DOI 10.1007/s10593-020-02707-3
Chemistry of Heterocyclic Compounds **2020**, *56*(5), 611–614

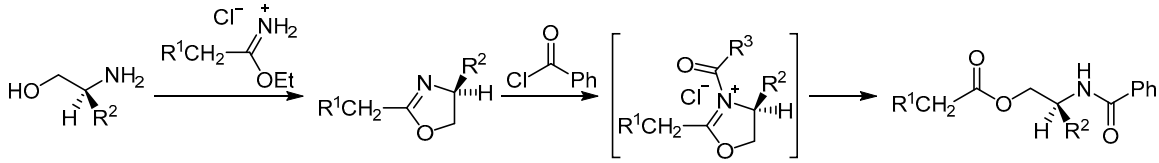
Generation and hydrolysis of *N*-acyloxazolinium salts allowing regiospecific acylation of chiral amino alcohols

R. Alan Aitken[1]*, Alexandra M. Z. Slawin[1], Andrew Wilson[1]

[1] *EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, United Kingdom; e-mail: raa@st-and.ac.uk*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2020, *56*(5), 611–614

Submitted March 4, 2020
Accepted after revision April 27, 2020

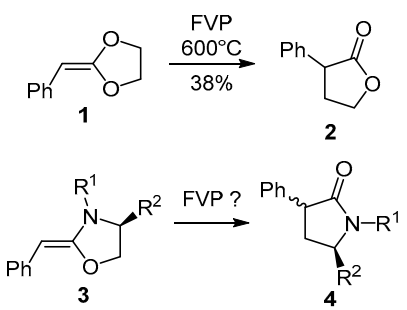


In an attempt to form 2-alkylidene-1,3-oxazolidines, chiral 2-oxazolines have been *N*-alkylated and *N*-acylated. Two new *N*-methyloxazolinium salts have been prepared and characterized, but alkaline treatment resulted in their decomposition. In contrast, attempts to isolate three *N*-benzoyloxazolinium salts gave the products of their ring hydrolysis: unsymmetrically diacylated amino alcohols whose structure was confirmed by X-ray diffraction in one case. Overall the method allows stepwise regiospecific *N*,*O*-diacylation of 2-amino alcohols.

Keywords: amino alcohols, oxazolines, oxazolinium salts, acylation, hydrolysis.

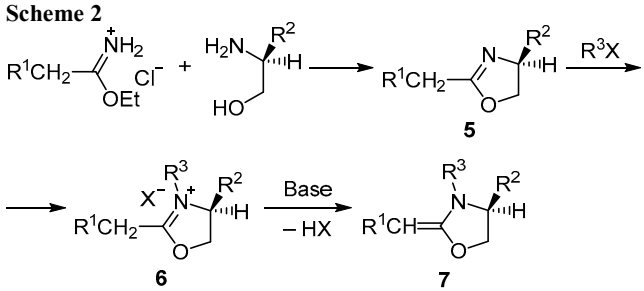
We recently reported that the thermal isomerization of 2-benzylidene-1,3-dioxolane (**1**) to give γ-lactone **2** (Scheme 1), which was previously carried out by gas-phase flow pyrolysis at atmospheric pressure,[1] could be achieved more efficiently using conditions of flash vacuum pyrolysis (FVP).[2] In the same paper, 1,3-oxathiolane derivatives including the sulfone analog of dioxalane **1** were also examined but in these cases the pyrolysis took a different course.[2] We were interested to examine the nitrogen analogs **3** since, if these reacted in the same way as dioxolane **1**, they would give the more useful γ-lactams **4** with the added advantage that a stereogenic center at position 4 in the starting oxazolidines would likely appear with retention of configuration at C-5 atom in the product and induce stereoselectivity at the newly formed C-3 center.

Scheme 1



We envisaged that the required 2-alkylideneoxazolidines **7** could be prepared starting from the readily available oxazolines **5** by *N*-alkylation to give salts **6** followed by base treatment (Scheme 2). Literature precedent for this is provided by sodium hydride treatment of 2,3,4,4-tetramethyloxazolinium iodide to give the 2-methylidene compound,[3] although it was noted to be extremely susceptible to acid-catalyzed hydrolysis, a feature also observed for similar *N*-methyloxazolinium salts in an earlier study.[4]

