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N-Substituted and *N*-unsubstituted 1,3-Oxazolium-5-olates cycloaddition reactions with 3-substituted coumarins

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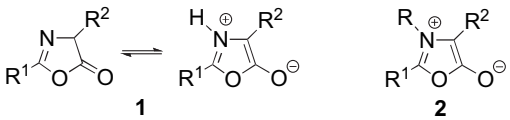
ABSTRACT

The 1,3-dipolar cycloaddition reaction of unsymmetrically *N*-substituted and *N*-unsubstituted 1,3-oxazolium-5-olates with selected 3-substituted coumarins has been examined. Various types of pyrrole derivatives are isolated and their formation seems to be a function of the regio- and diastereochemistry of the initial cycloaddition step.

1. Introduction

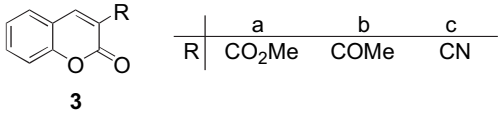
N-Substituted and *N*-unsubstituted 1,3-oxazolium-5-olates are a key family of building blocks employed in the construction of a variety of highly functionalized heterocyclic compounds.[1] The importance of these mesoionic-type oxazoles[1b] derived from their great reaction versatility,[2] and, in particular from the role they play in cycloaddition reactions.[1c] This versatility is particularly noticeable in *N*-substituted derivatives **2** (münchnones), which display more marked 1,3-dipolar reactivity than their parent *N*-unsubstituted oxazolones **1** (Fig. 1).



1 **2**

Figure 1.

As a part of a program of investigation of the synthetic utility of these attractive intermediates, their reactivity towards coumarin derivatives was explored. As is known,[3] these structural units display interesting dipolarophilic reactivity when activated at the styrenic double bond. This paper reports the results of a study of coumarins **3** bearing an electron withdrawing group at C-3 (Fig. 2) reacting with oxazolones **1** or münchnones **2**.



3

Figure 2.

2. Results and discussion

2.1. Reactions with oxazolones 1

The investigation used 4-methyl-2-phenyl-1,3-oxazol-5(4*H*)-one (MPO) **4** as an unsymmetrical oxazolone template (Scheme 1) and reactions with **3a**–**c** were performed both in solution and under solvent-free conditions (Experimental).

In solution (method A), the only product isolated in high yields in cases a and b was carboxylic acid **5**; the only reaction product isolated in case c was the unexpected derivative **6**. In the absence of solvent (method B), product **5** was again isolated in higher yields in cases a and b, while no product of interest was isolated in case c (Table 1).

Derivatives **5** and **6** were identified on the basis of analytical and spectroscopic data. Acid **5b** in dioxane/THF was esterified with ethereal diazomethane to give **7** (Scheme 2); the latter product then underwent single-crystal X-ray analysis (Fig. 3).[4]

This provided structural confirmation and, importantly, stereochemical assignment for **5**. The structure of **6** was then further confirmed by X-ray crystallographic analysis.[4]

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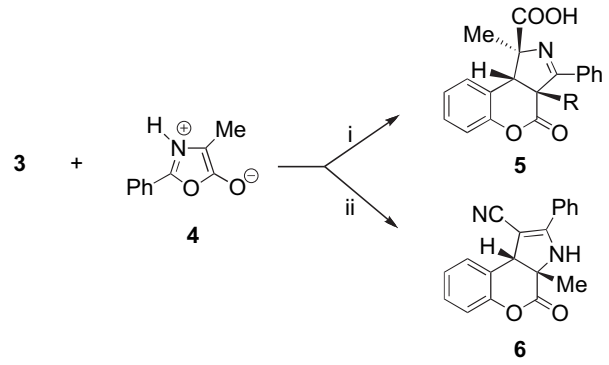
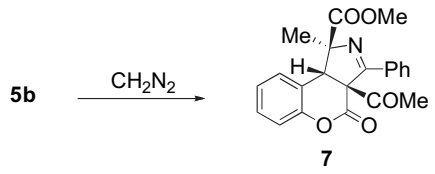


Scheme 1. (i) In solution or solvent free; (ii) only in solution when R=CN.

