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Facile Synthesis of Highly Substituted 3-Aminofurans from Thiazolium Salts, Aldehydes, and Dimethyl Acetylenedicarboxylate

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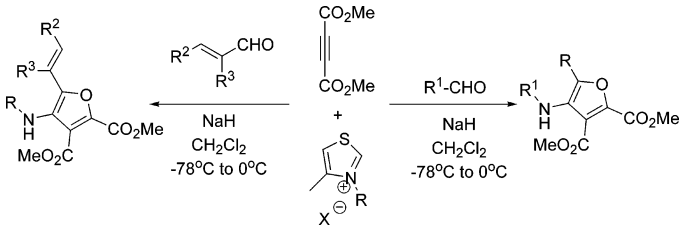

A facile preparation of 3-aminofuran derivatives via multicomponent reactions of thiazole carbenes, aldehydes, and dimethyl acetylenedicarboxylate (DMAD) is reported. In this process, the thiazole carbenes, generated in situ from thiazolium salts, reacted with aldehydes and DMAD at −78 to 0 °C in CH_2Cl_2 to afford the substituted furans in moderate to good yields. Eight substituted thiazolium salts were employed as carbene precursors in the reaction. Besides aryl aldehydes, α,β-unsaturated aldehydes, aliphatic aldehydes, and arenedial were also investigated and found to be applicable to this reaction.

Introduction

Ever since Breslow's original demonstration of the role of thiazole carbenes as nucleophilic catalysts in enzymatic reactions,[1] the intensive studies of N-heterocyclic carbenes (NHCs) as reaction intermediates by Wanzlick,[2] and the first isolation of stable diaminocarbene by Arduengo in 1991,[3] these species have attracted considerable attention in the past half century. Their role as excellent ligands for transition metals[4] and their ability to catalyze various C−C coupling reactions, namely, benzoin condensation, transesterification,[5] and Stetter reaction,[6] have contributed significantly to the enormous interest in NHCs. Recently, there is also a growing awareness of their potential application as reagents in organic reactions[7] as illustrated by diaminocarbene-mediated 1,3-dipolar cycloadditions,[8] [4 + 1] cycloaddition reactions,[9] and multicomponent reactions.[10]

The synthesis of furans has attracted tremendous interest for well over a century, primarily because many furans are key structural units in many natural products and important pharmaceuticals, and some are useful building blocks in synthetic chemistry.[11] While numerous strategies for furans synthesis exist, convergent annulation strategies from simple readily available starting materials without transition-metal catalysis are still very rare.[12,13] As the nucleophilic character of diheteroatom-substituted carbenes offers opportunities for constructing

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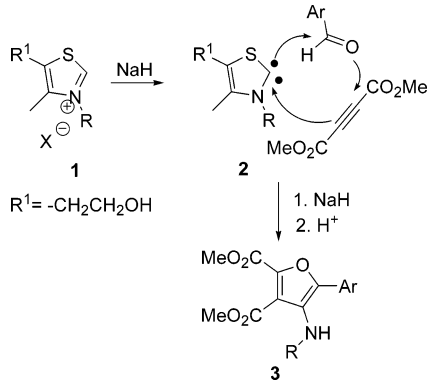
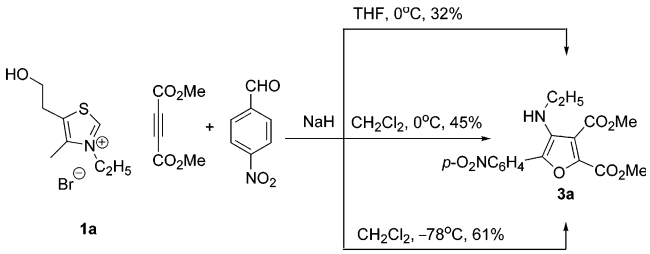
SCHEME 1. Thiazolium-Mediated Multicomponent Reaction for the Synthesis of 3-Aminofuran Derivatives



SCHEME 2. Effect of Reaction Conditions on the Thiazolium-Mediated Multicomponent Reaction for the Synthesis of 3a

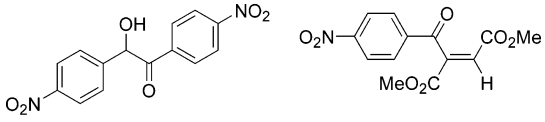


substituted heterocyclic compounds,[14] we were intrigued by the NHC-mediated reactions for the synthesis of substituted furans.

In a preliminary communication,[15] we described a three-component reaction of thiazolium salts **1**, aryl aldehydes, and dimethyl acetylenedicarboxylate (DMAD) for the preparation of substituted 3-aminofuran derivatives **3** (Scheme 1). While the implications of the results are not fully apparent, they clearly warranted further research. Moreover, it would be interesting to see if simple thiazolium precursors and other aldehydes could be used in the reaction. Here, we report the results of our detailed investigations on the reactions involving thiazolium salts, aldehydes and DMAD for the convergent construction of substituted furans.

