Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4657–4660

TETRAHEDRON LETTERS

Reactivity of 2-methyl thioisomünchnone with acid chlorides

Martín Ávalos,[a] Reyes Babiano,[a] Pedro Cintas,[a] Jesús Díaz,[a] Michael B. Hursthouse,[b] José L. Jiménez,[a] Mark E. Light,[b] Ignacio López[a] and Juan C. Palacios[a,*]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, Avda. Elvas s/n, E-06071 Badajoz, Spain*

[b]*Department of Chemistry, University of Southampton, Southampton SO17 1BJ, UK*

Received 21 March 2003; revised 23 April 2003; accepted 25 April 2003

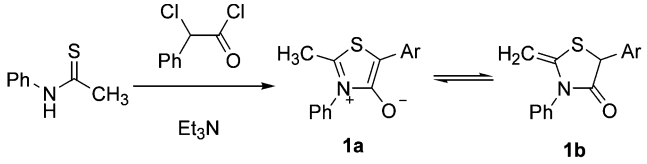
Abstract—This work describes the reactivity of 2-alkyl thioisomünchnones, exemplified here by the 2-methyl derivative, which behaves as nucleophile in the presence of both aliphatic and aromatic acid chlorides to give 2-heteroaryl ketones or 2-heteroaryl-1,3-diketones, respectively. However, 2-alkyl thioisomünchnones exhibit its characteristic 1,3-dipole behavior toward unsaturated systems.

The cycloaddition reactions with mesoionic compounds have stirred enormous interest and progress in the last decades.[1] These substances constitute a synthetically useful family of masked 1,3-dipoles and not only offer a potential for natural product syntheses, but also the possibility of constructing a series of uniquely different heterocycles from cycloadduct fragmentation. The anhydro-4-hydroxy-1,3-thiazolium hydroxides (thioisomünchnones), which contain a thiocarbonyl ylide dipole, can easily be prepared from thioamides and undergo [3+2] cycloadditions with reactive dipolarophiles.[1b] The ability to synthesize diverse heterocycles by this strategy is largely dependent on the substitution pattern of the parent thioisomünchnone. We have shown the profound stereodirecting effect exerted by a dialkylamino residue on the 2-position of the mesoionic ring leading to a wide range of heterocyclic systems, hitherto inaccessible by 1,3-dipolar cycloadditions such as dihydrothiophenes,[2] 1,2,3-triazin-4-ones,[3] azetidin-2-ones,[4] or thiiranes.[5]

It has long been thought that thioisomünchnones and their cousins the anhydro-4-hydroxy-1,3-oxazolium hydroxides (isomünchnones) exist in equilibrium with their neutral tautomeric form, although most experimental evidences suggest that only the zwitterionic form actually undergoes a 1,3-dipolar cycloaddition. In the early 1970s, Potts and Marshall reported the tautomerization of oxazol-4(5*H*)-ones to isomünchnones which readily react with acetylenes to afford the corresponding cycloadducts. These substances subsequently underwent a retro-Diels–Alder reaction with loss of isocyanic acid to give furans.[6] These authors also considered an alternative Diels–Alder pathway via an enol tautomer.[7] Nevertheless, this surmise was ruled out as other oxazol-4(5*H*)-ones and thiazol-4(5*H*)-ones did not undergo this transformation.

Apparently, only Baudy and co-workers were able to characterize spectroscopically the equilibrium between a 2-methyl thioisomünchnone derivative and its non-mesoionic tautomer 2-methylenethiazol-4(5*H*)-one.[8] Still, the latter compound did react as thioisomünchnone to produce cycloadducts or heterocycles derived thereof.[9]

To shed light into this class of tautomeric equilibria and their synthetic utility, as well as to develop a general synthesis of 2-alkyl thioisomünchnones, herein we describe a detailed exploration of their reactivity with acid chlorides. 3,5-Diphenyl-2-methyl thioisomünchnone (**1a**) was prepared by treatment of the commercially available thioacetanilide and 2-chloro-2-phenylacetyl chloride,[10] according to the improved pro-



Scheme 1.

Keywords: cycloadditions; 1,3-dicarbonyl compounds; mesoionics; tautomerism; thioisomünchnones.

* Corresponding author. Tel.: +34924289380; fax: +34924271149; e-mail: palacios@unex.es

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01087-6

tocol reported by Potts et al.[11] This sequence is more advantageous than that of Baudy and associates who employed the condensation of thioamides with *gem*-dicyano epoxides.[8] Both such a dicyano epoxide and the α-halo-α-phenylacetyl chloride provide the same heterocyclic fragment: the C-4 and C-5 atoms and their substituents. IR and ^{1}H NMR spectra of **1** reveal that this substance does exist in a tautomeric equilibrium (**1a**:**1b** = 1:3.8, Scheme 1).

