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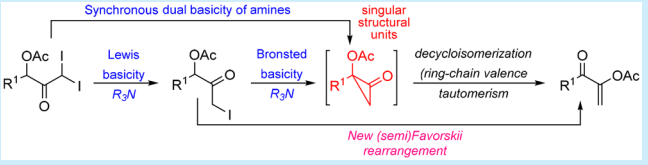
An Unprecedented (Semi)Favorskii Rearrangement. Evidence for the 2-(Acyloxy)cyclopropanones

Santu Sadhukhan and Beeraiah Baire*

Department of Chemistry, Indian Institute of Technology Madras, Chennai, Tamilnadu 600036, India

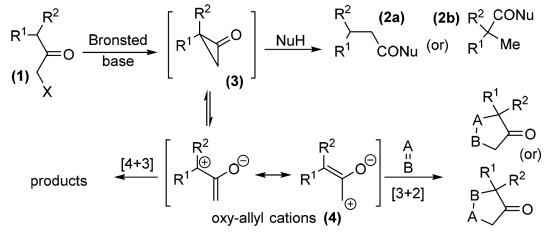
Supporting Information

ABSTRACT: Discovery and development of an unprecedented (semi)Favorskii rearrangement has been reported. The intermediacy of structurally singular (acyloxy)cyclopropanones has been unraveled by fruitful control experiments including a crossover experiment. This class of cyclopropanones is found to be inert for classical Favorskii functionalization and preferably undergoes a decycloisomerization (ring−chain valence tautomerism) to α-(acyloxy)enones. A cascade conversion of α,α-diiodo-α′-acetoxyketones to (acyloxy)cyclopropanones via α-iodo-α′-acetoxyketones has been achieved by the synchronous dual basicity (Lewis and Brønsted) of amines. The overall process is found to be very general for diverse substrates and highly efficient.



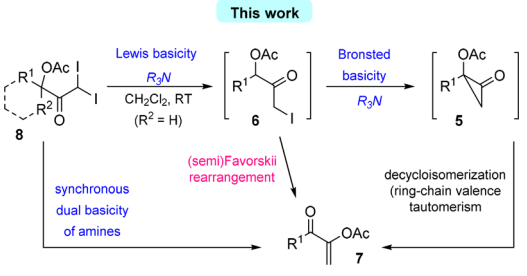
The classical Favorskii rearrangement[1] is the conversion of α-haloketones **1** (possessing α′-protons) to esters or amides or acids **2** with nucleophilic bases. It involves the formation of a cyclopropanone **3** as the key intermediate from the α-haloketone **1**. This cyclopropanone **3** upon nucleophilic addition−ring opening provides the ester/amide/acid **2**. On the other hand, in the presence of a non-nucleophilic base, cyclopropanones **3** can also be considered equivalents of oxyallyl cations **4** (a valence tautomer), and their reactivity has been explored as 1,3-dipoles in organic synthesis (Scheme 1).[2]

Scheme 1. Classical Favorskii Functionalizations



Any other type of reactivity of oxyallyl cations is almost unknown in the literature. Concomitantly, evidence for either α-hydroxy- or α-(acyloxy)cyclopropanones **5** is scarce.[3] Herein, we report an unprecedented Favorskii rearrangement of α-iodo-α′-acetoxyketones **6a** in the presence of non-nucleophilic base via structurally singular α-(acyloxy)cyclopropanone intermediate **5**. They (**5**) are found to be inert for classical Favorskii functionalization, instead preferably undergoing an unconventional decycloisomerization (ring−chain valence tautomerism) to yield α-(acyloxy)enones **7** (Scheme 2B).[4] In this process, the synchronous dual basicity (Lewis and Brønsted) of amines has been utilized for the cascade conversion of α,α-diiodo-α′-acetoxyketones **8** to the key and unique intermediates (acyloxy)cyclopropanones **5** via α-iodo-α′-acetoxyketones **6a**.

Scheme 2. A New (Semi)Favorskii Rearrangement



This transformation is unprecedented in organic synthesis, in terms of (acyloxy)cyclopropanone intermediates and their reactivity, and for the synchronous dual basicity of 3°-amines.