Results and Discussion

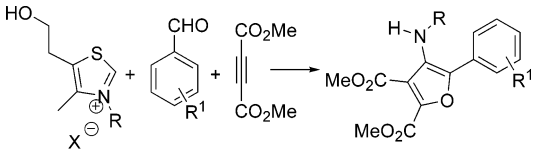
The multicomponent reaction was carried out by dropping the mixture of *p*-nitrobenzaldehyde and DMAD to thiazol-2-ylidene **2a**, generated in situ by the deprotonation of 3-ethyl-5-(2′-hydroxyethyl)-4-methyl-1,3-thiazolium bromide **1a** with sodium hydride in different solvents and at various reaction temperatures (Scheme 2). Although it is possible to use as little as 2 equiv of sodium hydride for this conversion, we typically employed



4 **5**

FIGURE 1. Structures of compounds **4** and **5**.

TABLE 1. Reaction of Thiazolium Salts 1a−c, Aryl Aldehydes, and DMAD[a]



1a: R = C_2H_5, X = Br
1b: R = CH_3, X = I
1c: R = Bn, X = Cl

entry	R	R^1	time[b] (h)	yield of **3**[c] (%)
1	C_2H_5	4-NO_2	3	**3a**, 61
2	Me	4-NO_2	4	**3b**, 53
3	Bn	4-NO_2	3.5	**3c**, 28
4	C_2H_5	4-F	3	**3d**, 87
5	Me	4-F	3	**3e**, 73
6	Bn	4-F	3	**3f**, 32
7	C_2H_5	H	3	**3g**, 62
8	Me	H	3	**3h**, 52
9	C_2H_5	4-Me	3	**3i**, 51
10	Me	4-Me	3	**3j**, 41
11	C_2H_5	3-NO_2	3	**3k**, 65
12	C_2H_5	2-Cl	3	**3l**, 74
13	C_2H_5	4-Cl	3	**3m**, 69
14	Me	4-Cl	3	**3n,** 51
15	C_2H_5	4-MeO	6	**3o**, 31
16	Me	3,4-dimethoxy	24	**3p,** 22

[a] Reaction conditions: (1) NaH (1.5 mmol), **1** (1.0 mmol), CH_2Cl_2, −78 °C, 10−15 min; then the mixture of aldehyde (0.5 mmol), DMAD (0.75 mmol), 2 h; then warm to 0 °C for due time; (2) ice-cooled $NaHCO_3$ (aq). [b] Times refer to keeping at 0 °C after 2 h at −78 °C. [c] Isolated yield based on the starting aldehyde.

an excess (3 equiv) to ensure complete consumption of the reactants. As shown in Scheme 2, aminofuran derivative **3a** was obtained in 32% yield when **1a** was treated with NaH in THF at 0 °C, while in CH_2Cl_2 at 0 °C, a higher yield up to 45% of **3a** was obtained. Further optimization of conditions demonstrated CH_2Cl_2 at −78 °C was more favorable, and **3a** was isolated in 61% yield. Moreover, only trace benzoin **4** and no conjugated addition product **5**[16] were found when the reaction temperature was kept below 0 °C (Figure 1).

The structure of the product **3a** was characterized by spectroscopic analysis. In the ^{1}H NMR spectrum, the carbomethoxy protons resonated as a singlet at δ 3.96. The ester carbonyl groups of **3a** displayed ^{13}C resonance signals at δ 163.5 and 158.2 supporting the IR absorption at 1724 and 1709 cm^{-1}. Final proof for the structure assigned for **3a** was derived from single-crystal X-ray analysis.[15]

In our further investigation, we discovered that the reaction demonstrates wide scope with respect to the aryl

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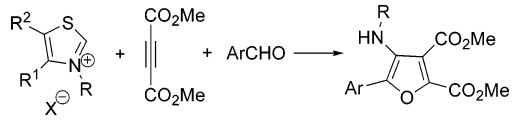
TABLE 2. Effect of Thiazolium Salts on the Multicomponent Reactions for the Synthesis of Furan Derivatives[a]



