NOVEL HETEROCYCLIC OUTER-RING DIENES: *N*-ALKYL- AND *N*-ARYL SUBSTITUTED 4,5-DIMETHYLENE-2-OXAZOLIDINONES

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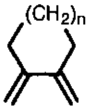
Abstract - The one-pot synthesis of the hitherto unknown *N*-substituted 4,5-dimethylene-1,3-oxazolidin-2-ones from diacetyl and the corresponding isocyanate in the presence of triethylamine is described. Diene (**4a**) undergoes Diels-Alder cycloaddition with *N*-phenylmaleimide (**10**), and, in the absence of a dienophile, gives a mixture of dimers (**12**) and (**13**), and the ring closure cyclobutene (**14**).

Outer-ring *o*-carbodimethylenes (**1**) [e.g. *o*-xylylene (**2**)] are of considerable interest both from a theoretical point of view, and for their potential in synthesis.[1] Recently, the preparation of exo-heterocyclic dienes (**3**) and their study in Diels-Alder cycloadditions have shown rapid development.[2] In particular, a bis-methylene system grafted to an oxazolidinone would be highly desirable, because the latter constitutes an important class of heterocyclic compounds.[3] Some *N*-substituted 4-methylene-2-oxazolidinones have been prepared and have found interesting use as intermediates in synthesis.[4] Nevertheless, the 4,5-dimethylene derivatives (**4**) have been hitherto unknown.



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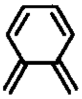

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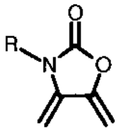

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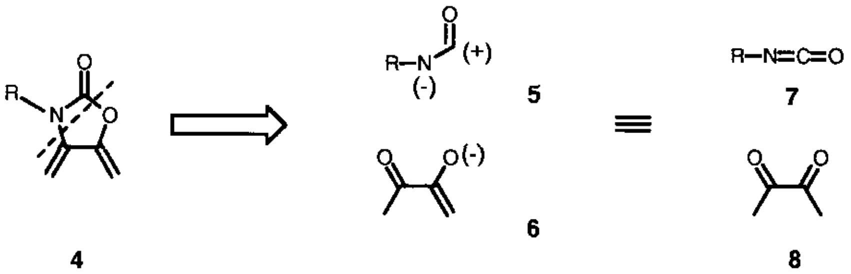
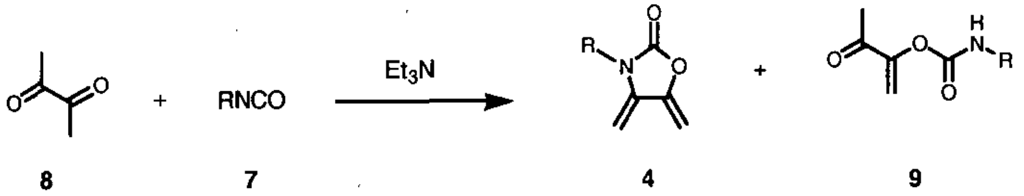
A highly convergent retrosynthetic scheme for the preparation of dienes (4) could be designed considering a disconnection as shown, which leads to fragments (5) and (6), whose synthetic equivalents may be the isocyanate (7) and diacetyl (8), respectively.



Herein, we describe a facile, one-pot preparation of **4** under mild conditions, starting from commercially available biacetyl (**8**) and isocyanates (**7**), in the presence of triethylamine. The reaction was dependent on the substituent on the nitrogen (Table). Aryl isocyanates gave the best yields of dienes (**4**). Electron-withdrawing groups on the *N*-benzene ring, such as the trifluoromethyl or nitro, afforded either poor yields or no reaction. Similar results were furnished by some alkyl isocyanates tested (R = *tert*-butyl and cyclohexyl) which were unreactive, even under heating.



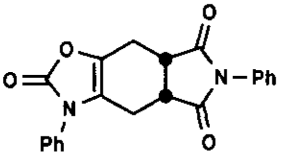
a, R = Ph
b, R = o-MeC$_6$H$_4$
c, R = p-MeC$_6$H$_4$
d, R = m-ClC$_6$H$_4$
e, R = p-ClC$_6$H$_4$
f, R = o-CF$_3$C$_6$H$_4$
g, R = o-NO$_2$C$_6$H$_4$
h, R = m-NO$_2$C$_6$H$_4$
i, R = p-NO$_2$C$_6$H$_4$
j, R = Cl(CH$_2$)$_2$

Interestingly, whereas in the case of aryl isocyanates the tlc and ^{1}H nmr monitoring of the crude did show dienes (**4**) as the main product and revealed only traces of possible olefins (**9**), the β-chloroethyl isocyanate provided, in addition to the expected diene (**4j**), the olefin (**9j**) as the major product. Moreover, an increase in olefin (**9j**) was observed as the temperature was raised, or when DMF was used; however, under dioxane/Li_2CO_3 conditions, only **4j** was obtained in relatively good yield (Table, Entries 20-23).