We have computed the energy difference between these tautomers and found that they have approximately the same stability (ΔE<0.02 kcal/mol at the PM3 or B3LYP/6-31G* levels of theory).[12] An analysis of Mulliken charges at the B3LYP/6-31G* level evidences the nucleophilic character of the exocyclic carbon and, therefore we did envisage the possibility of trapping the 2-methylenethiazol-4(5*H*)-one (**1b**) tautomer with reactive electrophiles. To this end, reactions of **1** with acid chlorides were conducted under mild conditions in the presence of triethylamine to capture the hydrogen chloride released.[13]

With acetyl, propanoyl and butanoyl chlorides, the monosubstituted derivatives **2b**–**4b** were obtained. NMR spectra showed that only the thiazol-4(5*H*)-ones (**2b**–**4b**) form exist. The *cis* relationship between the sulfur atom and the side chain acyl substituent could be unequivocally determined by X-ray diffraction analysis of **2b** (Fig. 1).[14] Remarkably both phenyl groups adopt an orthogonal disposition with respect to the heterocyclic ring, to presumably alleviate the steric congestion. It is equally interesting worth noting that the solid-state conformation found for the acyl group should be attributed to the intramolecular non-bonded interaction S···O (1,5-intra mode), which has its origin in $n_{(C=O)}$–$\sigma^*_{(C-S)}$ orbital overlap effect.[15]

On the other hand, reactions of **1** with benzoyl, 4-methoxybenzoyl, 4-chlorobenzoyl, 2-fluorobenzoyl, or 4-nitrobenzoyl chlorides produced the corresponding 2-heteroaryl-1,3-diketones **5**–**9**. In this case, however, NMR spectra of compounds **5**, **6**, and **8** suggest the exclusive existence of their thioisomünchnone tautomers, whereas **7** and **9** appear to be equilibrated between both forms (Scheme 2, Table 1).

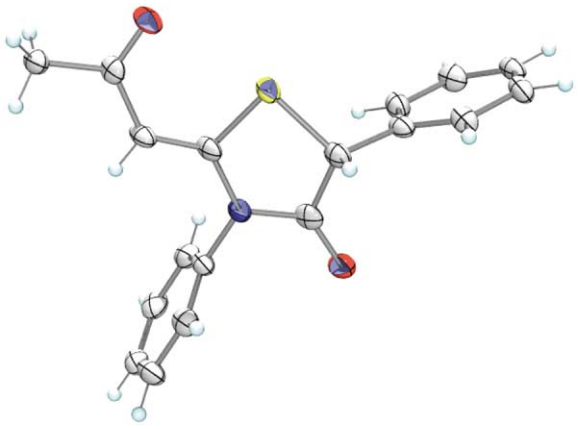
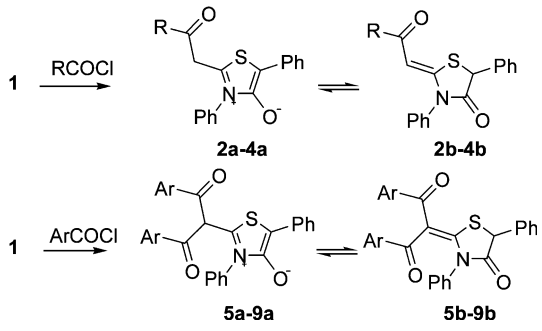


Figure 1.



Scheme 2.

Data collected in Table 1 also evidence that the formation of mono or diacylated derivatives invariably occurs regardless of the amount of acid chloride employed (entries 1–6, 9). Moreover, attempts to introduce a third acyl group by using a large excess of benzoyl or 4-chlorobenzoyl chlorides failed as well (entries 6 and 9).

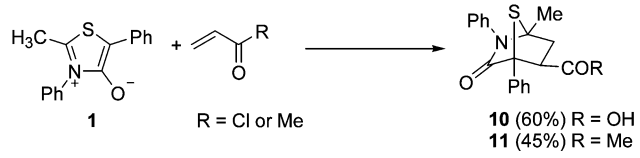
Table 1. Reactions of **1** with acyl chlorides and triethylamine