Table 1
Reactions of coumarins **3a–c** with MPO

Entry	Starting material	Products (yield %)[a]	
		Method A	Method B
1	**3a**	**5a** (77)	**5a** (89)
2	**3b**	**5b** (69)	**5b** (80)
3	**3c**	**6** (40)	—

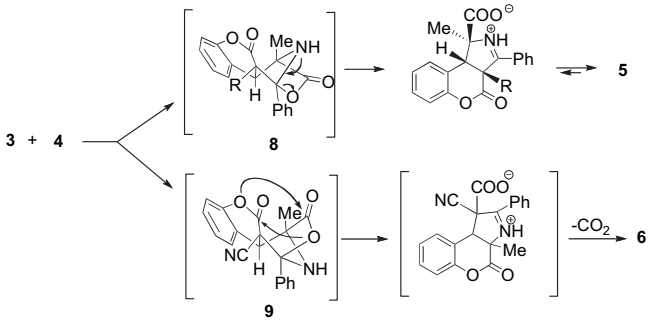
[a] Yield of pure isolated product.



Scheme 2.

The products isolated show that the cycloaddition reaction of the mesoionic heterocycle proceeds differently from the standard decarboxylative cycloreversion of the initial 1:1 cycloadduct.[1] Indeed, either (path i) retention of carboxylic function with formation of **5**, or (path ii) an unprecedented transformation into **6** are observed.

This unusual behaviour may be explained by the high levels of regiochemical control observed and by the *exo*/*endo* preference in the cycloaddition step. Indeed, as described in Scheme 3, the *exo* cycloadduct **8** fully accounts for the formation of the stable α-aminoacid **5**,[5] while only the *endo* diastereomer **9** can be expected to evolve to derivative **6** via translactonization and subsequent facile decarboxylation.



Scheme 3. Proposed mechanism of oxazolone reactions.

Reactions with MPO were performed with a variety of other coumarins, but with consistently negative results, and the starting coumarin was recovered along with the products of azlactone degradation. It thus appears that cycloaddition occurs without evolving towards stable products.

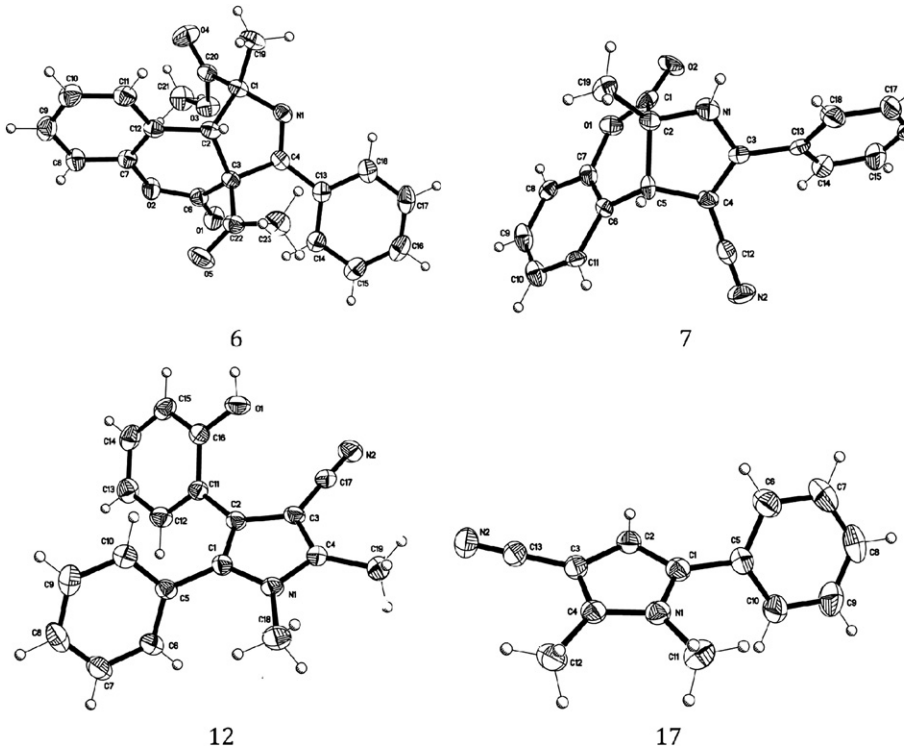
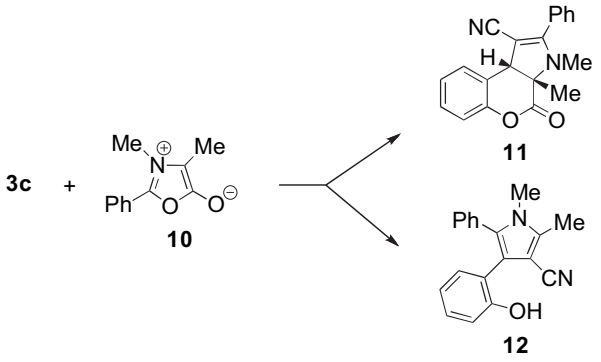


