Pergamon

Tetrahedron Letters 43 (2002) 3415–3418

TETRAHEDRON
LETTERS

Synthesis of 3-(alkylamino and anilino)-4-benzyloxycarbonyl-1*H*-pyrrole-2,5-diones via 5-[(alkylamino and anilino)(cyano)]-2,2-dimethyl-1,3-dioxane-4,6-diones

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Received 22 January 2002; revised 6 March 2002; accepted 8 March 2002

Abstract—Treatment of [(alkylamino and anilino)(cyano)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones with benzyl alcohol for 20 min at reflux gave 3-(alkylamino and anilino)-4-benzyloxycarbonylmaleimides. © 2002 Published by Elsevier Science Ltd.

In recent years *N*-substituted maleimides and 5-ylidenepyrrol-2(5*H*)-ones have received growing attention since the former have potential utility as fluorescent reagents for labeling different mutant proteins[1] and the latter have interesting features associated with regioselective synthesis of the molecules when different substituents are bonded to the positions 3 and 4 of the skeleton.[2]

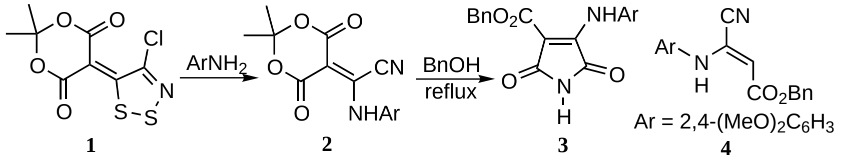
The majority of methods reported for the synthesis of maleimides are based on the reactions of the corresponding maleic anhydride with an amine or ammonium acetate.[3] Similarly, the reaction of maleamic acid with Et_3N in either toluene or benzene, yielding *N*-maleoylamino esters, may be in the same class as the foregoing reaction.[4] There exists one report of the synthesis of *N*-alkylmaleimides using alkylamines, maleic anhydride and cobalt naphthenate as a catalyst.[1]

In connection with an ongoing program for exploring the synthetic utility of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles,[5] we reported the facile synthesis of 5-[(alkylamino and anilino)(cyano)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **2** by treatment of 5-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **1** with primary alkylamines and anilines in CH_2Cl_2 at rt, respectively.[6] Compounds **2** are a kind of Meldrum's acid derivative, which would be expected to possess versatile synthetic potentials in view of reports describing the synthesis of a wide variety of organic compounds such as 1,3-dicarbonyl compounds[7] and β-enamino esters[8] via this type of Meldrum's acid derivative (Scheme 1).

We have found that treatment of **2** with benzyl alcohol for 20 min at reflux gave title compound **3** in moderate to fair yields.[9] Reaction temperature, time and yield and mp of **3** are summarized in Table 1.

When **2d** ($Ar=4\text{-}MeC_6H_4$) was treated with benzyl alcohol bearing a substituent such as F, Cl, and Me at the *para* position under the same conditions (reflux, 20 min), **3** were obtained in 20, 13, and 17% yields, respectively, together with unidentifiable mixtures.

In contrast, heating of **2d** in *t*-butyl alcohol for 3 days at reflux gave *t*-butyl 3-oxo-3-(4-tolylamino)propanoate



Scheme 1.

Keywords: cyano compounds; dithiazoles; imides.

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0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00467-7

Table 1. Reaction temperature and time, and yield and mps of **3**

Compound[a]	Ar	Temp. (°C)	Time (min)	Yield[b] (%)	Mp[d] (°C)
3a	Ph	Reflux	20	76	214–217[e]
3b	4-ClC_6H_4	Reflux	20	44	240–243[e]
3c	4-BrC_6H_4	Reflux	20	68	242–245[e]
3d	4-MeC_6H_4	Reflux	20	72	220–224[e]
3e	4-$MeOC_6H_4$	Reflux	20	56	196–203[e]
3f	2-MeC_6H_4	Reflux	20	48	203–204
3g	2,4-$F_2C_6H_3$	Reflux	20	75	220–222
3h	2,4-$(MeO)_2C_6H_3$	Reflux	20	35[c]	152–154
		155	180	45[c]	
		110	120 h	31[c]	
3i	$PhCH_2$	Reflux	20	32	156–158
		155	120	35	

[a] Compounds **3** are yellow except for **3f** (orange) and **3g** (pale yellow).

