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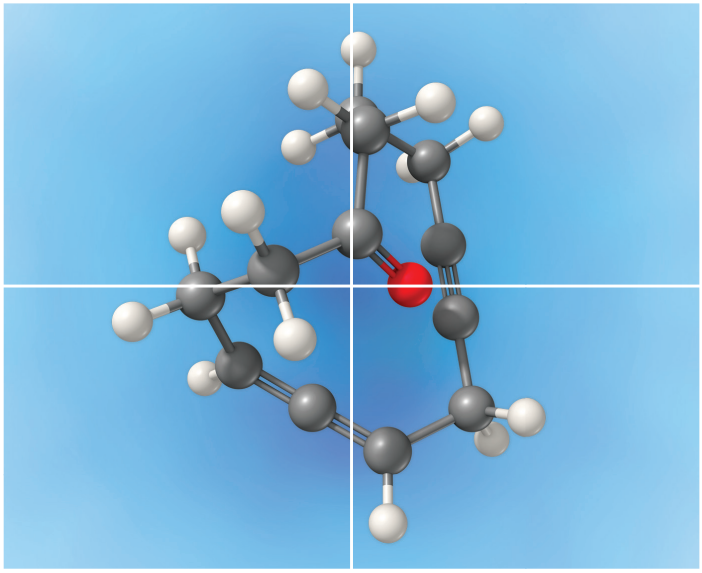

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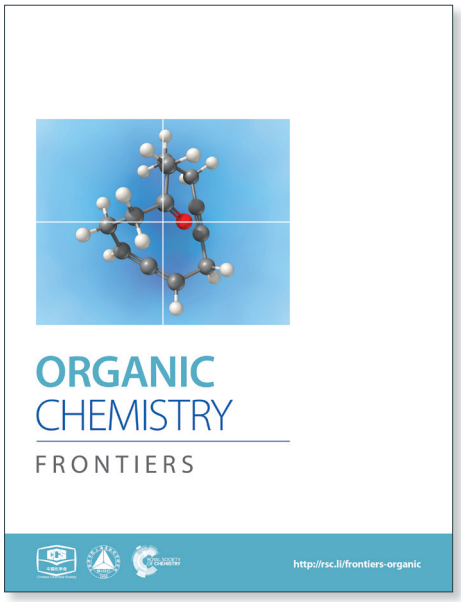

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RESEARCH ARTICLE

Radical vinylation of dioxolanes and *N*-acylpyrrolidines using vinyl bromides†‡

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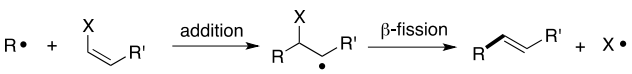
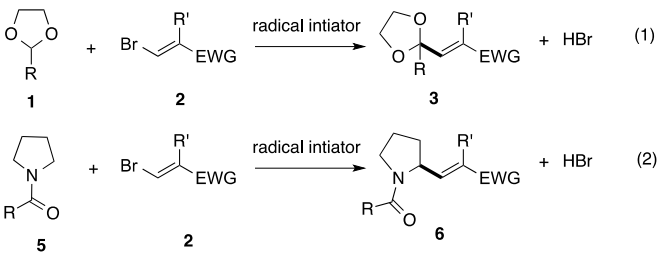
Radical vinylation was investigated using vinyl bromides with an electron-withdrawing substituent at β-position. The vinylation of 1,3-dioxolanes proceeded well to give 2-vinyl-1,3-dioxolanes in good yields. The α-vinylation of *N*-acylpyrollidines also proceeded well to give 2-vinyl-*N*-acylpyrollidines.