Recently, we reported a selective monodehalogenation of α,α-diiodo-α′-acetoxyketones **8** employing water (or alcohols) as Lewis base for the selective generation of α-iodo-α′-acetoxyketones.[5] In continuation of exploring this process for various bases (non-nucleophilic) in particular 3°-amines, we discovered the currently reported transformation.

Our investigation began when a α,α-diiodo-α′-acetoxyketone **9a** was treated with triethylamine (8 equiv) in acetonitrile at 0 °C (Table 1, entry 1). After 1 h, a α-iodo-α′-acetoxyketone **10a** was isolated in 80% yield. Increasing the reaction temperature to rt (∼30 °C) resulted in a 1:1.3 mixture of **10a** and a new compound, α-acetoxyenone **11a**, after 30 min. On the other hand, performing the reaction at rt for 1.5 h (entry 3) gratifyingly gave the α-acetoxyenone **11a** as an exclusive product in 66% yield. In the case of other amines like pyridine and diisopropylamine the reaction was not clean and gave poor yields of **11a** (entries 4 and 6). Employing diisopropylethyl-

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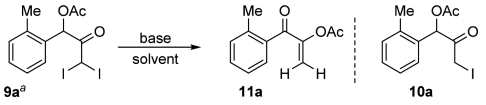
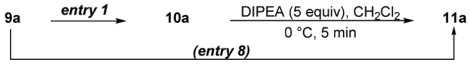
Table 1. Reaction Discovery and Optimization



entry	base	equiv	solvent	t (°C)	time (h)	product	yield (%)[b]
1	TEA	8	MeCN	0	1	**10a**	80
2	TEA	8	MeCN	0 to rt	0.5	**10a : 11a**	1:1.3
3	TEA	8	MeCN	0 to rt	1.5	**11a**	66
4	pyridine	8	MeCN	0 to rt	4	**11a**	37
5[c]	DIPEA	8	MeCN	0 to rt	1	**11a**	70
6[d]	DIPA	8	MeCN	0 to rt	1.5	**11a**	30
7	DIPEA	8	CH_2Cl_2	0	10 min	**11a**	85
8[e]	DIPEA	5	CH_2Cl_2	0	10 min	**11a**	90
9	DIPEA	5	dioxane	0 to rt	1.5	**11a**	52
10	DIPEA	5	Acetone	0 to rt	1.5	**11a**	57
11	DIPEA	5	THF	0 to rt	1.5	**10a**	35
12	DIPEA	5	EtOAc	0 to rt	1.5	**10a**	30
13	DIPEA	5	CH_3NO_2	0 to rt	1.5	**10a**	33
14	DIPEA	5	DMSO	0 to rt	1.5	**10a**	30



[a]All of the reactions were carried out on a 0.1 mmol scale of **9a** in 4 mL of solvent. [b]Yields after chromatographic purification. [c]Increase in temperature (50 and 70 °C) gave a complex mixture. [d]Reaction was sluggish with *sec*-amines like piperidine and pyrrolidine. [e]Further decrease in equivalents of DIPEA reduced the yields of **11a**.

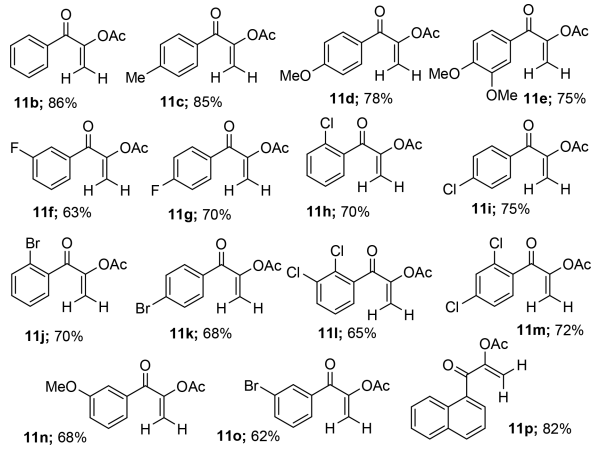
amine (DIPEA, 8 equiv, entry 5) in CH_3CN at rt resulted in an improved yield (70%) for **11a**.