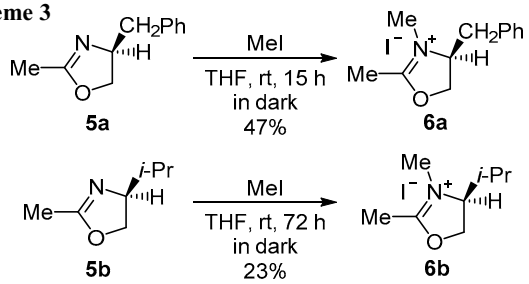
Scheme 2



We started by converting two readily available chiral oxazolines **5a** and **5b**, prepared by reaction of ethyl acetimidate hydrochloride with (*S*)-phenylalaninol and (*S*)-valinol, respectively,[5] into the corresponding *N*-methyloxazolinium salts **6a** and **6b**. Treatment with MeI in THF at room temperature in the dark gave the required salts in

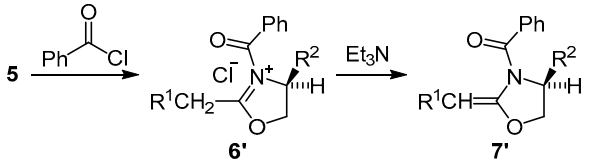
low to moderate yield as colorless crystals (Scheme 3). It was noticeable that the more sterically hindered compound **5b** reacted more slowly to give a lower yield of salt **6b** than oxazoline **5a**. These gave the expected HRMS and spectroscopic properties including significant movement to higher chemical shift in the ^{1}H NMR signals for the ring hydrogens and 2-methyl group as compared to the starting oxazolines. In the ^{13}C NMR spectra, the most prominent change was an increase in the chemical shift for the C-2 carbon from 164 ppm for oxazolines **5** to 176 ppm for compounds **6**.

Scheme 3



Unfortunately, treatment of salts **6a**,**b** with NaH in dry THF according to the literature method for the corresponding 4,4-dimethyl compounds,[3] led, after addition of petroleum and removal of the resulting precipitate of NaI, to solutions of compounds **7** that were too reactive to handle by usual methods and polymerized. In order to obtain less reactive and more easily handled 2-alkylidene-3-benzoyl-1,3-oxazolidines **7'**, we decided first to obtain *N*-benzoyloxazolinium salts **6'** (Scheme 4) since these are a well-known class of stable compounds[6] and are reported to undergo facile deprotonation using Et_3N,[7] although there are a number of possible complicating side reactions of the 2-methylidene-1,3-oxazolidines in the presence of excess acylating agent.[8]

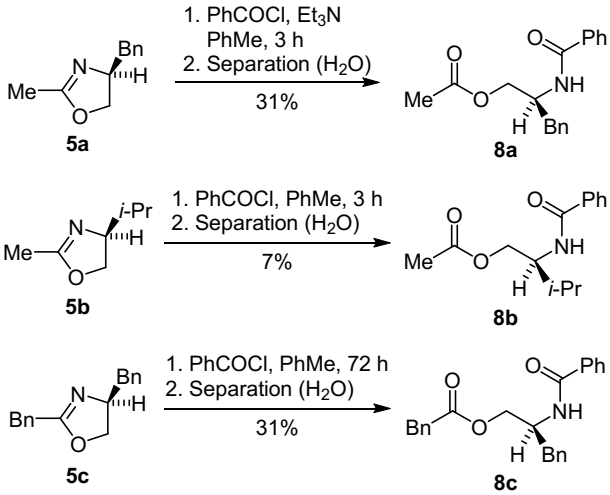
Scheme 4



Following the literature method,[7] oxazoline **5a** was stirred in PhMe with 1 equiv of Et_3N while 1 equiv of PhCOCl was added dropwise. After 3 h, the solution was filtered and evaporated to give, after trituration with Et_2O a solid that turned out to be hydrolysis product **8a** (Scheme 5).

It seems likely that the desired *N*-benzoyloxazolinium salt **6'** has been formed, but, rather than undergo deprotonation to form alkylidene compound **7'**, it has undergone hydrolysis in the course of isolation to give *O*-acetyl-*N*-benzoylphenylalaninol (**8a**). This compound was first prepared and characterized spectroscopically in 1992,[9] but it was recorded in the literature some time earlier[10] as a derivative of *N*-benzoylphenylalaninol occurring as a natural product in the leaves of *Alangium lamarckii*. More

Scheme 5



recently it has been mentioned under the trivial name "saropeptate", together with a range of steroidal components, as a constituent of *Pupalia lappacea*, a plant important in Ayurvedic medicine.[11]

The spectra of compound **8a** showed excellent agreement with the literature data.[9] It was obtained in well-formed crystals, and this provided a chance to confirm its structure using X-ray diffraction (Fig. 1). As might be expected, the presence of a secondary amide function leads to hydrogen bonding and the crystal structure shows chains of molecules formed by hydrogen bonding between the amide carbonyl group and amide NH group (Fig. 2).

