The Chemistry of α,β-Ditosyloxy Ketones: A New and Convenient Route to 4,5-Diarylisoxazoles from α,β-Chalcone Ditosylates

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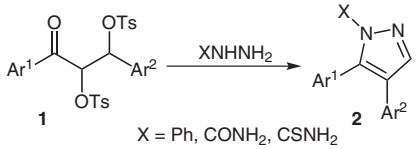
Abstract: The reaction of α,β-chalcone ditosylates with hydroxylamine hydrochloride under suitable conditions leads to a 1,2-aryl shift, thereby providing a new route to 4,5-disubstituted isoxazoles.

Key words: α,β-chalcone dibromides, α,β-chalcone ditosylates, hydroxy(tosyloxy)iodobenzene, 4,5-diarylisoxazoles

The present study is in connection with our ongoing interest in the synthetic potential of α,β-ditosyloxyketones in the synthesis of 4,5-diarylisoxazoles. The chemistry of α,β-chalcone dibromides has been well explored,[1] and the reactivity mode of α,β-chalcone ditosylates **1** has been studied recently in our research group. The aim of this study is to explore the potential of α,β-chalcone ditosylates **1** in heterocyclic synthesis with particular emphasis on comparison with their dibromo analogues. In our preliminary study it was reported that the reaction of α,β-chalcone ditosylates **1** with various reagents such as phenylhydrazine hydrochloride, semicarbazide hydrochloride, and thiosemicarbazide under suitable conditions leads to a 1,2-aryl shift, thereby providing a novel route to 1,4,5-trisubstituted pyrazoles **2** (Equation 1).[2] These results have shown that the reactivity pattern of α,β-chalcone ditosylates **1** is quite different from that of α,β-chalcone dibromides, which are known to give pyrazolines[1j,3] under similar reaction conditions.

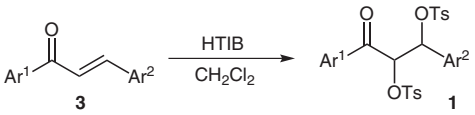


Equation 1

Prompted by the foregoing observations and coupled to our interest in the synthesis of heterocyclic compounds, we became interested in investigating the reactivity of α,β-chalcone ditosylates **1** with hydroxylamine hydrochloride with the hope of developing a convenient approach to the synthesis of 4,5-diarylisoxazoles. As consequence of this investigation, we report herein a novel and convenient route to 4,5-diarylisoxazoles, for which previous synthetic and structural studies are limited.

In the last decade it has been reported that 4,5-diarylisoxazole derivatives can act as potential therapeutic agents for the treatment of cancer,[4] novel inhibitors of cyclooxygenase-2 with analgesic and anti-inflammatory activities,[5] and can also inhibit metastasis of breast cancer cell lines. These compounds also have potential for the treatment of angiogenesis-related diseases including cancers, rheumatoid arthritis, and psoriasis.[6]

Various derivatives of α,β-chalcone ditosylates **1a–o** were prepared by treatment of the respective chalcones with hydroxy(tosyloxy)iodobenzene (HTIB) according to the method developed by Rebrovic and Koser[7] (Scheme 1 and Table 1).[2,8,9]



Scheme 1 α,β-Ditosyloxylation of chalcones using HTIB

We first examined the reaction of α,β-chalcone ditosylates **1** with hydroxylamine hydrochloride. Thus α,β-chalcone ditosylate **1a** (0.001 mol) was heated with hydroxylamine hydrochloride (0.002 mol) in the presence of sodium acetate (0.002 mol) in ethanol (25 mL). The reaction afforded a single colourless solid product in 72% yield, which was characterised as 4,5-diphenylisoxazole (**4a**) on the basis of its physical and spectroscopic data (IR, ^{1}H NMR, mass). The IR spectrum of the product showed the disappearance of a peak at 1680 cm^{-1} arising from the carbonyl group of α,β-chalcone ditosylate **1a**. The ^{1}H NMR spectrum showed a sharp singlet at δ = 8.2 ppm, corresponding to a single proton that can be ascribed to the C(3)-H of the isoxazole ring. The mass spectrum of the product **4a** showed the molecular ion, an intense fragment corresponding to $[PhCO]^+$ and a rearrangement peak at *m/z* 165 characteristic of 4,5-diphenylisoxazole,[10] as observed by Rao et al.[14]

