Multicomponent Reactions

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A Ring-Expansion Methodology Involving Multicomponent Reactions: Highly Efficient Access to Polysubstituted Furan-Fused 1,4-Thiazepine Derivatives**

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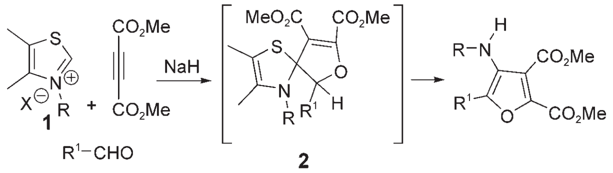
1,4-Thiazepine fragments are present in a wide range of natural and synthetic biologically active agents.[1] Among these, analogues of 1,4-thiazepines fused with aryl and heteroaryl groups represent an important class of compounds with interesting pharmacological properties,[2] such as antiarrhythmic, antispasmodic, angiogenic, and central nervous system activity, and are therefore promising synthetic targets for exploring novel physiologically active agents.[3]

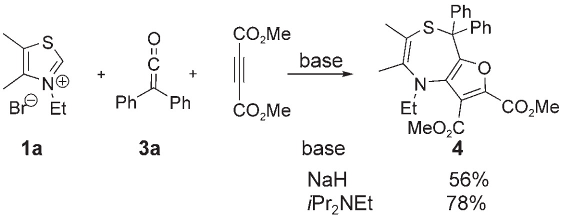
Ring transformations of heterocyclic compounds are an important area of chemistry from both theoretical and practical viewpoints.[4] Such processes may provide interesting synthetic routes to derivatives that can only be obtained with great difficulty or not at all by other procedures. We previously developed a facile method for the preparation of 3-aminofuran compounds[7] based on the nucleophilicity of N-heterocarbenes (NHCs) derived from thiazolium salts **1**.[5,6] These aminofuran compounds could not be formed according to other established protocols.[8] It was proposed that the formation of the aromatic furan through ring opening of the spirocycle intermediate **2** provides the driving force to complete the tandem reaction (Scheme 1).



Scheme 1. Thiazolium-mediated multicomponent reaction for the synthesis of 3-aminofuran derivatives.

Although ketenes react efficiently with some nucleophiles, their reaction with carbenes has received only scant attention.[9] Moreover, to the best of our knowledge, carbene-triggered multicomponent reactions from ketenes have not been disclosed thus far. As a part of our research into NHCs[7] and ketene chemistry,[10] we report herein a conceptually novel three-component synthesis of unique polysubstituted furan-fused 1,4-thiazepines from thiazolium salts, 1,1-disubstituted ketenes, and activated alkynes.[11]

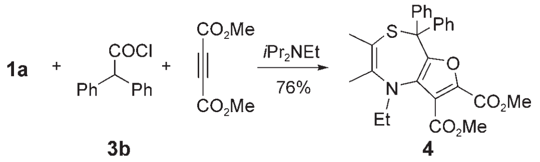
We began our investigations by looking into the reaction of 3-ethyl-4,5-dimethylthiazolium bromide (**1a**), 1,1-diphenylketene (**3a**), and dimethylacetylenedicarboxylate (DMAD) in the presence of NaH (Scheme 2). To our surprise, a three-component adduct **4** was isolated and the structure was unambiguously confirmed by single-crystal X-ray diffraction.[12] Interestingly, contrary to our previous results from the synthesis of 3-aminofurans, the yield of **4** was improved from 56% to 78% using $i\mathrm{Pr_2NEt}$ as the base instead of sodium hydride.



Scheme 2. Three-component reaction of thiazolium salt **1a**, diphenylketene (**3a**), and DMAD.

The cyclization of ketenes have attracted enormous attention from organic chemists since their first preparation in 1905.[13,14] In this context, ketenes typically add to substrates across one of their cumulated double bonds to construct cyclic compounds.[15] Very recently, we found that aryl methyl ketenes acted as one-carbon components to form five-membered rings on reaction with 1-methylimidazole and DMAD.[10b] In contrast, notably both of the double bonds (C=C and C=O) in 1,1-diphenylketene were used in the assembly of the highly substituted bicyclic compound **4** in this reaction.