Entry	R	RCOCl (equiv.)	Et_3N (equiv.)	Product (%)[a]	Tautomeric ratio[b]
1	Me	2	2	**2b** (52)	>99:1
2	Et	2	2	**3b** (46)	>99:1
3	Prop	2	2	**4b** (70)	>99:1
4	C_6H_5	2	2	**5a** (36)	>99:1
5	C_6H_5	1	1	**5a** (76)[c]	>99:1
6	C_6H_5	4	4	**5a** (40)	>99:1
7	4-$MeOC_6H_4$	2	2	**6a** (72)	>99:1
8	4-ClC_6H_4	2	2	**7a**+**7b** (55)	2.5:1
9	4-ClC_6H_4	4	4	**7a**+**7b** (70)	2.5:1
10	2-FC_6H_4	2	2	**8a** (50)	>99:1
11	4-$NO_2C_6H_4$	2	2	**9a**+**9b** (78)	2:1

[a] Yields refer to isolated, crystalline compounds.
[b] Determined by ^{1}H NMR integration at 400 MHz in $CDCl_3$.
[c] Calculated with respect to the limiting amount of PhCOCl.

With carbon–carbon unsaturated functionalities, compound **1** exhibits the typical dipole character of thioisomünchnones.[1–3,9] Reactions of **1** with acryloyl chloride in CH_2Cl_2 at room temperature gave the corresponding 2-aza-3-oxo-7-thiabicycle **10** in moderate yield (60%) and with complete regioselectivity (Scheme 3). The stereochemical outcome arises from an *exo* approach of the dipolarophile facing its C-2 and C-3 atoms to C-5 and C-2 positions respectively, of **1**. It is also remarkable the strong bias to favor a cycloaddition pathway in the case of acryloyl chloride, even though it is a good electrophile. Compound **10** was isolated as its acid derivative after chromatographic purification (Scheme 3). Crystals of **10** suitable for X-ray diffraction could not be obtained. However, its stereochemistry was established by comparison with the spectroscopic data of the cycloadduct **11** arising from reaction of **1** with methyl vinyl ketone, whose regiochemistry was determined by X-ray diffractometry (Fig. 2).[16]

To sum up, we have demonstrated that 2-methyl thioisomünchnones are in equilibrium with their 2-methylenethiazol-4(5*H*)-ones. This feature can be harnessed to develop a novel synthesis of 2-heteroaryl ketones and 2-heteroaryl-1,3-diketones by reaction with alkanoyl or aroyl chlorides, respectively. Moreover, the resulting substances contain a functionalized heteroaromatic ring, which can undergo further synthetic exploration en route to fused heterocycles. Within this context it should also be pointed out the facile incorporation of the 1,3-dicarbonyl moiety into the heterocyclic fragment, while other classical procedures possess important drawbacks. Thus, esters of aromatic acids are used rather less frequently in cross-Claisen reactions



Scheme 3.

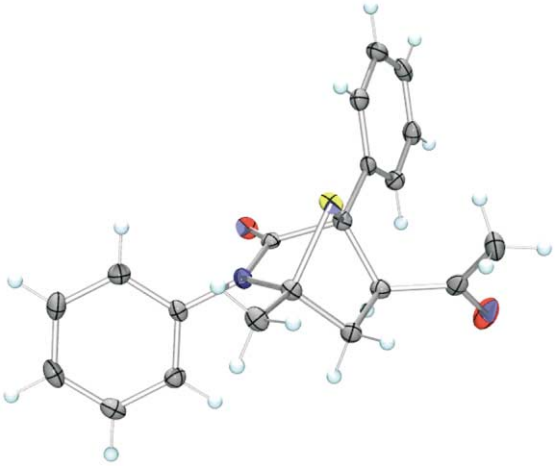


Figure 2.

because they are considerably less reactive than carbonates or formates. Likewise, Lewis acid-catalyzed acylation of enols is often hampered by other functional groups susceptible of undergoing complexation.[17] In addition, aldol, Claisen and related reactions are prone to give self-condensation products, although the problem can be circumvented by immobilization techniques.[18] Further studies with the present protocol along with extensions to other electrophiles are currently under way.

Acknowledgements

We thank the Spanish Ministry of Science and Technology (Grants No. BQU2000-0248 and PB98-0997) for financial support and J. Díaz thanks the Ministry of Education for a Ph.D. fellowship.