The addition/fragmentation reaction of carbon-centered radicals with hetero-substituted alkenes provides a potentially useful method for vinylation (Scheme 1),[1] and thus far a variety of vinylating agents have proven useful for this purpose. These include vinyltins,[2] vinylsulfides,[3] vinyl sulfones,[4] β-nitrostyrenes,[5] vinyl indiums,[6] vinyl galliums,[6b] and vinyl chlorides.[7]



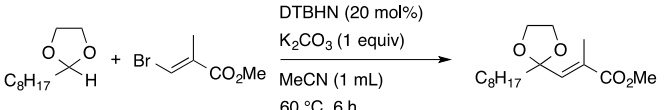
Scheme 1. Radical vinylation using vinylating agents

Since allyl bromides can serve as useful radical allylating reagents via radical addition/fragmentation reactions,[8,9,10] we naturally thought that vinyl bromides would also serve as potential radical vinylating reagents, although previous research examples are rare. In 1993, Singleton and Huval reported a radical vinylation reaction of alkyl bromides with 3-bromo-2-methylacrylonitrile in the presence of stoichiometric hexabutylditin.[11] In this reaction, ditin played a critical role in the conversion of a bromine radical to a tin radical, which was capable of abstracting a bromine atom from alkyl bromides to generate alkyl radicals. More recently, Heinrich and coworkers reported a non-chain radical addition of aryl radicals to ethyl 3-bromoacrylate, in which an aryl radical was formed by the one-electron reduction of an aryl diazonium salt by an iron(II) salt.[12] In a recent report by Liang and coworkers the α-vinylation of THF with 1,2-dibromostyrene took place in the presence of sodium fluoride as a base. This reaction suffered poor chain propagation and therefore harsh conditions (120 °C, 27 h) were employed.[13] We reasoned that the less-effective chain propagation of vinyl bromides compared with that of allyl bromides may have been due to the steric hindrance of vinyl carbon due to an α-bromine atom substituent slowing the radical addition step. In order to achieve effective radical vinylation with vinyl bromides, we thought that two items were crucial: (i) the judicious choice of easily broken C-H bonds; and, (ii) the introduction of a polar factor to vinyl bromides in order to encourage addition. In this work, we report that the vinylation of 1,3-dioxolanes **1**, readily available from aldehydes and 1,2-ethylene glycol, with vinyl bromides **2** having an electron-deficient substituent at the 2-position proceeded smoothly to give α-vinylated products in good yields (Scheme 2, eq 1). We also found that the α-vinylation of *N*-acylpyrrolidines **5** was successful using a similar vinylation reaction (eq 2).



Scheme 2. This work: radical vinylation of 1,3-dioxolanes **1** and *N*-acylpyrrolidines **5** using vinyl bromides **2**

In the initial study, we examined the reaction of 2-octyl-1,3-dioxolane (**1a**) derived from 1-nonanal with (*E*)-methyl 3-bromo-2-methylacrylate (**2a**) under several reaction conditions (Scheme 3). With acetonitrile solutions of **1a** and **2a** (3-fold excess) in the presence of di-*tert*-butylhyponitrite (DTBHN)[14] as a radical initiator, the envisaged α-vinylation product, (*E*)-2-vinyl-1,3-dioxolane **3a**, was formed, albeit in a 20% yield. The product yield of **3a** was increased in a system employing large excess amounts of **1a**. Thus, a 5-fold excess of **1a** gave **3a** in a 61% yield. The addition of two portions of DTBHN (10 mol% + 10 mol% (after 3 h)) resulted in a further increase in the yield of **3a** to 68%.

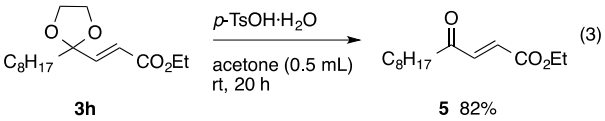


1a (mmol)	**2a** (mmol)	**3a** (%)
0.5	1.5	20
1.5	0.5	30
2.5	0.5	61
2.5*	0.5	68

*DTBHN was added in two portions

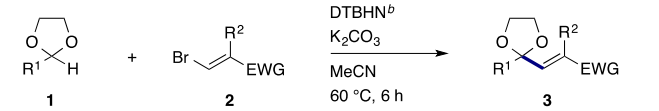
Scheme 3. Optimization of reaction conditions