Having established that hydrolysis of the *N*-benzoyloxazolidinium salts rather than any base-induced process was involved in the formation of compound **8a**, oxazolines **5b**,**c** were subjected to reaction with PhCOCl in the absence of Et_3N and in each case the product recovered after evaporation and trituration was the respective hydrolysis product **8b**,**c** (Scheme 5). Both *O*-acetyl-*N*-benzoylvalinol (**8b**) and *N*-benzoyl-*O*-phenylacetylphenylalaninol (**8c**)

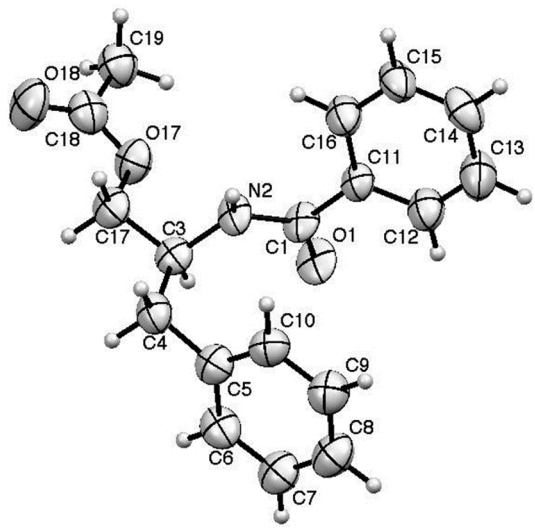


Figure 1. Molecular structure of compound **8a** with atoms represented by thermal vibration ellipsoids at the 50% probability level.

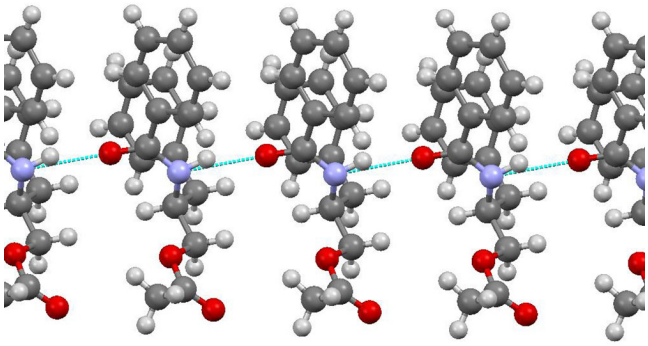
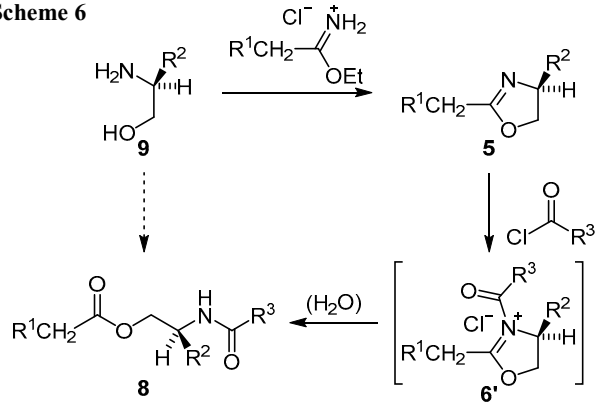


Figure 2. Hydrogen bonding pattern in crystal structure of compound **8a** viewed perpendicular to the *a* axis (hydrogen bond N(2)–H(2)···O(1): bond lengths N(2)–H(2) 0.98(5) Å, H(2)···O(1) 1.94(5) Å, N(2)···O(1) 2.870(7) Å; bond angle 157(6)°).

are apparently new compounds and gave spectroscopic data in good agreement with the proposed structures and with that of compound **8a**. 2-Benzyloxazoline **5c** took much longer to react than 2-methyloxazolines **5a**,**b**, presumably due to the electron-withdrawing phenyl group making it less nucleophilic.