As ketenes are rarely isolable species and usually are generated as transient intermediates, (for example, by the action of diisopropylethylamine (Hunig's base) on acyl halides) the replacement of ketenes by their precursors (which were transformed to ketenes in situ) should be of greater synthetic interest. Thus we were pleased to find that the reaction of **1a**, diphenylacetyl chloride (**3b**), and DMAD with $i\mathrm{Pr_2NEt}$ (2.25 equiv) as the base proceeded smoothly and gave **4** in almost the same yield as in the reaction using **3a** (Scheme 3).



Scheme 3. Three-component reaction of thiazolium salt **1a**, diphenylacetyl chloride (**3b**), and DMAD.

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We investigated the effect of the reaction conditions by using **1a**, α-methylphenylacetyl chloride (**5a**), and DMAD as the model system (Table 1). An initial screen of the solvents demonstrated that CH_2Cl_2 is the solvent of choice (entries 1 and 2, Table 1). It was shown that the reaction temperature played a significant role in this transformation. The best yield was obtained when the reaction was conducted by adding a mixture of **5a** and DMAD dropwiseto the solution of **1a** and *i*Pr$_2$NEt in CH_2Cl_2 at −78 °C, and then stirring the reaction mixture at room temperature for an additional four hours (entry 2, Table 1). Only a trace amount of product was obtained when the reaction temperature was maintained below 0 °C (entry 3, Table 1). Moreover, *i*Pr$_2$NEt proved to be the optimum base among those we examined, and the yield decreased dramatically when another base such as NEt_3[16] or DBU was used (entries 8 and 9, Table 1).

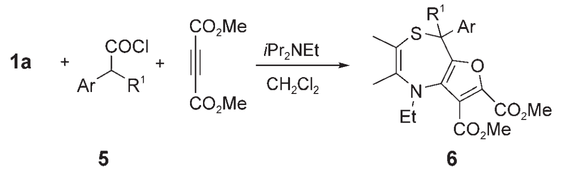
Table 1: Reaction of thiazolium salt **1a**, acetyl chloride **5a**, and DMAD under differing conditions.[a]

Entry	Base	Solvent	*T* [°C]	*t* [h][b]	Yield [%][c]
1	*i*Pr$_2$NEt	CH_2Cl_2	−20 to 25	8	64
2	*i*Pr$_2$NEt	CH_2Cl_2	−78 to 25	4	83
3	*i*Pr$_2$NEt	CH_2Cl_2	−78 to 0	3	< 5
4	*i*Pr$_2$NEt	THF	−78 to 25	8	< 5
5	*i*Pr$_2$NEt	toluene	−25 to 25	8	0
6	*i*Pr$_2$NEt	CH_3CN	−40 to 25	8	45
7	*i*Pr$_2$NEt	DME	−65 to 25	9	0
8	NEt_3	CH_2Cl_2	−78 to 25	7	25
9	DBU	CH_2Cl_2	−78 to 25	8	0

[a] General conditions: **1a** (1 mmol), **5a** (1 mmol), DMAD (1.5 mmol), and base (2.25 mmol). [b] Reaction time for consuming all of the starting materials. [c] Yields of isolated products. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DME = 1,2-dimethoxyethane.

As shown in Table 2, the reaction was found to be applicable to a variety of α-alkyl aryl acetyl chlorides **5**, to give furan-fused 1,4-thiazepines **6a–i** in good to excellent yields, regardless of whether the aromatic group of the acetyl chloride was bulky (entries 4, 7, and 8, Table 2), electron rich (entries 2–4), or electron poor (entries 5–9). However, the acetyl chlorides with an electron-rich aromatic group performed better than their electron-poor counterparts; for example, α-methyl 4-nitrophenylacetyl chloride afforded the product **6j** in only 28 % yield (entry 10, Table 2). Moreover, a larger alkyl group on the acetyl chloride **5** was shown to have some positive effects on the reaction, with a shorter reaction time observed for **5k** (entry 11, Table 2) possibly because of the increased bulk assisting the ring-expansion step.[17]

Table 2: Reaction of thiazolium salt **1a**, α-alkyl arylacetyl chlorides **5**, and DMAD for the synthesis of furan-fused 1,4-thiazepines **6a–k**.