To study the scope of the reaction, a wide range of substituted α,β-chalcone ditosylates (**1b–o**) were treated with hydroxylamine hydrochloride under similar conditions. It was observed that each of the substrates behaved in a similar manner, affording the corresponding isoxazoles **4b–o** in good yield (64–78%; Scheme 2 and Table 2).[11]

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Table 1 Physical Data of α,β-Chalcone Ditosylates **1**

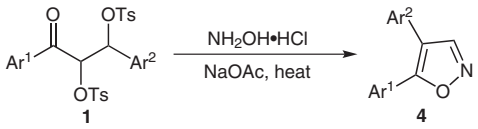
Entry	**1**	Ar^1	Ar^2	Mp (Lit.)[2,7,8]	Yield (%)[a]
1	**1a**	Ph	Ph	134–136 (136–138)	67
2	**1b**	Ph	4-MeC_6H_4	113–114 (114–115)	61
3	**1c**	Ph	4-$MeOC_6H_4$	138–139 (138–140)	73
4	**1d**	Ph	4-ClC_6H_4	101–102	62
5	**1e**	Ph	2-thienyl	120–122	62
6	**1f**	4-MeC_6H_4	Ph	113–114	68
7	**1g**	4-MeC_6H_4	4-MeC_6H_4	127–128 (128–129)	67
8	**1h**	4-MeC_6H_4	2-thienyl	138–139	67
9	**1i**	4-$MeOC_6H_4$	Ph	130–132 (132–133)	64
10	**1j**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	92–94 (93–94)	66
11	**1k**	4-$MeOC_6H_4$	2-thienyl	154–155	65
12	**1l**	4-ClC_6H_4	Ph	108–110 (108–110)	62
13	**1m**	4-ClC_6H_4	2-thienyl	128–130	57
14	**1n**	4-ClC_6H_4	5-methyl-2-thienyl	144–145	62
15	**1o**	4-BrC_6H_4	Ph	134–135	58

[a] Yield was calculated with respect to the corresponding chalcones.

Table 2 Physical Data of 4,5-Disubstituted Isoxazoles **4**

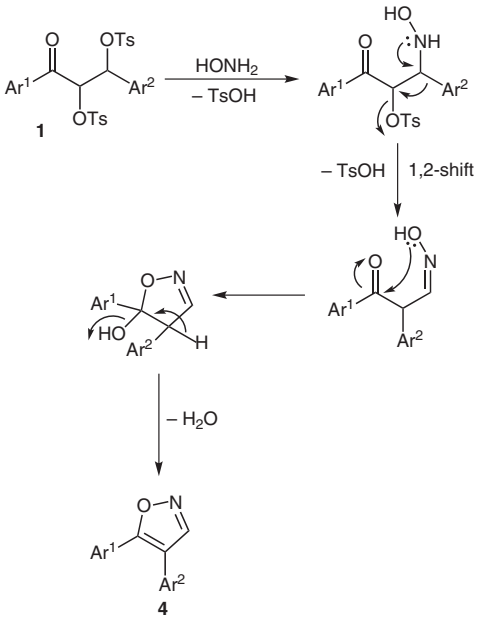
Entry	**4**	Ar^1	Ar^2	Mp (Lit.)[12–15]	Yield (%)[a]
1	**4a**	Ph	Ph	74–76 (75–76)	72
2	**4b**	Ph	4-MeC_6H_4	82–84 (84–85)	76
3	**4c**	Ph	4-$MeOC_6H_4$	68–70 (69–70)	78
4	**4d**	Ph	4-ClC_6H_4	108 (109)	73
5	**4e**	Ph	2-thienyl	105–107	53
6	**4f**	4-MeC_6H_4	Ph	109–110 (110)	68
7	**4g**	4-MeC_6H_4	4-MeC_6H_4	88–89	64
8	**4h**	4-MeC_6H_4	2-thienyl	Oil	55
9	**4i**	4-$MeOC_6H_4$	Ph	50–52 (53)	69
10	**4j**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	68–69	66
11	**4k**	4-$MeOC_6H_4$	2-thienyl	Oil	61
12	**4l**	4-ClC_6H_4	Ph	103–104 (103–104)	74
13	**4m**	4-ClC_6H_4	2-thienyl	138–140	48
14	**4n**	4-ClC_6H_4	5-methyl-2-thienyl	121–22	52
15	**4o**	4-BrC_6H_4	Ph	73–75	72

[a] Yield was calculated with respect to the corresponding α,β-chalcone ditosylates.