Although it has clearly been arrived at by accident rather than design, the overall formation of the selectively diacylated amino alcohols **8a**–**c** starting from 2-amino alcohols is a rather useful transformation. Recent studies have proposed various catalysts to bring about enzyme-like selectivity in such reactions.[12] In this case, the general method for overall conversion of an amino acid-derived chiral 2-amino alcohol into diacylated derivative **8** involves formation of oxazoline **5** with the ultimate *O*-substituent at position 2, *N*-acylation with the ultimate *N*-substituent, and hydrolytic isolation to give product **8** (Scheme 6).

Scheme 6



Thus, in contrast to *N*-methyloxazolinium salts which were easily prepared and isolated, the *N*-benzoyloxazolinium salts proved to be much more reactive and could not be isolated as such. However, the isolation of their hydrolysis products in low to moderate yield does form the basis of a useful overall synthetic transformation.

Experimental

IR spectra were recorded using the ATR technique on a Shimadzu IR Affinity 1S instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer (400 and 100 MHz, respectively), except that ^{13}C NMR spectra of compounds **6a** and **8b** were recorded on a Bruker AVIII 500 spectrometer (125 MHz) in $CDCl_3$; internal standard TMS. The ^{13}C signals were assigned with the help of DEPTQ experiment. High-resolution mass spectra were recorded on a Micromass LCT spectrometer with electrospray ionization. Melting points were determined using a Gallenkamp 50 W melting point apparatus and are uncorrected. THF was dried over sodium wire.

(*S*)-4-Benzyl-2-methyloxazoline (**5a**) and (*S*)-4-isopropyl-2-methyloxazoline (**5b**) were prepared from ethyl acetimidate hydrochloride by respective reaction with (*S*)-phenylalaninol and (*S*)-valinol as previously reported,[5] while (*S*)-2,4-dibenzyloxazoline **5c** was similarly prepared,[13] using ethyl 2-phenylacetimidate hydrochloride[14] and (*S*)-phenylalaninol.

(*S*)-4-Benzyl-2,3-dimethyl-4,5-dihydrooxazol-3-ium iodide (6a). A solution of oxazoline **5a** (2.0 g, 11.4 mmol) in dry THF (2.5 ml) was stirred at room temperature while MeI (0.87 ml, 1.99 g, 14 mmol) was added, and the resulting mixture was stirred in the dark for 15 h. The resulting solid was filtered off and dried. Yield 1.65 g (47%), colorless crystals, mp 176–178°C. IR spectrum, ν, cm^{-1}: 1668, 1483, 1279, 1033, 984, 758, 704. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.59 (3H, s, 2-CH_3); 3.20 (1H, dd, *J* = 14.4, *J* = 7.6) and 3.35 (1H, dd, *J* = 14.4, *J* = 4.8, $PhCH_2$); 3.51 (3H, s, 3-CH_3); 4.68 (1H, dd, *J* = 9.0, *J* = 6.4, OCH_2); 5.08–5.16 (1H, m, 4-CH); 5.19 (1H, dd, *J* = 10.3, *J* = 9.0, OCH_2); 7.23–7.27 (2H, m, H Ph); 7.30–7.41 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 15.3 (2-CH_3); 34.5 (3-CH_3); 36.3 (Ph$\underline{C}H_2$); 64.6 (4-CH); 75.4 (CH_2O); 128.1 (CH Ph); 129.1 (2CH Ph); 129.4 (2CH Ph); 133.0 (C Ph); 176.7 (C-2). Found, *m*/*z*: 190.1224 [M–I]$^+$. $C_{12}H_{16}NO$. Calculated, *m*/*z*: 190.1226.

(*S*)-4-Isopropyl-2,3-dimethyl-4,5-dihydrooxazol-3-ium iodide (6b). A solution of oxazoline **5b** (1.40 g, 11.0 mmol) in dry THF (2.5 ml) was stirred at room temperature while MeI (0.87 ml, 1.99 g, 14 mmol) was added, and the resulting mixture was stirred in the dark for 72 h. The resulting solid was filtered off and dried. Yield 0.69 g (23%), colorless crystals, mp 143–144°C. IR spectrum, ν, cm^{-1}: 1675, 1483, 1276, 1039, 987, 925, 830. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.95 (3H, d, *J* = 6.9, $CHC\underline{H}_3$); 1.02 (3H, d, *J* = 6.9, $CHC\underline{H}_3$); 2.28–2.37 (1H, m, $C\underline{H}(CH_3)_2$); 2.65 (3H, s, 2-CH_3); 3.44 (3H, s, 3-CH_3); 4.62 (1H, dd, *J* = 9.2, *J* = 6.8, OCH_2); 4.70–4.80 (1H, m, 4-CH); 5.27 (1H, dd, *J* = 11.0, *J* = 9.2, OCH_2). ^{13}C NMR spectrum, δ, ppm: 14.9 ($CH\underline{C}H_3$); 15.1 ($CH\underline{C}H_3$); 17.9 (2-CH_3); 26.5 ($\underline{C}H(CH_3)_2$); 34.0 (3-CH_3); 68.6 (4-CH); 72.0 (CH_2O); 176.8 (C-2). Found, *m*/*z*: 142.1223 [M–I]$^+$. $C_8H_{16}NO$. Calculated, *m*/*z*: 142.1226.