Figure 3. Ortep drawing of **6**, **7**, **12** and **17**.

2.2. Reaction with münchnones 2

This investigation used 4,5-dimethyl-2-phenyl-1,3-oxazolium-5-olate (DMPO) **10** as an unsymmetrical münchnone template, and its behaviour was observed with the previously selected coumarins. Of the reactions studied only case c (R=CN) produced results of any interest, namely isolation of the fused pyrrole derivative **11** (15%) and fully substituted pyrrole **12** (35%) (Scheme 4).



Scheme 4.

The structures of derivatives **11** and **12** were assigned on the basis of analytical and spectroscopic data, and confirmed by X-ray crystallographic analysis (Fig. 3).[4]

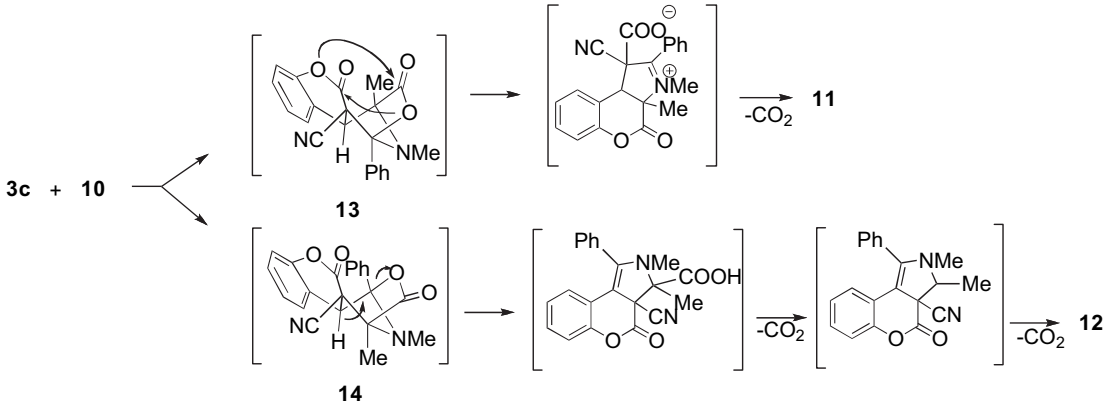
These results appear to confirm the reaction mechanism previously hypothesized with azlactone.

With the more reactive münchnone a lower level of regiochemical control is observed in the initial cycloaddition step, and when R=CN *endo* selective attack is confirmed.

