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Stereoselective Synthesis of (*E*)-4-Alkylidenecyclopent-2-en-1-ones by a Tandem Ring Closure–Michael Addition–Elimination

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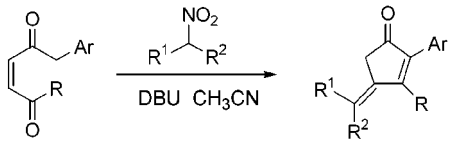
ABSTRACT



Reaction of (*Z*)-1,4-diketones with various functionalized nitroalkanes in the presence of DBU gives 4-alkylidenecyclopent-2-en-1-ones with *E* selectivity. A cyclopentadienone intermediate is probably formed by intramolecular aldol condensation, and this reacts with a nitroalkane giving a Michael addition–elimination.

The cyclopentenone ring is one of the most recurring structural unit in targets of relevant practical interest.[1] Functionalized cyclopentenones are also important building blocks that provide an efficient entry to substituted cyclopentanone frameworks.[2] The classical approach for the synthesis of cyclopentenones makes use of an intramolecular aldol condensation of 1,4-dicarbonyl derivatives.[3] This strategy is particularly effective when 1,4-keto aldehydes or symmetrical 1,4-diketones are used as substrates but undoubtedly poses some chemoselectivity problems with unsymmetrical diketo derivatives. To overcome this drawback, a number of alternative protocols involving multicomponent couplings,[4] rearrangements,[5] and other transformations[6] have been devised. A practical synthetic route to 4-substituted cyclopentenones may exploit the reactivity of cyclopentadienones **I** that react with nucleophilic reagents giving the corresponding addition products **II** (Scheme 1). Unfortunately, cyclopentadienones are rather unstable compounds, and this prevents their direct use although a "masked" form of these reactive substrates has found some synthetic applications.[7]

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(2) For some recent references, see: (a) Pastor, I. M.; Yus, M. *Tetrahedron Lett.* **2000**, *41*, 1589−1592. (b) Yakura, T.; Tanaka, K.; Iwamoto, M.; Nameki, M.; Ikeda, M. *Synlett* **1999**, 1313−1315. (c) Keller, E.; Maurer, J.; Naasz, R.; Shader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2409−2413. (d) Grieco, P. A.; May, S. A.; Kaufman, M. D. *Tetrahedron Lett.* **1998**, *39*, 7047−7050. (e) Yan, M.; Yang, L.-W.; Wong, K.-Y.; Chan, A. S. C. *Chem. Commun.* **1999**, 11−12. (f) Kondo, Y.; Kon-i, K.; Iwasaki, A.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 414−416.

(3) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867−889.

(4) (a) Trost, B. M.; Pinkerton, A. B. *Org. Lett.* **2000**, *2*, 1601−1603. (b) Rajesh, T.; Perisamy, M. *Organometallics* **1999**, *18*, 5709−5712. (c) Langer, P.; Köhler, V. *Org. Lett.* **2000**, *2*, 1597−1599.

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(6) (a) Balaczewsky, P.; Mikolajczyk, M. *Org. Lett.* **2000**, *2*, 1153−1155. (b) Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2000**, *41*, 6859−6863.

(7) (a) Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419−420. (b) Dols, P. P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 8515−8538.

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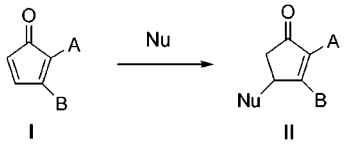
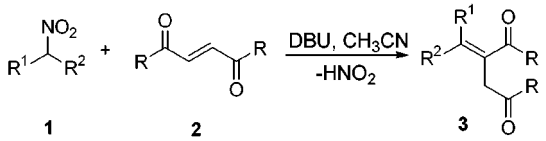
Scheme 1



A solution to this problem may be the exploitation of a tandem process[8] in which the cyclopentadienone readily reacts with a nucleophile as soon as it is formed.

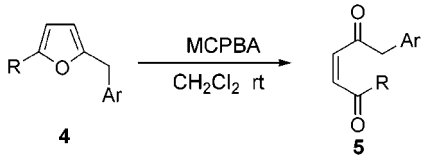
Recently, we have reported that nitroalkanes **1** react with enones **2** in a tandem Michael addition−elimination process giving unsaturated 1,4-diketones **3** with enhanced *E* stereoselectivity[9] (Scheme 2).

Scheme 2



The application of this strategy to unsymmetrical 1,4-diketones, usually leads to a regioisomeric mixture of products that jeopardizes the efficiency of the synthetic procedure.[9a] (*Z*)-1,4-Diketones **5** are easily obtained by ring cleavage of furans **4** with *m*-CPBA[10] (Scheme 3, Table 1).

Scheme 3



Nitroalkanes **1** react with diketones **5** in the presence of DBU in acetonitrile, affording 4-alkylidene-cyclopent-2-en-1-ones **6** in good yield and high *E* diastereoselectivity[11] (Scheme 4, Table 2).

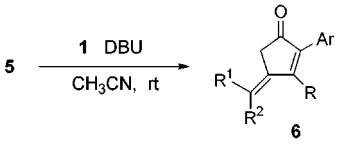
Cyclopentenones **6** are usually prepared by metal-mediated

Table 1. Synthesis of Diketones **5**

entry		furan R	Ar	diketone	yield,[a] %
1	**4a**	Me	C_6H_5	**5a**	88
2	**4b**	Et	C_6H_5	**5b**	79
3	**4c**	Me	3-$MeOC_6H_4$	**5c**	91
4	**4d**	Et	4-FC_6H_4	**5d**	85
5	**4e**	Me	3-ClC_6H_4	**5e**	83

[a] Yields of pure, isolated products.