(*S*)-2-Benzoylamino-3-phenylpropyl acetate (8a). A solution of oxazoline **5a** (0.35 g, 2 mmol) and Et_3N (0.33 ml, 0.25 g, 2.4 mmol) in dry PhMe (60 ml) was stirred at room temperature while PhCOCl (0.23 ml, 0.28 g, 2 mmol) was added dropwise. After stirring for 3 h, the reaction mixture was filtered and the filtrate was evaporated. The residue was triturated with Et_2O to give the solid product. Yield 0.18 g (31%), colorless crystals, mp 124–126°C (mp 125–127°C[9]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, $COCH_3$);

2.91 (1H, dd, *J* = 13.6, *J* = 8.0) and 3.06 (1H, dd, *J* = 13.6, *J* = 5.8, C$\underline{H}_2$Ph); 4.14 (1H, dd, *J* = 11.6, *J* = 3.8) and 4.23 (1H, dd, *J* = 11.6, *J* = 6.0, CH_2O); 4.60–4.70 (1H, m, CHN); 6.41 (1H, br. d, *J* = 8.0, NH); 7.20–7.30 (2H, m, H Ph); 7.30–7.34 (3H, m, H Ph); 7.40–7.45 (2H, m, H Ph); 7.48–7.52 (1H, m, H Ph); 7.70–7.73 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 20.9 (CH_3); 37.5 ($\underline{C}H_2$Ph); 50.3 ($\underline{C}$HN); 64.8 (CH_2O); 126.8 (3CH Ph); 128.6 (2CH Ph); 128.7 (2CH Ph); 129.3 (2CH Ph); 131.6 (CH Ph); 134.3 (C Ph); 136.9 (C Ph); 167.0 (NCO); 171.5 (OCO). Both ^{1}H and ^{13}C NMR spectra showed excellent agreement with literature data.[9]

(*S*)-2-Benzoylamino-3-methylbutyl acetate (8b). A solution of oxazoline **5b** (0.51 g, 4 mmol) in dry PhMe (120 ml) was stirred at room temperature while PhCOCl (0.46 ml, 0.56 g, 4 mmol) was added dropwise. After stirring for 3 h, the reaction mixture was evaporated and the residue was triturated with Et_2O to afford the title compound. Yield 77 mg (7%), colorless crystals, mp 74–76°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (6H, d, *J* = 6.8, CH(C$\underline{H}_3$)$_2$); 1.95 (1H, octet, *J* = 6.8, C$\underline{H}$(CH$_3$)$_2$); 2.06 (3H, s, COCH_3); 4.15 (1H, dd, *J* = 11.6, *J* = 3.6, CH_2O); 4.20–4.30 (1H, m, C$\underline{H}$NH); 4.39 (1H, dd, *J* = 11.6, *J* = 6.6, CH_2O); 6.24 (1H, br. d, *J* = 8.4, NH); 7.40–7.60 (3H, m, H Ph); 7.70–7.80 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 18.7 (CH_3); 19.3 (CH_3); 20.9 (CO$\underline{C}H_3$); 29.8 ($\underline{C}$H(CH$_3$)$_2$); 54.0 (CHN); 64.5 (CH_2O); 126.8 (2CH Ph); 128.6 (2CH Ph); 131.5 (CH Ph); 134.6 (C Ph); 167.3 (NCO); 171.4 (OCO). Found, *m*/*z*: 250.1449 $[M+H]^+$. $C_{14}H_{20}NO_3$. Calculated, *m*/*z*: 250.1438.