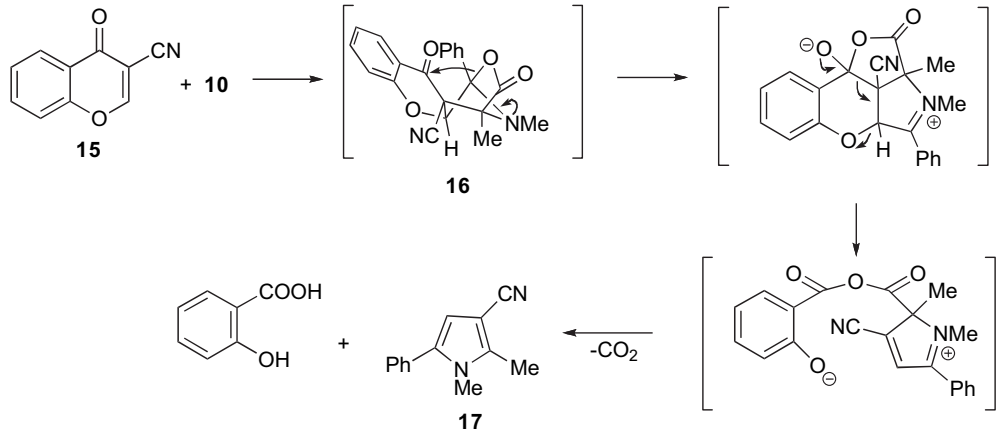
As illustrated in Scheme 5, the two non-isolated regioisomeric *endo* cycloadducts **13** and **14** evolve, respectively, into **11** via transesterification/decarboxylation, in a similar way as described with MPO, or into **12** through decarboxylative degradation.

Our proposed mechanism of fragmentation of the cycloadduct **13** to cyanopyrrole **11** is perfectly in line with a similar result obtained in the reaction between 3-cyanochromone **15**[6] and DMPO **10**. A cyanopyrrole derivative was isolated together with salicylic acid as summarized in Scheme 6.

This result is consistent with the initial formation of the *endo* cycloadduct **16** and its subsequent decarboxylative degradation to pyrrole **17**. X-ray crystallographic analysis confirmed the structure (Fig. 3).[4]



Scheme 5. Proposed mechanism of münchnone reactions.



Scheme 6. Cycloaddition of münchnone to 3-cyanochromone.

In the other cases, cycloaddition with DMPO probably always occurs but the primary 1:1 cycloadduct quickly degrades to form the starting coumarin and the products of münchnone fragmentation.[1]

3. Conclusions

In conclusion, our results show that the reaction of selected coumarins with *N*-substituted or *N*-unsubstituted unsymmetrical

1,3-oxazolium-5-olates is an intriguing process and that the regio- and diastereochemistry of the initial 1:1 cycloadduct determine the competitive routes that lead to the diverse types of isolated pyrrole derivatives.

4. Experimental section

4.1. General method

Melting points were determined on a Kofler melting apparatus and are uncorrected. IR spectra were recorded in Nujol with a Nicolet Impact 410D spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AMX R300. Mass spectrometry analyses and Microanalyses were carried out on a 3200 QTRAP (Applied Biosystems SCIEX) and on a Carlo Erba EA 1102, respectively. All solvents and reagents were obtained from commercial sources and purified before use if necessary. 3-Substituted coumarins,[7] MPO[8] and DMPO[9] were prepared according to literature method. Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063–0.100 mm) for column chromatography.

4.2. Reactions of MPO 4 with coumarins 3

Method A. 3-Substituted coumarin **3** and MPO **4** were dissolved in anhydrous toluene and heated at reflux under a N_2 atmosphere for 2–3 h. After evaporation the product was purified by chromatographic column (10% ethyl acetate/chloroform).

Method B. 3-Substituted coumarin **3** and MPO **4** were triturated together in a mortar rapidly and then reacted in a sealed vial in a bath set at 100 °C for 15–20 min. The product was washed with ether and purified in good yields by crystallization in methanol.