[b] Isolated yields.

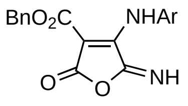
[c] *cis*-Benzyl 3-cyano-3-(2,4-dimethoxyphenylamino)propenoate (**4**)[10] was isolated in 30, 18, and 6% yields at reflux, 155 and 110°C, respectively.

[d] Recrystallized from a mixture of $CHCl_3$ and acetone except for **3e**–**g** and **3i** (from *n*-hexane and CH_2Cl_2).

[e] Decomposition temperature.

5 (32%) along with the recovery of **2d** (22%) (Scheme 2). Similar treatment of **2d** with EtOH for 3 days under the same conditions gave ethyl 3-oxo-3-(4-tolylamino)propanoate **6** (13%), 5-[(ethoxy)(4-tolylamino)-methylene]-2,2-di-methyl-1,3-dioxane-4,6-dione **7** (34%) together with unreacted **2d** (19%).

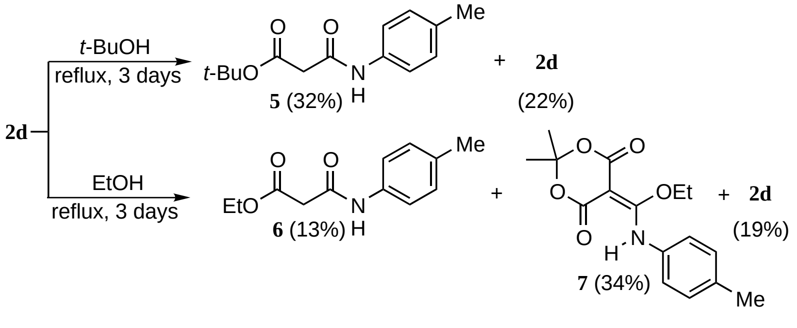
The structures of **3** were determined based on spectroscopic and analytical data. In particular, the IR spectra exhibited three characteristic peaks at 1715–1755, 1638–1651 and 1587–1624 cm^{-1}, assigned to the three carbonyl groups. The IR bands are consistent with those at 1738, 1655 and 1623 cm^{-1} exhibited by 3-anilino-4-ethoxycarbonyl-1-phenylmaleimide.[11] The HMBC spectrum of **3i** shows that the N–H proton at position 1 correlates with the C-2, C-3, C-4 and C-5 carbons, which rules out the possible formation of the structural isomer, isoimide **8g**.