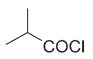
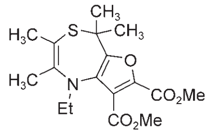
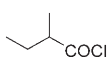
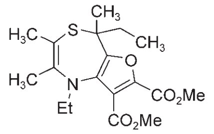
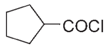
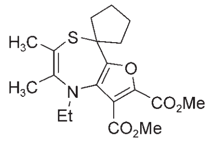
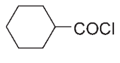
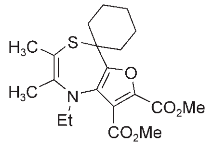


Entry	R^1	Ar	**5**	*t* [h][a]	Yield of **6** [%][b]
1	Me	Ph	**5a**	4	**6a**, 83
2	Me	4-MeOC$_6$H$_4$	**5b**	5.5	**6b**, 85
3	Me	4-MeC$_6$H$_4$	**5c**	7	**6c**, 84
4	Me	1-naphthyl	**5d**	9.5	**6d**, 59
5	Me	4-ClC$_6$H$_4$	**5e**	8	**6e**, 74
6	Me	4-BrC$_6$H$_4$	**5f**	7	**6f**, 72
7	Me	2-ClC$_6$H$_4$	**5g**	3.5	**6g**, 81
8	Me	2-BrC$_6$H$_4$	**5h**	4.5	**6h**, 77
9	Me	3-ClC$_6$H$_4$	**5i**	7	**6i**, 83
10	Me	4-NO$_2$C$_6$H$_4$	**5j**	17	**6j**, 28
11	Et	Ph	**5k**	2.5	**6k**, 91

[a] Reaction time for consumption of all of the starting materials. [b] Yields of isolated products.

Furthermore, the reactions of 1,1-dialkyl acetyl chlorides **7a–d** with the thiazolium salt **1a** and DMAD were also investigated (Table 3). Under the same experimental conditions, the furo[2,3-c]thiazepines **8** were formed in good yields. In the case of the cyclic carboxylic chlorides **7c** and **7d**, the tricyclic products **8c** and **8d** were easily and efficiently formed from simple substrates.

Table 3: Formation of product **8a–d** by the reaction of thiazolium salt **1a**, 1,1-dialkyl acetyl chloride **7a–d**, and DMAD.

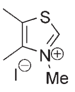
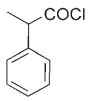
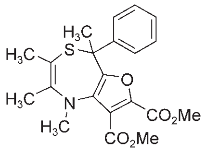
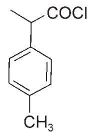
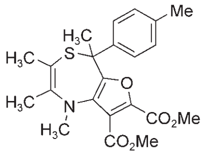
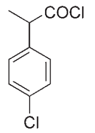
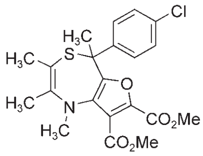
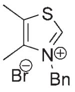
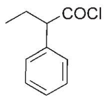
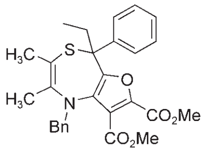
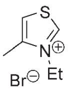
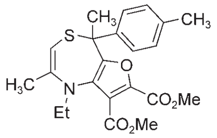
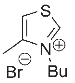
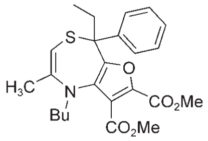
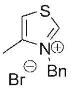
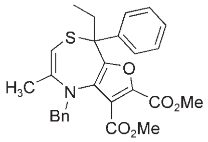
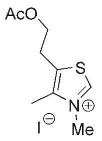
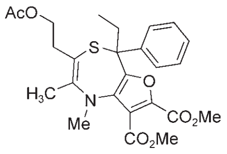
Entry	Acetyl chloride **7**		*t* [h][a]	Product **8**, yield[b]	
1	 COCl	**7a**	7		**8a**, 84 %
2	 COCl	**7b**	7		**8b**, 88 %
3	 COCl	**7c**	6		**8c**, 81 %
4	 COCl	**7d**	7		**8d**, 85 %