*4.2.1. Compound **5a**.* Method A. From 3-acetyl-coumarin **3a** (0.5 g, 2.6 mmol) and MPO **4** (1.0 g, 5.7 mmol) in toluene (10 ml) was obtained after purification a light orange solid (0.72 g, yield 77%). Method B. From 3-acetyl-coumarin **3a** (0.3 g, 1.6 mmol) and MPO **4** (0.5 g, 2.9 mmol) was obtained after crystallization in MeOH a white solid (0.51 g, yield 89%). Mp 134–137 °C; IR (cm^{-1}): 2800–2500 (br, COOH), 1749, 1722, 1712 (CO); ^{1}H NMR (DMSO-d_6, ppm): 10.90 (1H, s, COO*H*), 7.98–7.14 (9H, m, CH_{arom}), 4.15 (1H, s, C*H*), 2.16 (3H, s, CO*Me*), 1.87 (3H, s, *Me*); ^{13}C NMR (DMSO-d_6, ppm): 203.0, 171.2, 168.6, 161.6, 149.9, 131.9, 129.6, 128.6, 128.2, 127.4, 124.5, 116.5, 116.3, 83.3, 74.6, 53.6, 26.1, 23.6; ESI-MS (*m*/*z*)=380.3 [M+1]$^+$. Anal. Calcd for $C_{21}H_{17}NO_6$: C, 66.49; H, 4.52, N, 3.69. Found: C, 66.13; H, 4.69; N, 3.31.

*4.2.2. Compound **5b**.* Method A. From 3-carbomethoxy-coumarin **3b** (0.5 g, 2.45 mmol) and MPO **4** (1.0 g, 5.7 mmol) in toluene (10 ml) was obtained after purification a white solid (0.64 g, yield 69%). Method B. From 3-carbomethoxy-coumarin **3b** (0.3 g, 1.47 mmol) and MPO **4** (0.5 g, 2.9 mmol) was obtained after crystallization in MeOH a white solid (0.45 g, yield 80%). Mp 160–161 °C; IR (cm^{-1}): 2800–2400 (br, COOH), 1767, 1740, 1713 (CO); ^{1}H NMR (DMSO-d_6, ppm): 7.92–7.16 (9H, m, CH_{arom}), 4.02 (1H, s, C*H*), 3.66 (3H, s, COO*Me*), 1.78 (3H, s, *Me*); ^{13}C NMR (DMSO-d_6, ppm): 171.2, 169.2, 167.9, 160.3, 149.9, 131.7, 131.4, 129.6, 129.3, 128.4, 124.8, 116.4, 83.2, 66.6, 56.3, 54.2, 23.6; ESI-MS (*m*/*z*)=364.4 [M+1]$^+$. Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72, N, 3.85. Found: C, 69.94; H, 4.62; N, 4.07.

*4.2.3. Compound **6**.* Method A. From 3-cyano-coumarin **3c** (0.5 g, 2.9 mmol) and MPO **4** (1.0 g, 5.7 mmol) in toluene (10 ml) was obtained after purification a light yellow solid (0.35 g, yield 40%). Mp 175–180 °C; IR (cm^{-1}): 3373 (NH), 2199 (CN), 1766 (CO); ^{1}H NMR ($CDCl_3$, ppm): 7.70–7.09 (9H, m, CH_{arom}), 5.48 (1H, s, N*H*), 4.24 (1H, s, C*H*), 1.66 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$, ppm): 173.6, 161.6, 152.2, 134.8, 133.2, 128.8, 128.2, 127.9, 127.4, 126.3, 125.9, 121.5, 117.2, 81.5, 66.8, 48.5, 22.5; ESI-MS (*m*/*z*)=303.3 [M+1]$^+$. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67, N, 9.27. Found: C, 75.29; H, 4.50; N, 9.41.

4.3. Esterification of 5b

N-Methyl-*N*-nitrosotoluene-*p*-sulfonamide (2.14 g, 10 mmol) was dissolved in ether (30 ml) and cooled in an ice bath, KOH (0.4 g, 70 mmol) in ethanol 96% (10 ml) was added. If a precipitate formed, more ethanol was added until it just dissolved. After 5 min, ethereal diazomethane solution was distilled from a water bath.

3-Acetyl-[3,4-*c*]pyrrole-coumarin acid **5b** (1.3 g, 3.58 mmol) was dissolved in a solution of dioxane/THF 7:3 (30 ml) and fresh ethereal diazomethane solution (30 ml) was added dropwise. The mixture was stirred for an hour at room temperature then the solvent was removed by rotavapor and hot methanol (10 ml) was added. After cooling a white solid **7** was obtained.