(*S*)-2-Benzoylamino-3-phenylpropyl phenylacetate (8c). A solution of oxazoline **5c** (1.50 g, 6 mmol) in dry PhMe (80 ml) was stirred at room temperature while PhCOCl (0.69 ml, 0.84 g, 6 mmol) was added dropwise. After stirring for 72 h, the mixture was evaporated and the residue was triturated with Et_2O to afford the title compound. Yield 0.73 g (31%), colorless crystals, mp 122–123°C. IR spectrum, ν, cm^{-1}: 3292, 1720, 1638, 1537, 1263, 1152, 1011, 694. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.79 (1H, dd, *J* = 13.6, *J* = 8.2) and 2.96 (1H, dd, *J* = 13.6, *J* = 5.8, C$\underline{H}_2$Ph); 3.67 (2H, s, COC$\underline{H}_2$Ph); 4.16 (1H, dd, *J* = 11.2, *J* = 4.0) and 4.21 (1H, dd, *J* = 11.2, *J* = 5.6, CH_2O); 4.55–4.65 (1H, m, CHN); 6.19 (1H, br. d, *J* = 8.4, NH); 7.15 (2H, d, *J* = 8.0, H Ph); 7.20–7.35 (8H, m, H Ph); 7.41 (2H, t, *J* = 8.0, H Ph); 7.50 (1H, t, *J* = 7.0, H Ph); 7.60 (2H, d, *J* = 7.2, H Ph). ^{13}C NMR spectrum, δ, ppm: 37.4 ($\underline{C}H_2$Ph); 41.5 ($\underline{C}H_2$Ph); 50.2 (CHN); 64.8 (CH_2O); 126.8 (3CH Ph); 127.3 (CH Ph); 128.5 (2CH Ph); 128.7 (4CH Ph); 129.2 (2CH Ph); 129.3 (2CH Ph); 131.6 (CH Ph); 133.8 (C Ph); 134.1 (C Ph); 136.8 (C Ph); 166.8 (NCO); 171.7 (OCO). Found, *m*/*z*: 374.1745 $[M+H]^+$. $C_{24}H_{24}NO_3$. Calculated, *m*/*z*: 374.1751.

X-ray diffraction study of compound 8a. Data were collected on a Rigaku XtaLAB P200 system using graphite-monochromated CuKa radiation (λ 1.54187 Å). Crystal data: $C_{18}H_{19}NO_3$, *M* 297.35, colorless needles; crystal dimensions 0.12 × 0.01 × 0.01 mm; orthorhombic, space group $P2_12_12_1$; *a* 5.0182(4), *b* 16.208(3), *c* 19.498(3) Å; *V* 1585.9(4) Å^3; *Z* 4; D_{calc} 1.245 g·cm^{-3}; *T* 125 K; *R* 0.1219; *wR* 0.3082 for 1890 reflections with $I > 2\sigma(I)$ and 203 variables. The complete crystallographic information on compound **8a** has been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1861267).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds is available at the journal website http://link.springer.com/journal/10593.

References

1. Oda, M.; Morimoto, K.; Thanh, N. C.; Ohta, R.; Kuroda, S. *Heterocycles* **2003**, *60*, 1673.
2. Aitken, R. A.; Henderson, S.; Slawin, A. M. Z. *J. Sulfur Chem.* **2018**, *39*, 422.
3. Zhou, A.; Pittman, C. U., Jr. *Synthesis* **2006**, 37.
4. Allen, P., Jr.; Ginos, J. *J. Org. Chem.* **1963**, *28*, 2759.
5. Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc.*, *Perkin Trans 1* **1997**, 935.
6. Tomalia, D. A.; Paige, J. N. *J. Org. Chem.* **1973**, *38*, 422.
7. Zhou, A.; Njogu, M. N.; Pittman, C. U., Jr. *Tetrahedron* **2006**, *62*, 4093.
8. De Silva, H. I.; Song, Y.; Henry, W. P.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2012**, *53*, 2965.
9. Huneck, S.; Porzel, A.; Schmidt, J.; Follmann, G. *Z. Naturforsch.*, *C: J. Biosci.* **1992**, *47*, 785.
10. Achari, B.; Pal, A.; Pakrashi, S. C. *Ind. J. Chem.* **1974**, *12*, 1218.
11. Naidu, P. P.; Madakka, M.; Rajesh, B. *Asian J. Pharm. Clin. Res.* **2014**, *7(Suppl. 1)*, 15.
12. Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130,* 2944.
13. Shibata, S.; Matsushita, H.; Kaneko, H.; Noguchi, M.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3546.
14. Dalko, P. I.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 8107.