[a] Reaction time for consumption of all of the starting materials. [b] Yields of isolated products.

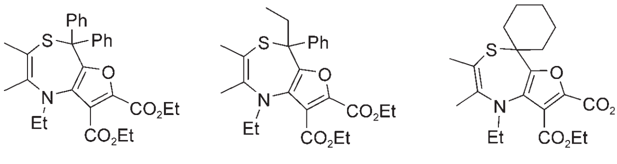
Next, we examined the reactions of the thiazolium salts **1b–g** from the commercially available thiazoles substituted in the 4- and 4,5-positions (Table 4). As a result, a range of furo[2,3-c]thiazepines **6l–6s** with various substituents were obtained in one step by simply mixing thiazolium salts, 1,1-disubstituted acetyl chlorides, and DMAD.

Finally, the scope of activated alkynes was studied. When diethylacetylenedicarboxylate was used as the alkyne component, the anticipated products **9a–c** were afforded from the corresponding substrates under the optimum conditions we had used for the reactions using DMAD (Scheme 4). To further increase the molecular diversity of this process, the possibility of using 4-oxo-2-alkynoates as the alkyne compo-

Table 4: Formation of product **6** by the reaction of thiazolium salts **1b–g**, acetyl chloride **5**, and DMAD.

Entry	Tiazolium salt **1**	Acetyl chloride **5**	*t* [h][a]	Yield of **6**[b]
1	 **1b**	 **5a**	5.5	 **6l**, 78%
2	**1b**	 **5c**	5	 **6m**, 80%
3	**1b**	 **5e**	7	 **6n**, 74%
4	 **1c**	 **5k**	6	 **6o**, 84%
5	 **1d**	**5c**	7	 **6p**, 78%
6	 **1e**	**5k**	4.5	 **6q**, 86%
7	 **1f**	**5k**	3	 **6r**, 81%
8	 **1g**	**5k**	7	 **6s**, 71%

[a] Reaction time for consumption of all of the starting materials. [b] Yields of isolated products.



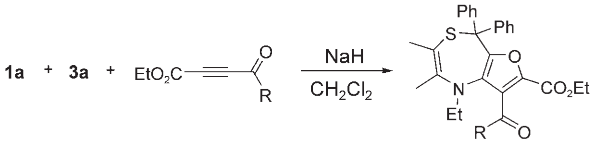
9a, 78% **9b**, 83% **9c**, 81%

Scheme 4. Products from diethylacetylenedicarboxylate and corresponding substrates.

nent was explored (Scheme 5). The preliminary results revealed that, when treated with sodium hydride, both aryl- and *tert*-butyl-substituted alkynes **10a–d** performed well in these reactions and furnished 1,4-thiazepines **11a–d** exclusively.[18] However, *i*Pr_2NEt proved to be unsuitable for this transformation with only trace amounts of the products detected.[19]

The mechanism of this novel domino reaction has not been unequivocally established, but one reasonable possibility is outlined in Scheme 6. Thus, the thiazol-2-ylidene **A**, first generated in situ from a thiazolium salt, would react with the 1,1-disubstituted ketene to afford the zwitterion **B**. Presumably, for steric reasons, the latter would undergo an oxa-Michael addition to the activated alkyne, followed by intramolecular annulation to furnish the spirocycle intermediate **C**. Finally, the ring expansion of **C** would occur, thus providing the furothiazepine **D** through a [1,3] sigmatropic sulfur shift.[20]