A variety of reaction conditions were examined in order to optimize the process. Three bases were tested: triethylamine, sodium hydride and DBU; solvents like DMF, methylene chloride, dioxane and THF were assessed; besides, the effect of the temperature of the reaction was evaluated (Table). Addition of a dehydrating agent (Entries 3, 11-15), or a co-solvent like HMPA (Entries 5 and 7), increased the yield of the desired product. The best yields were afforded using triethylamine with preferably dioxane as the solvent in the presence of dry lithium carbonate.[5]

Even though dienes (**4**) were prepared, for the most part, in fair yields, these are comparable and even better than those usually obtained by multistep synthetic approaches to similar heterocyclic exo-dienes. These yields are probably due to the particularly high reactivity of the exo-methylenes toward electrophilic species and radicals. Hence, the purification of the reaction mixtures gave, in addition to the aforementioned dienes (**4**) and olefins (**9**), a polar and complex mixture of products. Dienes (**4**) are crystalline solids and all of them exhibit the expected spectroscopic properties.[6]

Diene (**4a**) underwent Diels-Alder cycloaddition with *N*-phenylmaleimide (**10**) at 190°C in xylene for 5 h to give adduct (**11**) (90%). Otherwise, when **4a** in xylene was heated to 130°C for 10 h in the absence of a dienophile, a mixture of dimerization products (**12**) and (**13**), and cyclobutene (**14**) were obtained. The ratio between them is, as expected, reaction time depending: the longer the reaction time, the less proportion of **14**. This was detected even when the reaction took place at room temperature, showing that this unusual and probable electrocyclic ring closure process, thermodynamically unfavorable for this kind of equilibria,[7] turned out to be quite favorable. **14** proved to be stable enough to be handled and characterized.[8]



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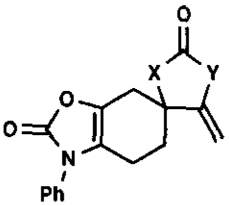
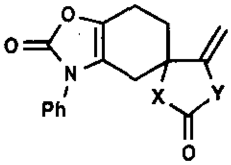
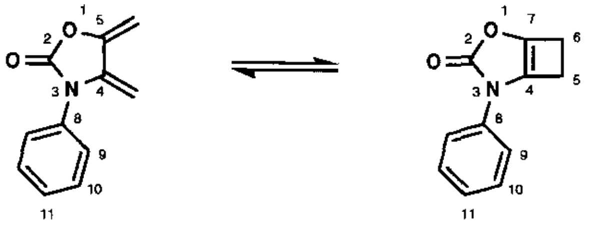


12a, X = O; Y = NPh
12b, X = NPh; Y = O



13a, X = O; Y = NPh
13b, X = NPh; Y = O



4a **14**

Table. Condensation Reaction of Diacetyl (**8**) with Aryl and Alkyl Isocyanates **7** (RNCO).