Next various solvents were screened (entries 7−14) against DIPEA (8 equiv). In dichloromethane (entry 7), the reaction was very fast (10 min) and efficient to give the product **11a** in 85% yield. Since the reaction took only 10 min, next we performed the reaction with a lower amount (5 equiv) of DIPEA (entry 8). Delightfully, further improvement of the yield of **11a** (90%) was observed with similar reaction time (10 min). 1,4-Dioxane and acetone resulted in reduced yields (52% and 57%) of acetoxyenone **11a**, whereas THF, EtOAc, CH_3NO_2, and DMSO gave only the monoidodoketone **10a** in poor yields (30−35%) after 1.5 h at rt.

Therefore, the screening study suggested that DIPEA (5 equiv) in CH_2Cl_2 at 0 °C is a suitable condition for the direct conversion of **9a** to **11a**. Entries 1−3 (Table 1) revealed that the monoiodoketone **10a** can possibly be one of the intermediates during the formation of α-acetoxyenone **11a** from α,α-diiodo-α'-acetoxyketone **9a**. To further confirm, **10a** was subjected to the standard reaction conditions (Table 1, entry 8). Fittingly, the α-acetoxyenone **11a** was isolated as an exclusive product (75%) after 5 min.

With the optimized conditions in hand, we turned our attention to understanding the scope of this novel process. To begin with, secondary α'-(acyloxy)-α,α-diiodoketones were studied (Scheme 3). Various functional groups such as methoxy-, fluoro-, chloro-, bromo-, and dichloro- on the aromatic ring and at various positions, i.e., *ortho*-, *meta*-, and *para*-, were well tolerated to provide the corresponding α-(acyloxy)enones **11b−p** in good yields (62−86%) within short reaction times (5−10 min). Heteroaromatics such as 2-furanyl-, 2-thienyl-, and 3-indolyl-based diiodoketones were also employed for the synthesis of the respective enones **11q−s** in

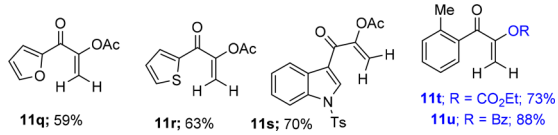
Scheme 3. Scope Study for Aromatic *sec*-Acetoxydiiodoketones[a]



[a]Reaction conditions: **9** (1 equiv), DIPEA (5 equiv), CH_2Cl_2, 0 °C, 5−10 min.

good yields (Scheme 4). Further, benzyloxy and carbonate functionalities in place of acyloxy group smoothly underwent the migration to yield the corresponding products **11t** and **11u** in excellent yields.

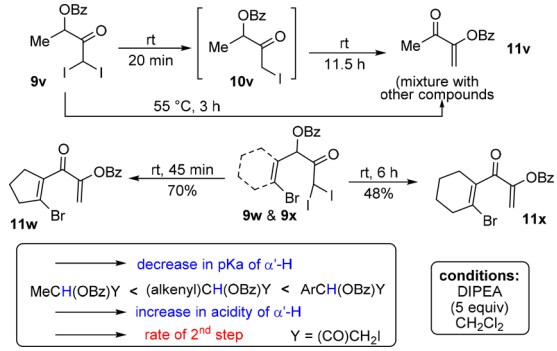
Scheme 4. Extension to Heteroaromatics: Benzyloxy and Carbonate Groups[a]



[a]Reaction conditions: **9** (1 equiv), DIPEA (5 equiv), CH_2Cl_2, 0 °C, 5−10 min.

Surprisingly, substituting the methyl group (**9v**) in place of aromatics (Scheme 5) resulted in a sluggish reaction. In this

Scheme 5. Distinct Rates for Aliphatic *sec*-Acetates Support Dependency on the α'-H and Its pK_a Value



case, formation of monoiodoketone **10v** was faster, but conversion to (acyloxy)ketone **11v** was found to be very slow (11.5 h) at rt yet resulted in a mixture of unidentifiable products. An increase in temperature (55 °C) reduced the reaction time (3 h) but did not improve the cleanliness of the process.