Scheme 2 Synthesis of 4,5-diarylisoxazoles from α,β-chalcone ditosylates

The exclusive formation of rearranged products reveals that the conversion involves 1,2-aryl migrations. The mechanism of this migration is closely related to that of the pinacol rearrangement and is outlined in Scheme 3. The first step of the reaction probably involves nucleophilic substitution of the OTs group, situated at position 3, by the amino group of the reagent. The substitution is followed by 1,2-aryl migration, resulting in the formation of intermediate, which subsequently undergoes cyclization in the usual manner to afford the rearranged product. Of the various reported examples of rearrangement of this sort, two important ones are bistosyloxylation of 1,1-diphenylethylene leading to desoxybenzoin,[7] and copper-catalysed rearrangement of hydroxyl ketones.[16] It is interesting to note that bis-brominated homologues of **1** were never reported to undergo such rearrangement.[1c,j,3] Instead, the reaction of α,β-chalcone dibromides with hydroxylamine hydrochloride is known to give 3,5-diarylisoxazoles.[1c]



Scheme 3 Plausible mechanistic pathway for the formation of rearranged products

It is worthy of note that synthetic and structural studies of 4,5-diarylisoxazoles in the literature are limited. One of the literature reports includes a three-step synthesis of 4,5-diarylisoxazoles, starting from the respective chalcones.[14]

In conclusion, this study further reveals that the reactivity pattern of α,β-chalcone ditosylates **1** is quite different from that of α,β-chalcone dibromides. The reason for this remarkable difference in the reactivity pattern is not yet clear. Nevertheless, the reaction offers a novel route for the synthesis of 4,5-diarylisoxazoles. This newly developed route involves simple experimentation and yields are good using α,β-chalcone ditosylate derivatives to effect selective transformations that are not possible from α,β-chalcone dibromides.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) (a) Bickel, C. L.; Phillips, E. A.; Exeter, N. H. *J. Am. Chem. Soc.* **1950**, *72*, 349. (b) Sharma, T. C.; Patel, H.; Bokadia, M. M. *Indian J. Chem.* **1973**, *11*, 703. (c) Elkasaby, M. A.; Salem, M. A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1980**, *19*, 571. (d) Khurana, J. M.; Markap, G. C.; Sahoo, P. K. *Synthesis* **1991**, 827. (e) Holla, B. S.; Shridhara, K. *Chim. Acta Turc.* **1992**, *20*, 161. (f) Vijayshree, N.; Samuelson, A. G. *Tetrahedron Lett.* **1992**, *33*, 559. (g) Saoudi, A.; Hamelin, J.; Benhaoua, H. *J. Chem. Res., Synop.* **1996**, *11*, 491. (h) Khurana, J. M.; Seghal, A. *Synth. Commun.* **1996**, *26*, 3791. (i) Elba, M. E.; Darwish, A. I.; Hamada, N. M. *Egypt. J. Chem.* **1997**, *40*, 81. (j) Elba, M. E.; Darwish, A. I.; Hamada, N. M. *J. Indian Chem. Soc.* **1997**, *74*, 202. (k) Elba, M. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *160*, 233. (l) Ranu, B. C.; Janna, R. *J. Org. Chem.* **2005**, *70*, 8621.

(2) Prakash, O.; Sharma, D.; Kamal, R.; Kumar, R.; Nair, R. R. *Tetrahedron* **2009**, *65*, 10175.

(3) Joshi, M. G.; Wadodkar, K. N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1981**, *20*, 1090.