Mp 178–179 °C; IR (cm^{-1}): 1766, 1738, 1709 (CO); ^{1}H NMR ($CDCl_3$, ppm): 8.08–7.13 (9H, m, CH_{arom}), 3.73 (1H, s, C*H*), 3.35 (3H, s, COO*Me*), 2.18 (3H, s, CO*Me*), 1.96 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$, ppm): 201.5, 170.6, 168.1, 161.9, 150.5, 132.0, 131.2, 129.8, 128.6, 128.4, 128.1, 127.5, 124.6, 116.5, 74.4, 53.8, 52.3, 40.1, 26.5, 22.9; ESI-MS (*m*/*z*)=378.4 [M+1]$^+$. Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07, N, 3.71. Found: C, 69.84; H, 4.89; N, 3.58.

4.4. Reaction of DMPO 10 with 3c

DMPO **10**, generated in situ from *N*-benzoyl-*N*-methylalanine (0.62 g, 3 mmol) and acetic anhydride (0.61 g, 6 mmol), was heated with coumarin **3c** (0.5 g, 2.9 mmol) in anhydrous toluene (30 ml) at reflux under a N_2 atmosphere for 3 h. The solvent was removed by vacuum evaporation and the residue was purified in column chromatography (3%AcOEt/$CHCl_3$).

The first eluted component was a light yellow solid **12** (0.29 g, yield 35%). Mp 128 °C; IR (cm^{-1}): 3300 (OH), 2216 (CN); ^{1}H NMR ($CDCl_3$, ppm): 7.33–6.78 (9H, m, CH_{arom}), 3.50 (3H, s, N*Me*), 2.50 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$, ppm): 155.6, 150.4, 138.5, 131.5, 129.3, 130.1, 129.2, 128.8, 128.7, 128.5, 120.6, 120.0, 118.3, 118.0, 116.0, 115.5, 32.5, 12.0; ESI-MS (*m*/*z*)=289.4 [M+1]$^+$. Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59, N, 9.72. Found: C, 78.92; H, 5.68, N, 9.87.

The second eluted component was a white solid **11** (0.14 g, yield 15%). Mp 155–158 °C; IR (cm^{-1}): 2177 (CN), 1744 (CO); ^{1}H NMR ($CDCl_3$, ppm): 7.35–7.07 (9H, m, CH_{arom}), 4.40 (1H, s, C*H*), 2.97 (3H, s, N*Me*), 2.14 (1H, s, *Me*); ^{13}C NMR ($CDCl_3$, ppm): 172.4, 162.3, 152.0, 134.8, 133.2, 128.8, 128.0, 127.3, 127.0, 126.1, 125.8, 121.3, 117.3, 79.0, 75.9, 48.8, 33.0, 19.7; ESI-MS (*m*/*z*)=317.4 [M+1]$^+$. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10, N, 8.86. Found: C, 75.53; H, 5.02, N, 8.69.

4.5. Reaction of DMPO 10 with 3-cyanochromone 15

3-CN-Chromone **15** (1 g, 5.8 mmol) and *N*-methyl-*N*-benzoyl-alanine (1.6 g, 7.7 mmol) were dissolved in anhydrous dioxane (30 ml) and acetic anhydride (1.6 g, 15.7 mmol) and the solution heated at reflux for 0.5 h. After the usual workup process and column chromatographic purification ($CHCl_3$) light brown solid **17** (0.45 g, yield 40%) and salicylic acid were isolated.

*4.5.1. Compound **17**.* Mp 112–114 °C; IR (cm^{-1}): 2216 (CN); ^{1}H NMR ($CDCl_3$, ppm): 7.43–7.33 (5H, m, Ph), 6.33 (1H, s, CH_{pyrr}), 3.50 (3H, s, N*Me*), 2.43 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$, ppm): 138.7, 134.9, 131.6, 129.0, 128.6, 127.9, 117.3, 109.5, 91.0, 32.2, 11.8; ESI-MS (*m*/*z*)=197.5 [M+1]$^+$. Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16, N, 14.27. Found: C, 79.77; H, 6.04, N, 14.48.

Salicylic acid was identified by comparison with an authentic sample.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.02.009.

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