References

1. (a) Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121–158; (b) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, *1*, 123–141; (c) Potts, K. T. In 1,3-*Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, pp. 1–82.
2. (a) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **1996**, *61*, 3738–3748; (b) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C.; Raithby, P. R. *J. Org. Chem.* **2000**, *65*, 5089–5097; (c) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2001**, *66*, 5139–5145.
3. Arévalo, M. J.; Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Tetrahedron Lett.* **1999**, *40*, 8675–8678.
4. (a) Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Chem. Commun.* **1999**, 1589–1590; (b) Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C.; Silvero, G. *Chem. Eur. J.* **2001**, *7*, 3033–3042.
5. Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2265–2268.
6. Potts, K. T.; Marshall, J. L. *J. Chem. Soc., Chem. Commun.* **1972**, 1000.
7. Potts, K. T.; Marshall, J. L. *J. Org. Chem.* **1979**, *44*, 626–628.
8. Baudy, M.; Robert, A.; Foucaud, A. *J. Org. Chem.* **1978**, *43*, 3732–3736.
9. (a) Baudy, M.; Robert, A.; Guimon, G. *Tetrahedron* **1982**, *38*, 1241–1252; (b) Baudy, M.; Robert, A.; Guimon, C. *Tetrahedron* **1982**, *38*, 2129–2137.
10. To a solution of thioacetanilide (6.6 mmol) in CH_2Cl_2 (20.0 mL) was added successively under stirring a solution of 2-chloro-2-phenylacetyl chloride (6.6 mmol) in CH_2Cl_2 (5.0 mL) and, after 25 min, a solution of triethylamine (13.2 mmol) in CH_2Cl_2 (5.0 mL). After 15 min,

the reaction mixture was washed with a saturated solution of NaCl (3×120 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting residue crystallized on cooling as a yellow solid (60%). IR (KBr): 1628 (**1a**), 1705 (**1b**) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.46 (s, 3H) (tautomer **1a**), 5.22 (s, 1H), 4.39 (d, $J=3.1$ Hz, 1H), 4.27 (d, $J=3.1$ Hz, 1H) (tautomer **1b**).

11. Potts, K. T.; Chen, S. J.; Kane, J.; Marshall, J. L. *J. Org. Chem.* **1977**, *42*, 1633–1638.
12. Calculations have been carried out with the Gaussian94 package: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. M.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Revision D.1, Gaussian, Inc., Pittsburgh, PA, 1995.
13. *Typical procedure*: To a solution of **1** (50 mg, 0.19 mmol) in CH_2Cl_2 (2.0 mL) were added acetyl chloride (26.6 μL, 0.37 mmol) and triethylamine (52.2 μL, 0.37 mmol). After 48 h at room temperature, the solvent was evaporated and the residue purified by preparative thin-layer chromatography (ethyl acetate:hexane, 1:3) to afford **2**, which was further crystallized from ethyl acetate (30 mg, 52%); mp: 156°C: IR (KBr): 1720, 1647, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.25 (m, 10H), 5.65 (s, 1H), 5.09 (s, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 173.3, 158.0, 135.6, 130.1, 129.8, 129.1, 128.6, 128.3, 127.9, 100.9, 50.0, 30.1.
14. The authors have deposited crystallographic data for compound **2b** (CCDC 194712) with the Cambridge Crystallographic Data Centre. Copies of this material can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK. Crystal data for **2b**, $C_{18}H_{15}NO_2S$, $M_r=309.37$, monoclinic, $P2_1/c$, $a=5.4079(9)$, $b=16.685(3)$, $c=16.587(3)$ Å, $V=1496.5(4)$ Å^3, $Z=4$, $D_{calcd}=1.373$ g cm^{-3}, λ(MoKα)=0.71073 Å, $\mu=2.23$ cm^{-1}, $F(000)=648$, $T=120(2)$ K, GooF$^2=1.031$, independent reflections=2272 [$R_{int}=0.0624$] of a total of 3635 collected reflections, $R(F)$ obeying $F^2>2\sigma(F^2)=0.0824$, $wR(F^2)=0.2176$, R(all data)=0.1122, $wR(F^2)=0.2481$.
15. Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Siro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104–3110.
16. The authors have deposited crystallographic data for compound **11** (CCDC 197967) with the Cambridge Crystallographic Data Centre. Copies of this material can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK. Crystal data for **11**, $C_{20}H_{19}NO_2S$, $M_r=337.42$, monoclinic, $P2_1/c$, $a=6.16440(10)$, $b=10.8967(3)$, $c=24.7631(7)$ Å, $V=1660.48(7)$ Å^3, $Z=4$, $D_{calcd}=1.350$ g cm^{-3}, λ(MoKα)=0.71073 Å, $\mu=2.07$ cm^{-1}, $F(000)=712$, $T=120(2)$ K, GooF$^2=1.035$, independent reflections=2901 [$R_{int}=0.0243$]of a total of 5309 collected reflections, $R(F)$ obeying $F^2>2\sigma(F^2)=0.0352$, $wR(F^2)=0.0810$, R(all data)=0.0506, $wR(F^2)=0.0867$.
17. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2001; p. 732, 741.
18. Ley, S. V.; Baxendale, I. R. *Nature Rev.: Drug Discovery* **2002**, *1*, 573–586.