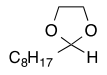
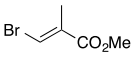
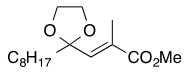
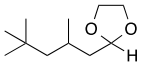
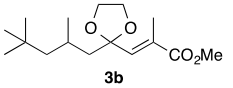
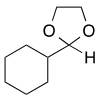
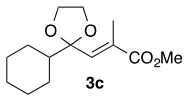
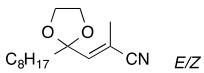
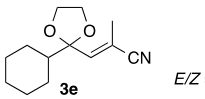
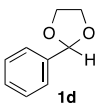
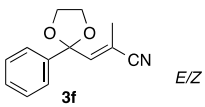
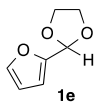
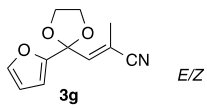
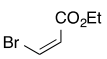
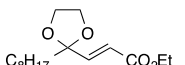
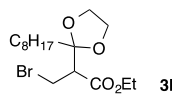
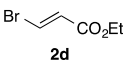
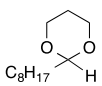
With the optimized conditions in hand, we studied the scope and limitations of the present vinylation method using a variety of 1,3-dioxolanes **1** and vinyl bromides **2** (Table 1). Larger scale reaction using 2 mmol of **2a** gave **3a** in 69% yield after isolation by silica gel chromatography (entry 1). Dioxolane **1b** reacted with **2a** to give 2-vinyl-1,3-dioxolane **3b** in a 79% yield (entry 2). The reaction of 2-cyclohexyl-1,3-dioxolane (**1c**) with **2a** gave **3c** in a 56% yield (entry 3). Also, 3-bromo-2-methacrylonitrile (**2b**, *E*/*Z* = 44/56) reacted with **1a** and **1c** to give **3d** and **3e** in 79 and 56% yields, respectively (entries 4 and 5), and 2-aryl-1,3-dioxolanes **1d** and **1e** reacted with **2b** to give **3f** and **3g** in 85 and 64% yields, respectively (entries 6 and 7). In these reactions, products **3d**-**3g** were given as an *E*/*Z* mixture that was enriched by an *E* isomer. It is noteworthy that unlike in the case of **2a**, the regiochemistry of the reaction using 3-bromoacrylate (**2c**) was not perfect, in which a mixture of desired 1,2-disubstituted alkene **3h** and bromine-containing regioisomer **3h'** was obtained in 51 and 19% yields, respectively (entry 8). The use of *E*-form bromide **2d** gave similar results (entry 9). It was also interesting that essentially no reaction took place when we carried out the reaction of 1,3-dioxane **4**, derived from nonanal and 1,3-propanediol, with **2a** (entry 10). Obtained vinylated 1,3-dioxolanes **3** can be converted to unsaturated 1,4-dicarbonyl compounds by standard acid treatment. For example, when dioxolane **3h** was treated with p-TsOH in acetone at r.t.,[15] γ-keto-α,β-unsaturated ester **5** was obtained in 82% yield (eq 3).



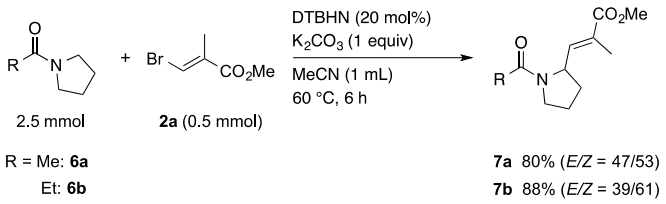
Next, we tried to extend this protocol to the α-vinylation of *N*-heterocycles using *N*-acetylpyrrolidine (**6a**) as a model. When a mixture of **6a**, **2a**, DTBHN, and K_2CO_3 in MeCN was heated at 60 °C for 6 h, an α-vinylation reaction took place efficiently to give the corresponding vinylated amide **7a** in 80% yield (Scheme 4). In a similar manner, the vinylation of *N*-propanoylpyrrolidine (**6b**) with **2a** gave **7b** in 88% yield. As we experienced in the reaction of 1,3-dioxanes, the reactivity of *N*-acetylpiperidine, six-membered substrate, was low, giving a low yield of the corresponding vinylated product along with a large amount of the starting material recovered.

