 (C4), 42.3 (CH_2Ph), 27.4 (Me), 25.8 (Me), 24.5 (CH_2, Et), 10.2 (CH_3, Et); ν_{max}($CHCl_3$)/cm^{-1} 974, 1348, 1379, 1393, 1693, 1769, 2879, 2937, 2969, 3505, 3605.
Compound (**5b**) as a clear oil (170 mg; 99%); *m*/*z* (ESI) calculated for $C_{20}H_{21}NNaO_3$ 346.1419, found 346.1412; minor diastereoisomer δ_H ($CDCl_3$, 400 MHz) 0.48 (t, 3H, $J = 7.4$ Hz, CH_3CH_2), 1.32 (m, 2H, CH_3CH_2), 2.78 (dd, 1H, $J = 2.7$, 4.3, H-4), 2.85 (ddd, 1H, $J = 4.3$, 5.4, 6.9, H-3), 4.65 (d, 1H, $J = 14.4$, CH_2Ph), 4.70 (d, 1H, $J = 14.4$, CH_2Ph), 5.48 (d, 1H, $J = 2.7$, CHOH), 7.20–7.40 (m, 10H, Ar); δ_C ($CDCl_3$, 100 MHz) 179.3 (C=O), 177.8 (C=O), 140.9 (C), 135.7 (C), 128.7 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 125.2 (CH), 71.5 (CHOH), 52.9 (C3), 42.3 (C4), 40.7 (CH_2Ph), 23.7(CH_2, Et), 9.9 (CH_3, Et); major diastereoisomer δ_H ($CDCl_3$, 400 MHz) 0.67 (t, 3H, $J = 7.4$, CH_3CH_2), 1.19 (dqd, 1H, $J = 5.6$, 7.4, 14.7, CH_3CH_2), 1.45 (m, 1H, CH_3CH_2), 2.48 (m, 1H, H-3), 2.85 (dd, 1H, $J = 4.8$, 8.2, H-4), 4.60 (d, 1H, $J = 14.1$, CH_2Ph), 4.65 (d, 1H, $J = 14.1$, CH_2Ph), 4.88 (d, 1H, $J = 8.2$, CHOH), 7.20–7.40 (m, 10H, Ar); δ_C ($CDCl_3$, 100 MHz) 178.5 (C=O), 178.4 (C=O), 139.4 (C), 135.4 (C), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 127.6 (CH), 126.4 (CH), 74.3 (CHOH), 51.3 (C3), 43.2 (C4), 42.2 (CH_2Ph), 22.9 (CH_2, Et), 9.8 (CH_3, Et); ν_{max} ($CHCl_3$)/cm^{-1}: 1055, 1347, 1396, 1694, 1770, 2878, 2936, 2967, 3496, 3611. Compound (**5h**) as a yellow oil (145 mg; 85%); *m*/*z* (ESI) calculated for $C_{20}H_{19}NO_3$ 322.1443 found: 322.1441; δ_H ($CDCl_3$, 270 MHz) 0.20 (t, 3H, $J = 8.4$, CH_3CH_2), 1.40 (dqd, 1H, $J = 5.5$, 8.4, 16.7, CH_3CH_2), 1.07 (m, 1H, CH_3CH_2), 3.11 (m, 1H, H-4), 4.21 (d, 1H, $J = 5.1$, H-3), 4.32 (d, 1H, $J = 15.8$, CH_2Ph), 4.43 (d, 1H, $J = 15.8$, CH_2Ph), 7.30–7.50 (m, 8H, Ar), 8.21 (m, 2H, Ar); δ_C ($CDCl_3$, 67 MHz) 192.8 (C=O), 178.1 (C=O), 172.1 (C=O), 135.6 (C), 135.3 (C), 134.2 (CH), 133.7 (CH), 130.1 (CH), 129.7 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 54.2 (C3), 44.7 (C4), 42.8 (CH_2Ph), 23.5 (CH_2, Et), 10.0 (CH_3, Et); ν_{max} ($CHCl_3$)/cm^{-1}: 895, 1071, 1096, 1292, 1319, 1348, 1395, 1698, 1777, 2878, 2934, 2966.
8. For overviews, see: (a) Howell, G. P.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2006**, *4*, 1278; (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346; For preparation of the ligands, see: (c) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865.
9. *Procedure for asymmetric synthesis of* **8**. A solution of copper triflate (6 mg, 16 μmol, 0.03 equiv) and phosphoramidite **7** (17 mg, 0.06 equiv) in THF (3 ml) was stirred for 1 h at room temperature under argon. To this solution maleimide **4** (0.53 mmol, 1.0 equiv) was added and the reaction mixture was cooled to −78 °C. TMSCl (10 equiv) was added and then a solution of Et_2Zn in toluene (1.6 mmol of a 1.1 M solution, 3.0 equiv) was added. After 1 h the reaction was quenched by addition of a saturated solution of NH_4Cl(aq) (2 ml), the product extracted into Et_2O (2 × 10 ml), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 8:2) to give imide **8** as a clear oil (106 mg; 92%); $[\alpha]_D^{25}$ −5.4 (*c* 0.75, $CHCl_3$); *m*/*z* (ESI) calculated for $C_{13}H_{15}NNaO_2$ 240.0995 found 240.0990; δ_H ($CDCl_3$, 270 MHz) 0.24 (t, 3H, $J = 8.2$, CH_3CH_2), 0.96 (dd, 1H, $J = 8.3$, 16.3, CH_3CH_2), 1.31 (m, 1H, CH_3CH_2), 1.84 (dd, 1H, $J = 2.5$, 18.1, H-4), 2.28 (m, 2H, H-3 and H-4), 4.35 (s, 2H, CH_2Ph), 7.20–7.40 (m, 5H, Ar); δ_C ($CDCl_3$, 67 MHz) 179.5 (C=O), 176.3 (C=O), 135.9 (C), 128.7 (CH), 128.6 (CH), 127.9 (CH), 42.3 (CH_2Ph), 41.1 (C3), 33.8 (C4), 24.3 (CH_2, Et), 10.8 (CH_3, Et); ν_{max} ($CHCl_3$)/cm^{-1} 1156, 1180, 1315, 1340, 1403, 1433, 1713, 1772, 2878, 2936, 2967, 3036, 3068. The ee was determined on a chiracel OD column using 5% ^{i}PrOH–hexane as eluent and a flow rate of 0.3 ml/min; elution times were 63.4 min (minor) and 67.1 min (major).
10. Pohlmann, J.; Lampe, T.; Shimada, M.; Nell, P. G.; Pernerstorfer, J.; Svenstrup, N.; Brunner, N. A.; Schiffer, G.; Freiberg, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1189.
11. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 646534. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
12. Bettoni, G.; Celluci, C.; Berardi, F. *J. Heterocycl. Chem.* **1980**, *17*, 603.