Entry	Isocyanate R-	Base	Solvent	Additive	Temperature (°C)	Time (h)	Yield[a] (%)	Products
1	Ph	Et_3N	DMF	—	25	29	14	**4a**
2	Ph	Et_3N	DMF	$MgSO_4$	25	40	17	**4a**
3	Ph	Et_3N	DMF	$MgSO_4$	60	6	23	**4a**
4	Ph	Et_3N	DMF	$MgSO_4$	80	6	12	**4a**
5	Ph	Et_3N	DMF/HMPA, 9:1	—	25	24	23	**4a**
6	Ph	Et_3N	THF	—	25	30	13	**4a**
7	Ph	Et_3N	THF/HMPA, 9:1	—	25	24	17	**4a**
8	Ph	Et_3N	CH_2Cl_2	—	25	10	14	**4a**
9	Ph	NaH	DMF	—	25	25	7	**4a**
10	Ph	DBU	DMF	—	25	30	9	**4a**
11	Ph	Et_3N	dioxane	Li_2CO_3	25	12	54	**4a**
12	*o*-MeC_6H_4	Et_3N	dioxane	Li_2CO_3	25	12	20	**4b**
13	*p*-MeC_6H_4	Et_3N	dioxane	Li_2CO_3	25	24	18	**4c**
14	*m*-ClC_6H_4	Et_3N	dioxane	Li_2CO_3	25	30	45	**4d**
15	*p*-ClC_6H_4	Et_3N	dioxane	Li_2CO_3	25	30	41	**4e**
16	*o*-$CF_3C_6H_4$	Et_3N	DMF	$MgSO_4$	25	23	13	**4f**
17	*o*-$NO_2C_6H_4$	Et_3N	DMF	—	60	6	0	**4g**
18	*m*-$NO_2C_6H_4$	Et_3N	DMF	—	60	6	0	**4h**
19	*p*-$NO_2C_6H_4$	Et_3N	DMF	—	60	6	0	**4i**
20	$Cl(CH_2)_2$	Et_3N	THF/HMPA, 9:1	—	25	28	31	**4j**/**9j** (38:62)[b]
21	$Cl(CH_2)_2$	Et_3N	DMF	—	25	23	29	**4j**/**9j** (23:77)[b]
22	$Cl(CH_2)_2$	Et_3N	DMF	—	40	7	15	**4j**/**9j** (10:90)[b]
23	$Cl(CH_2)_2$	Et_3N	dioxane	Li_2CO_3	60	6	69	**4j**

[a] Isolated yields after column chromatography. [b] Determined by ^1H nmr.

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5. In a typical experiment, at room temperature with N_2 atmosphere, dropwise addition of a solution of phenyl isocyanate (0.62 g, 5.2 mmol) in anhydrous dioxane (2.5 ml) to a solution of diacetyl (**8**) (0.3 g, 3.5 mmol), triethylamine (0.71 g, 7.0 mmol) and anhydrous Li_2CO_3 (0.3 g, 4.0 mmol) in dry dioxane (1.0 ml) was followed by stirring at room temperature for 12 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel impregnated with 10% of Et_3N (hexane/EtOAc, 95:5), to give 0.53 g (54%) of **4a**, as colorless crystals.[6]
6. All new compounds were characterized spectroscopically and gave satisfactory combustion analysis. E. g. physical and spectral data for **4a**: mp 75-76°C. Ir (KBr) 3120, 3060, 1770, 1690, 1640, 1500, 1400, 1290, 1060, 980, 830, 770 cm^{-1}. ^{1}H Nmr (270 MHz, $CDCl_3$) δ 4.35 (d, J = 3.0 Hz, 1H, HC=), 4.76 (d,

J = 3.0 Hz, 1H, HC=), 4.93 (d, J = 3.0 Hz, 1H, HC=), 4.98 (d, J = 3.0 Hz, 1H, HC=), 7.3-7.5 (m, 5H, PhH). ^{13}C Nmr (75 MHz, $CDCl_3$) δ 84.5 (CH_2=), 86.9 (CH_2=), 126.9 (C-9), 128.7 (C-11), 129.7 (C-10), 133.7 (C-8), 138.9 (C-4 or C-5), 148.9 (C-5 or C-4), 152.3 (C-2). Ms (70 eV) 187 (M^+, 100), 143 (32), 104 (47), 91 (18), 77 (86), 51 (42). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.57; H, 4.84; N, 7.48. Found: C, 70.39; H, 4.87; N, 7.33 %.

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8. Spectral data for **14**: Ir (film) 3120, 1740, 1690, 1750, 1490, 1390, 1140 cm^{-1}. ^{1}H Nmr (300 MHz, $CDCl_3$) δ 2.50-2.55 (m, 2H, CH_2), 2.88-2.93 (m, 2H, CH_2), 7.29-7.32 (m, 2H, PhH), 7.40-7.53 (m, 3H, PhH). ^{13}C Nmr (75 MHz, $CDCl_3$) δ 22.2 (CH_2), 23.0 (CH_2), 122.2 (C-4 or C-7), 127.4 (C-9), 128.9 (C-11), 129.7 (C-10), 133.3 (C-8), 134.2 (C-7 or C-4), 154.1 (C-2). Ms (70 EV) 187 (M^+, 100), 143 (39), 142 (38), 117 (47), 104 (54), 103 (36), 91 (28), 77 (92), 51 (57).

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