Table 1 Radical vinylation of 1,3-dioxolanes **1** with vinyl bromides **2**[a]



Entry	1	2	3	Yield (%)[c]
1	 **1a**	 **2a**	 **3a**	68 (69)[d] only *E*
2	 **1b**	**2a**	 **3b**	79 only *E*
3	 **1c**	**2a**	 **3c**	56 only *E*
4	**1a**	 **2b** (*E*/*Z* = 44/56)	 **3d**	79 *E*/*Z* = 93/17[e]
5	**1c**	**2b**	 **3e**	56 *E*/*Z* = 74/26[e]
6	 **1d**	**2b**	 **3f**	85 *E*/*Z* = 79/21[e]
7	 **1e**	**2b**	 **3g**	64 *E*/*Z* = 78/21[e]
8[f]	**1a**	 **2c**	 **3h**	51 only *E*
			 **3h'**	19
9[f]	**1a**	 **2d**	**3h** **3h'**	53 20
10	 **4**	**2a**	trace[g]	

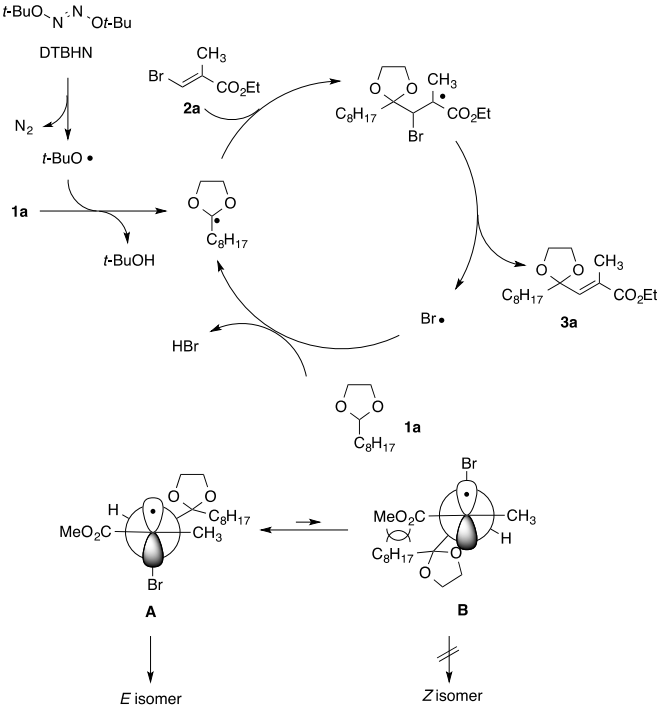
[a] Conditions: **1** (2.5 mmol), **2** (0.5 mmol), K_2CO_3 (0.5 mmol), DTBHN (20 mol%), MeCN (1 mL), 60 °C, 6 h [b] At the beginning of the reaction, DTBHN (10 mol%) was used and after 3 h additional DTBHN (10 mol%) was added. [c] Isolated yield after column chromatography on SiO_2. [d] Reaction was performed on a 2 mmol scale of **2a** with 30 mol% of DTBHN (three portion addition) at 60°C for 12 h. For detailed procedure, see Electronic Supplementary Information. [e] *E*/*Z* ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. [f] C_6H_6 was used as a solvent. [g] Detected by GC-MS.