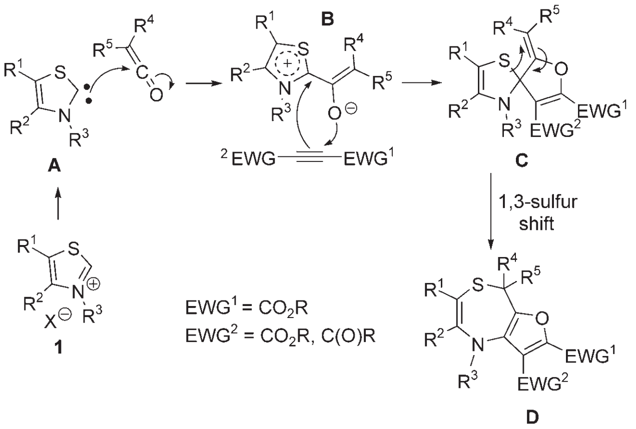
In conclusion, we have developed a novel and very efficient ring-expansion process for the synthesis of furan-fused 1,4-thiazepine derivatives from thiazole-carbene-triggered multicomponent reactions, which involve activated alkynes and 1,1-disubstituted ketenes generated in situ. This process generates compounds with a high level of complexity from simple and readily accessible starting materials. Furthermore, the operational simplicity and good chemical yields, combined atom-economic aspects and a small number of steps, make this new synthetic strategy highly attractive and promising for the formation of 1,4-thiazepine compounds with potential synthetic and biological uses.



10 **11**

10a: R = Ph **11a**, 81%
10b: R = 4-MePh **11b**, 83%
10c: R = 4-BrPh **11c**, 87%
10d: R = *t*Bu **11d**, 85%

Scheme 5. Three-component reaction of thiazolium salt **1a**, diphenylketene (**3a**), and 4-oxo-2-alkynoates **10a–d**.



Scheme 6. Proposed mechanism for the formation of furan-fused 1,4-thiazepine derivatives **D**. EWG = electron-withdrawing group.

Experimental Section

Representative procedure (Table 2, entry 1): $i\text{Pr}_2\text{NEt}$ (290 mg, 2.25 mmol) was added to a solution of thiazolium salt **1a** (222 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (3 mL) at −78 °C. After 10–15 min, a solution of α-methyl *p*-methylphenylacetyl chloride (183 mg, 1.0 mmol) and DMAD (213 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 min and the reaction mixture was stirred at this temperature for 30 min. The reaction temperature was then raised slowly to RT over 4 h. On completion of the reaction, the solvent was removed under vacuum, the residue was quickly passed through a short pad of neutral Al_2O_3 (hexane/diethyl ether 5:1), and the product thus obtained was recrystallized from hexane to afford **6a** (345 mg, 83 % yield) as a colorless solid: m.p. 124–126 °C; IR (film): $\tilde{\nu} = 3005$, 2970, 1718, 1710, 1437, 1419, 1345, 1296, 828, 767 cm^{-1}; ^{1}H NMR (500 MHz, [D$_6$]DMSO, tetramethylsilane): $\delta = 7.32$ (t, $J = 7.5$ Hz, 2H), 7.25 (t, $J = 7.0$ Hz, 1H), 7.11 (d, $J = 7.5$ Hz, 2H), 3.91 (s, 3H), 3.75 (s, 3H), 3.35–3.22 (m, 2H), 1.98 (s, 3H), 1.88 (s, 3H), 1.48 (s, 3H), 1.05 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, tetramethylsilane): $\delta = 164.5$, 157.8, 150.8, 147.2, 144.2, 136.5, 130.9, 128.6, 127.6, 126.7, 122.2, 118.4, 53.5, 52.7, 49.8, 44.3, 27.1, 22.8, 17.0, 14.7 ppm; HRMS (ESI): calcd for $C_{22}H_{25}NO_5SNa$: $[M+Na]^+$ 438.1346, found 438.1325.

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Keywords: carbenes · cyclization · ketenes · multicomponent reactions · ring expansion

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