(4) Brough, P. A.; Aherne, W.; Barril, X.; Borgognoni, J.; Boxall, K.; Cansfield, J. E.; Cheung, K.-M. J.; Collins, I.; Davies, N. G. M.; Drysdale, M. J.; Dymock, B.; Eccles, S. A.; Finch, H.; Fink, A.; Hayes, A.; Howes, R.; Hubbard, R. E.; James, K.; Jordan, A. M.; Lockie, A.; Martins, V.; Massey, A.; Matthews, T. P.; McDonald, E.; Northfield, C. J.; Pearl, L. H.; Prodromou, C.; Ray, S.; Raynaud, F. I.; Roughley, S. D.; Sharp, S. Y.; Surgenor, A.; Walmsley, D. L.; Webb, P.; Wood, M.; Workman, P.; Wright, L. *J. Med. Chem.* **2008**, *51*, 196.

(5) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 2921.

(6) Kwon, B. M.; Son, K. H.; Han, D. C.; Lee, ; S, K.; Shin, K. D.; Jeon, S. B.; Oh, J. H. US Patent; 0131036, **2005**.

(7) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 2462.

(8) Prakash, O.; Kumar, R.; Sharma, D.; Pannu, K.; Kamal, R. *Synlett* **2007**, 2189.

(9) **Experimental procedure used to prepare α,β-chalcone ditosylates 1:** Prepared from the corresponding chalcones[17–22] **3** using a procedure similar to that reported previously by our research group. Compounds **1a–c**,**g**,**i–j**,**l** were previously reported, whereas **1d–f**,**h**,**k**,**m–o** are novel compounds. Spectroscopic data of the latter compounds are given in the Supporting Information.

(10) Simons, B. K.; Kallury, R. K. M. R.; Bowie, J. H. *Org. Mass Spectrom.* **1969**, *2*, 739.

(11) **Experimental procedure used to prepare 4,5-diarylisoxazoles 4:** A mixture of chalcone ditosylate (**1a**; 0.550 g, 0.001 mol), hydroxylamine hydrochloride (0.138 g, 0.002 mol) and sodium acetate (0.164 g, 0.002 mol) in EtOH (25 mL) was heated at reflux for approximately 3 h. The reaction mixture was then poured onto ice-cold water. The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extract was dried over anhydrous Na_2SO_4 and filtered. Evaporation of CH_2Cl_2 in vacuo gave the crude product, which was purified by column chromatography on silica gel (100–200 mesh; PE–EtOAc) to give pure pyrazole **4a** (72%, 0.159 g). Other derivatives were prepared in a similar manner. Compounds **4e**,**g**,**h**,**j**,**k**,**m**–**o** are novel. Spectroscopic data of these compounds are given in the Supporting Information.

(12) Lang, S. A. Jr.; Lin, Y.-i. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**, 4.16.

(13) Murthy, M. S. R.; Rao, E. V. *Indian J. Chem.* **1985**, *24*, 667.

(14) Subba, G. V.; Rao, K. S. *Curr. Sci.* **1987**, *56*, 1280.

(15) Seishi, T. I.; Hiroyuki, Y. *Yakugaku Zasshi* **1959**, *79*, 467.

(16) Marques, C. S.; Moura, N.; Burke, A. J. *Tetrahedron Lett.* **2006**, *47*, 6049.

(17) E1-Sadany, S. K.; Sharaf, S. M.; Hamed, E. A.; Fleishaur, J.; Darwish, A.-I.; Youssef, A. A. *Egypt. J. Chem.* **1991**, *34*, 401.

(18) Orloov, V. D.; Kolos, N. N.; Theni, M.; Yurr'eve, E.; Ivkov, S. M. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1992**, *28*, 788.

(19) Kuroda, C.; Matsukuma, T. *Sci. Papers Inst. Phys. Chem. Research, Tokyo* **1932**, *18*, 51.

(20) Weygand, C.; Stroblet, F. *Ber. Dtsch. Chem. Ges. B* **1935**, *68*, 1839.

(21) Emerson, W. S.; Patrick, T. M. Jr. *J. Org. Chem.* **1949**, 790.

(22) Dannhardt, G.; Kiefer, W.; Kraemer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. *Eur. J. Med. Chem.* **2000**, *35*, 499.