Scheme 4. Vinylation of *N*-acylpyrrolidines **6** with vinyl bromide **2a**

The reactivity difference that varied in the ring size led us to examine MO calculations to elucidate each transition state for the hydrogen abstraction by a bromine radical. Calculated reaction profiles of α-hydrogen abstraction are shown in ESI. At the HF/6-311G**(C,H,O,N)+LanL2DZdp(Br) level,[16] activation energies for the α-hydrogen abstraction of 2-methyl-1,3-dioxolane and 2-methyl-1,3-dioxane were calculated to be 69.4 and 75.8 kJmol^{-1} respectively, while those of *N*-acetylpyrrolidine and *N*-acetylpiperidine were predicted to be 71.8 and 75.3 kJmol^{-1}, respectively. These results indicated that abstraction of α-hydrogens in five-membered rings with a bromine radical proceeds more easily than that in six-membered rings.[17]

A proposed reaction mechanism for the present radical vinylation of 1,3-dioxolane **1** was outlined in Scheme 5, which consists of one radical initiation step and three chain propagation steps: (i) the formation of an α,α-dioxy radical via the hydrogen abstraction of a *tert*-butoxy radical generated from the radical initiator DTBHN; (ii) the addition of the resultant α,α-dioxy radical to vinyl bromide **2**; (iii) the β-elimination of the bromine radical to give 2-vinyl-1,3-dioxolane **3**; and, (iv) the regeneration of the α,α-dioxy radical by hydrogen abstraction of the liberated bromine radical. The selective formation of *E*-isomer can be rationalized by an equilibrium between two rotamers **A** and **B**, in which steric repulsion between dioxolanyl group and methoxy carbonyl group would destabilize **B**, rendering *E*-isomer major product.



Scheme 5. Proposed reaction mechanism

In conclusion, we have demonstrated that a radical vinylation of 2-alkyl- and 2-aryl-1,3-dioxolanes using vinyl bromides proceeded well to give 2-vinyl-1,3-dioxanes in good yields. We also developed a radical vinylation of *N*-acylpyrrolidines using vinyl bromides. Chain propagation of the vinylation was quite sensitive to the ring-size of the substrates, which presumably affected the H-abstraction step by the bromine radical. Further applications of the present vinylation method are currently in progress in our laboratory.

Experimental section

Typical procedure for radical vinylation of 1,3-dioxolanes 2

To a 20 mL screw-capped test tube, di-*tert*-butylhyponitrite (DTBHN, 8.7 mg, 0.05 mmol), potassium carbonate (69.1 mg, 0.5 mmol), 2-octyl-1,3-dioxolane (**1a**, 465.7 mg, 2.5 mmol), methyl (*E*)-3-bromo-2-methylacrylate (**2a**, 89.5 mg, 0.5 mmol), and degassed MeCN (0.5 mL) were added. The test tube was purged with argon and sealed. Then, the mixture was stirred at 60 ℃. After 3 h, an additional portion of a solution of DTBHN (8.7 mg, 0.05 mmol) in MeCN (0.5 mL) was added and the resultant mixture was stirred at 60 ℃ for 3 h. The reaction mixture was filtered through a short plug of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (Hexane/EtOAc = 100/1 to 30/1) to give the vinylated product **3a** as a single *E* diastereomer (96.7 mg, 68%).

Typical procedure for radical vinylation of 1-acylpyrrolidines 6

To a 20 mL screw-capped test tube, di-*tert*-butylhyponitrite (DTBHN, 17.4 mg, 0.1 mmol), potassium carbonate (69.1 mg, 0.5

mmol), 1-acetylpyrrolidine (**6a**, 282.9 mg, 2.5 mmol), methyl (*E*)-3-bromo-2-methylacrylate (**2a**, 89.5 mg, 0.5 mmol), and degassed (Ar bubbling for 15 min before use) MeCN (1.0 mL) were added, and the test tube was purged with argon and sealed. The mixture was stirred at 60 ℃ for 6 h. The reaction mixture was filtered through a short plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (Hexane/EtOAc = 25/75 to 0/100) to give methyl 3-(1-acetylpyrrolidin-2-yl)-2-methylacrylate (**7a)** (84.5 mg, *E*/*Z* = 47/53 (by ^{1}H NMR), 80%).

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†Dedicated to Professor Max Malacria on the occasion of his 65th birthday.

‡Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

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