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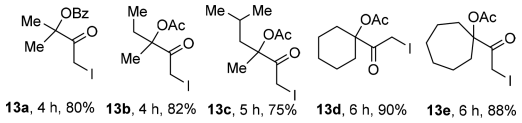
On the other hand, with the allylic−propargylic acetates **9w** and **9x**, the rate of the reactions (45 min and 6 h) and yields of the corresponding enone products **11w** and **11x** (70% and 48%) were comparable with their aromatic counterparts. These observations suggest that the rate of the conversion of monoiodoketone to (acyloxy)enone is highly dependent on the nature of the group attached to α′-carbon. In other words, as the acidity of the α′-H increases (or pK_a of the α′-H decreases)[6] among **9a**, **9v**, and **9w**, the rate of the conversion of monoiodoketones to the corresponding (acyloxy)enones **11a**, **11v**, and **11w** also gradually increases. Therefore, we hypothesized that the α′-H might be involving during the second step.

To further confirm the role of the α′-H, we next employed substrates possessing *tert*-acetates which lack α′-H (Scheme 6).

Scheme 6. Evidence for the Involvement of α′-H Employing *tert*-Propargylic Acetates (Lacking α′-H)[a]

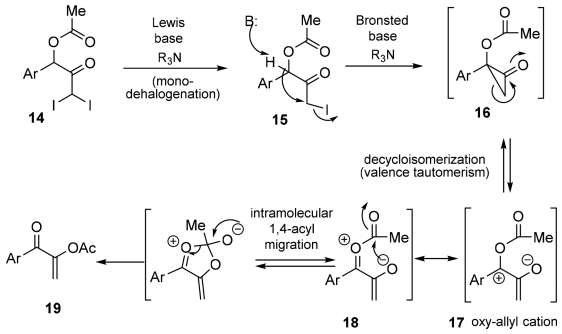


[a]Reaction conditions: **12** (1 equiv), DIPEA (5 equiv), CH_2Cl_2, 0 °C to rt.

When these α,α-diiodo-α′-acetoxyketones **12a−e** were subjected to standard reaction conditions, DIPEA (5 equiv), CH_2Cl_2, 0 °C to rt, only the corresponding monoiodoketones **13a−e** were isolated as the sole products. No trace of α-(acyloxy)enones was detected even after prolonged reaction times. This observation indicated involvement of the α′-H for the conversion of monoiodoketones to α-(acyloxy)enones.

On the bais of the above observations (Schemes 5 and 6), we propose a possible mechanistic pathway (Scheme 7). The

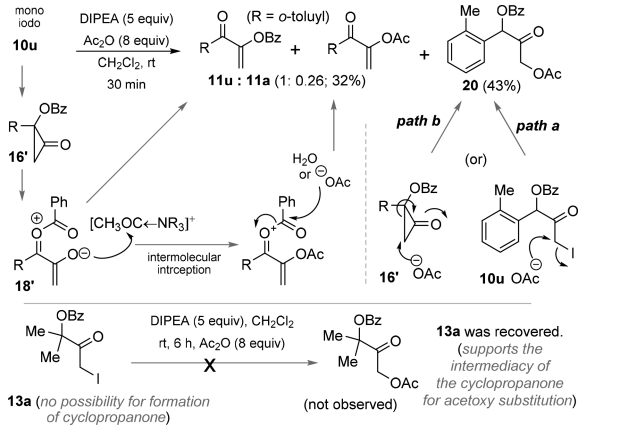
Scheme 7. Proposed Mechanism via a (Semi)Favorskii Rearrangement to 2-Acyloxycyclopropanones and Their Decycloisomerization



amine initially acts as a Lewis base and transforms the diiodoketone **14** to the corresponding monoiodoketone **15** via a monodeiodination. Next,deprotonation of the α′-H in **15** (by amine as a Brønsted base) followed by an intramolecular S_N^2 process with α-iodide generates the (acyloxy)cyclopropanone **16** in a net (semi)Favorskii rearrangement. Since no nucleophile is present for a classical Favorskii reaction, the cyclopropanone **16** may undergo a decycloisomeirzation (ring−chain valence tautomerism) to give oxyallyl cation **17** which is a resonance structure of 1,4-dipole **18**. This **18** further undergoes an intramolecular 1,4-acyl migration to generate the α-(acyloxy)enone **19**.