Scheme 4



cycloaddition of alkynes.[12] The nature of product **6** obtained is consistent with a mechanism depicted in Scheme 5. A

Table 2. Synthesis of Cyclopentenones **6**

entry		nitroalkane R^1	R^2	**5**	**6**	yield,[a] %
1	**1a**	Me	Me	**5a**	**6a**	77
2	**1b**	i-Pr	H	**5a**	**6b**	63
3	**1c**	n-C_5H_{11}	H	**5a**	**6c**	81
4	**1d**	n-C_9H_{19}	H	**5a**	**6d**	76
5	**1e**	CH_2=$CH(CH_2)_3$	H	**5a**	**6e**	68
6	**1f**	dioxolanylethyl[b]	H	**5a**	**6f**	73
7	**1g**	$HO(CH_2)_5$	H	**5a**	**6g**	78
8	**1h**	$CH_3COCH_2CH_2$	H	**5a**	**6h**	84
9	**1i**	$MeO_2CCH_2CH_2$	H	**5a**	**6i**	80
10	**1j**	$MeO_2C(CH_2)_4$	H	**5a**	**6j**	67
11	**1k**	Ph	H	**5a**	**6k**	65
12	**1i**			**5b**	**6l**	79
13	**1c**			**5c**	**6m**	87
14	**1i**			**5c**	**6n**	68
15	**1j**			**5d**	**6o**	73
16	**1c**			**5e**	**6p**	93
17	**1j**			**5e**	**6q**	67

[a] Yields of pure, isolated products. [b] 

chemoselective intramolecular aldol condensation of enedione **5**, promoted by the presence of the aromatic ring, gives cyclopentadienone **7** as reactive intermediate that, under the same conditions, reacts with nitroalkane **1** to afford the Michael adduct **8**. As previously observed,[9] the nitroenone **8** undergoes a base-assisted elimination of nitrous acid giving cyclopentenone **6**.[13]

(8) For some recent reviews on this topic, see: (a) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159.

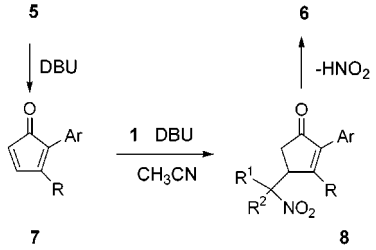
(9) (a) Ballini, R.; Barboni, L.; Bosica, G.; Petrini, M. *Synlett* **2000**, 391−393. (b) Ballini, R.; Bosica, G.; Petrelli, L.; Petrini, M. *Synthesis* **1999**, 1236−1240. (c) Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213−4222.

(10) Compounds **4** were prepared by alkylation of 2-alkylfurans: Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661−663. Oxidation of furan ring with peracids: (a) Dominguez, C.; Csáky, A. G.; Plumet, J. *Tetrahedron Lett.* **1990**, *31*, 7669−7670. (b) Kobayashi, Y.; Katsuno, H.; Sato, F. *Chem. Lett.* **1983**, 1771−1774.

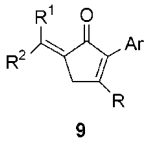
(11) No detectable amount of the *Z* diastereoisomer was found in the ^{1}H NMR spectra of compounds **6**. **General Procedure.** To a solution of enedione **5** (5 mmol) in acetonitrile (25 mL), the nitroalkane **1** (5 mmol) followed by DBU (5 mmol) were added at room temperature. After the solution was stirred for 6 h at room temperature, the solvent was evaporated at reduced pressure and the residue was purified by column chromatography (hexanes−ethyl acetate 8:2).

(12) (a) Ahmar, M.; Antras, F.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 4417−4420. (b) Ahmar, M.; Chabanis, O.; Ghautier, J.; Cazes, B. *Tetrahedron Lett.* **1997**, *38*, 5277−5280. (c) Pürro, S.; Pryde, A.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1978**, *61*, 266−278. (d) Martin, G. J.; Rabiller, C.; Mabon, C. *Tetrahedron* **1972**, *28*, 4027−4037.

Scheme 5



The proposed mechanistic pathway is also supported by the lack, in the reaction mixture, of any regioisomeric product as **9** that could arise by a conjugate addition of the nitroalkanes **1** on diketones **5** before the ring closure.



Any attempt to prepare the cyclopentadienone **7** carring out the reaction in the absence of nitroalkane led to frustrating results since only a complex mixture of various products was obtained. The *E* configuration of the exocyclic double bond in compounds **6** has been verified by NOE experiments and by comparison of spectral data obtained for compound **6k** with those appeared in the literature.[14]

In conclusion, 4-alkylidenecyclopent-2-en-1-ones **6** are now readily available compounds, achievable from (*Z*)-1,4-diketones **5** by a simple procedure involving three different reactions carried out in a tandem sequence. The efficiency of the whole process is witnessed by the good yield and the outstanding *E* stereoselectivity of products prepared.

Application of this synthetic methodology to other functionalized enediones is currently in progress in our laboratory.

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Supporting Information Available: Spectral and physical data for new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Conjugate addition of the nitroalkane to a cyclopentenone, before the elimination of the aldol, is also conceivable. At any event, this dehydration process should occur before the elimination of nitrous acid, since the presence of an acidic hydrogen at C-4 is necessary to afford the exocyclic double bond (see ref 9).

(14) Pasto, J. D.; Huang, N.-Z.; Eigenbrot, C. W. *J. Am. Chem. Soc.***1985**, *107*, 3160−3172.