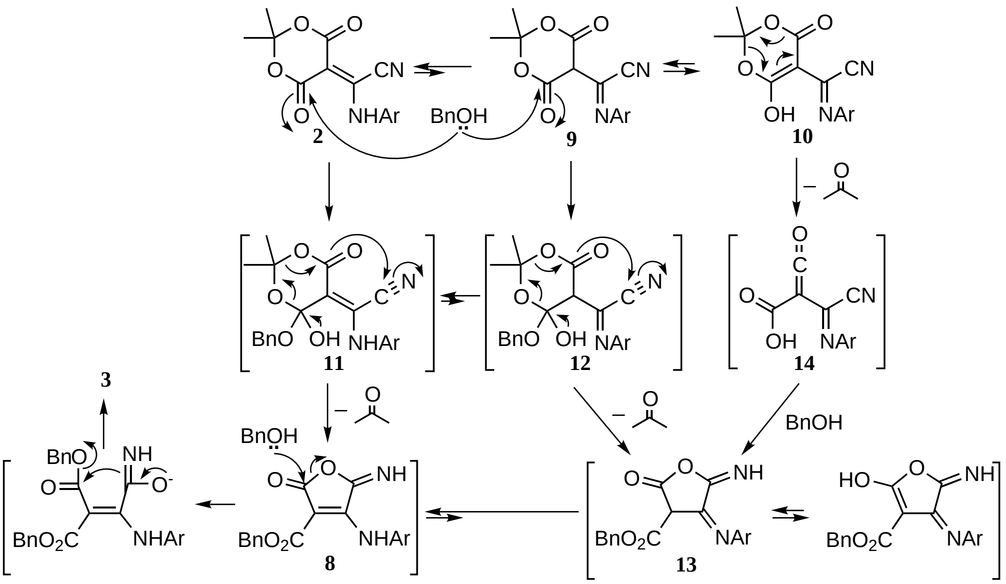
8g

The mechanism for the formation of **3** may be rationalized by assuming an equilibrium mixture of tautomers **2**, **9** and **10** in which the thermodynamically more stable tautomer **2** exists predominantly[12] (Scheme 3). A nucleophilic attack of the hydroxy group of benzyl alcohol on tautomers **2** and **9** would give intermediates **11** and **12**, respectively. An analogous type of nucleophilic attack has been reported for the reactions of acyl Meldrum's acid with alcohols and amines.[7b,7e] Subsequent extrusion of an acetone molecule from **11** and **12** concomitant with an intramolecular cyclization would give isoimide **8** and its tautomer **13**,[11] respectively. Rearrangement of isoimide **8** to imide **3** may be achieved by either nucleophilic attack of benzyl alcohol on the carbonyl carbon of isoimide **8**, followed by a ring closure[13] or thermal reaction.[14] Alternatively, the intermediate **13** might be formed by extrusion of an acetone molecule at reflux temperature to give a ketene **14** in view of reports of the formation of numerous products via ketene intermediates.[7a,8c,15] Subsequent nucleophilic attack of benzyl alcohol on **14**, followed by cyclization would give **13**. It is worthwhile to note that imides are generally more stable than the corresponding isoimides.[16] To the best of our knowledge, no example involving benzyl alcohol as a catalyst has been reported although several dehydrating agents and catalysts have been utilized for the rearrangement of isoimides to imides.[17]

In summary, we have prepared unsymmetrically 3,4-disubstituted maleimides from [(alkylamino and



Scheme 2.



Scheme 3.

anilino)(cyano)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones and benzyl alcohol at reflux temperature.

Acknowledgements

This research project has been supported by a grant from the Brain Korea 21 program.

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9. Typical procedure: Compound **2a** (65 mg, 0.24 mmol) in benzyl alcohol (1 mL) was heated with stirring for 20 min at reflux temperature. The reaction mixture was cooled to rt, followed by chromatography on a silica gel column (230–400 mesh, 3.5×15 cm). Elution with a mixture of *n*-hexane and EtOAc (3:1) gave benzyl alcohol. Subsequent elution with the same solvent mixture (2:1) gave **3a** (59 mg, 76%): mp 214–217°C (dec.) ($CHCl_3$ and acetone); IR (KBr) 3192, 1746, 1645, 1605, 1336, 1264 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.91 (s, 2H, CH_2), 7.13–7.25 (m, 5H, ArH), 7.27–7.37 (m, 5H, ArH), 10.35 (br. s, 1H, NH), 10.88 (br s, 1H, NH). Anal. calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.15; H, 4.29; N, 8.61.
10. Spectroscopic and analytical data of compound **4**: mp 104–106°C (dec.) (*n*-hexane); IR (KBr) 3280, 2928, 1662, 1610, 1507, 1474, 1454, 1270, 1240, 1206, 1160, 1123, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.19 (s, 2H, CH_2), 5.38 (s, 1H, CH), 6.44–6.52 (m, 2H, ArH), 7.27 (d, 1H, $J=8.5$ Hz, ArH), 7.31–7.42 (m, 5H, ArH), 9.61 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 55.7, 66.0, 96.4, 99.4, 103.9, 114.1, 120.8, 123.3, 128.2, 128.3, 128.6, 131.3, 135.9, 152.9, 158.8, 168.3. Anal. calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.54; H, 5.21; N, 8.03.
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12. Tautomerization of 5-(aminomethylidene)-2,2-dimethyl-1,3-dioxane-4,6-diones has not been studied in detail. However, **2** is believed to be the most stable tautomer (refer to Refs. 7 and 8).

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