To provide an evidence for (acyloxy)cyclopropanones and their decycloisomerization process, we designed a few control experiments (Scheme 8). At first, a crossover experiment using

Scheme 8. Control Experiments To Study the Proposed (Semi)Favorskii Rearrangement and Acyloxycyclopropanone Intermediates



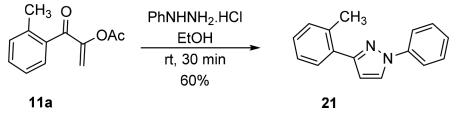
α-iodo-α′-benzyloxyketone **10u** and Ac_2O was performed (Scheme 8A). Accordingly, **10u** was subjected to standard reaction conditions but in the presence of Ac_2O (8 equiv). To our delight, it resulted in a (1:0.26) mixture of α-benzyloxyenone **11u** (routine product) and the crossover product α-(acyloxy)enone **11a** along with 43% of α-(acyloxy)-α′-benzyloxy ketone **20**. Isolation of **11a** supports the intermediacy of the benzyloxycyclopropanone **16′** followed by an intermolecular interception of the isomeric 1,4-dipole **18′** with acylium ion (generated from DIPEA and Ac_2O).

On the other hand, formation of the α-(acyloxy)-α′-benzyloxy ketone **20** can be possible either via a simple S_N^2 displacement of iodide in **10u** with acetate ion (path a) or via a regioselective ring opening of (benzyloxy)cyclopropanone **16′** by acetate ion (path b). To distinguish between these two processes, a monoiodoketone **13a** (lacks the α′-H there by possibility for cyclopropanone formation) was subjected to standard reaction conditions in the presence of Ac_2O (Scheme 8B). Surprisingly no reaction observed and the iodoketone **13a** was recovered. This experiment manifested the formation of **20** through the ring opening of the benzyloxycyclopropanone intermediate **16′** (path b) over a simple S_N^2 displacement (path a).[7,8]

Finally, the synthetic utility of derived products was described by converting the α-(acyloxy)enone **11a** to corresponding 1,3-diarylpyrazole derivative **21** (Scheme 9).[9] The enone **11a** upon reaction with phenylhydrazine hydrochloride in ethanol gave the pyrazole **21** in 60% yield.[10]

In conclusion, we discovered and developed an unprecedented (semi)Favorskii rearrangement cascade of α-iodo-α′-

Scheme 9. Synthesis of 1,3-Diarylpyrazoles



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acetoxyketones. The intermediacy of (acyloxy)cyclopropanones has been proved by various fruitful control experiments including a crossover experiment. These cyclopropanones were found to undergo an unconventional decycloisomerization to yield α-(acyloxy)enones and were inert for classical Favorskii functionalizations. During this process, the synchronous dual basicity (Lewis and Brønsted) of amines was also explored for the efficient conversion of α,α-diiodo-α′-acetoxyketones to α-(acyloxy)enones via α-iodo-α′-acetoxyketones. This process was found to be very general for diverse substrates, highly efficient, and spontaneous.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00218.

General experimental procedures, characterization data which includes soft copy of each ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: beeru@iitm.ac.in.

ORCID

Beeraiah Baire: 0000-0001-8810-1620

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. S. Sankararaman on the occasion of his 60th birthday.

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(7) At this stage we do not have any other strong evidence to rule out the possibility of the S_N^2 displacement; hence, we presume that both of them can contribute to the formation of **20**.

(8) We also performed experiments in the presence of various electrophiles (MeI) or 2π (dimethyacetylene dicarboxylate) and 4π (furan) systems to trap the 1,4-dipoles/1,3-dipoles, respectively. In all cases, we observed only our regular product α-(acyloxy)enone.

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