1

3

1d: R = CH_3, R^1 = CH_3, R^2 = CH_3, X = I
1e: R = CH_3, R^1 = CH_3, R^2 = H, X = I
1f: R = C_2H_5, R^1 = CH_3, R^2 = H, X = Br
1g: R = n-C_4H_9, R^1 = CH_3, R^2 = H, X = Br
1h: R = Bn, R^1 = CH_3, R^2 = H, X = Br

entry	thiazolium salt **1**	R	Ar	time[b] (h)	yield of **3**[c] (%)
1	**1d**	CH_3	4-$NO_2C_6H_4$	4	**3b** (59)
2	**1e**	CH_3	4-$NO_2C_6H_4$	4	**3b** (61)
3	**1h**	Bn	4-$NO_2C_6H_4$	3.5	**3c** (30)
4	**1g**	*n*-C_4H_9	4-$NO_2C_6H_4$	4	**3q** (62)
5	**1e**	CH_3	C_6H_5	4	**3h** (54)
6	**1g**	*n*-C_4H_9	C_6H_5	4	**3r** (58)
7[c]	**1e**	CH_3	3,4-dimethoxyphenyl	24	**3p** (29)
8	**1e**	CH_3	4-ClC_6H_4	4	**3n** (49)
9	**1e**	CH_3	1-naphthyl	12	**3s** (45)
10	**1e**	CH_3	thiophene-2-yl	5	**3t** (55)
11	**1f**	C_2H_5	furan-2-yl	4	**3u** (78)

[a] Reaction conditions: (1) NaH (1.0 mmol), **1** (1.0 mmol), CH_2Cl_2, −78 °C, 10−15 min; then solution of aldehyde (0.5 mmol), DMAD (0.75 mmol), 2 h; then warm to 0 °C for due time; (2) ice-cooled $NaHCO_3$ (aq). [b] Times refer to keeping at 0 °C. [c] Isolated yields based on starting aldehyde.

aldehydes and the 3-aminofuran derivatives **3a**−**p** were obtained in moderate to good yields (Table 1). Electron-deficient aldehydes performed much better than their electron-rich counterparts; 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde required longer reaction times relative to the parent compound (entries 15 and 16, Table 1). Two other commercially available thiazolium salts **1b** and **1c** were also tested in this reaction to afford the corresponding furans. Due to the poor solubility of **1b** and **1c** in CH_2Cl_2, the yields of furans were lower than their **1a** counterparts.

As the base-induced oxa-Michael addition of alcohol to DMAD would afford alkoxysuccinic ester,[17] the action of the hydroxy groups in the thiazolium salts **1a**−**c** in the reaction process was still unclear. In addition, it would be interesting to see if simple thiazolium precursors could be used in the reaction, a factor that might also have a favorable impact on solubility issues, and the amount of base required in the transformation. Then, thiazolium salts **1d**−**h** and various aromatic aldehydes were chosen as substrates using 2 equiv of sodium hydride to carry out the reaction. The reaction results were summarized in Table 2. In fact, it is observed that simple thiazolium salts **1d**−**f** afforded almost the same yields as thiazolium salts **1a**−**c** using the same aldehyde as substrates (entry 1−3, 5, 7, and 8, Table 2). Therefore, it was demonstrated that the hydroxy groups in the thiazolium salts **1a**−**c** have no positive effect on the transformation, and when the thiazolium salts **1e**−**h**, derived from 4-methylthiazole were employed, an improved overall economy of the process was achieved.[18]

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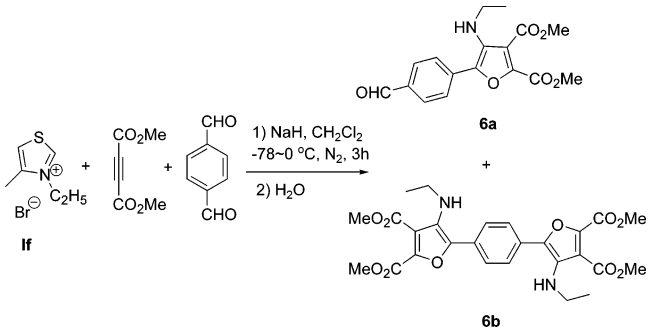
SCHEME 3. Reaction of Terephthalaldehyde with Thiazolium Salt 1f and DMAD

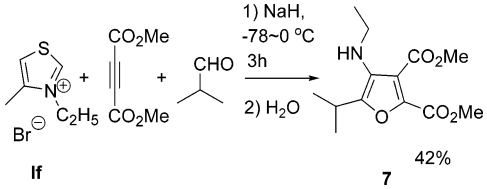


6a

If

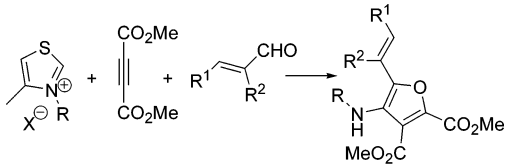
6b

SCHEME 4. Synthesis of Furan Derivative 7



If **7** 42%

TABLE 3. Reaction of α, β-Unsaturated Aldehydes with DMAD and Thiazolium Salts 1e−g



1e-g **8a-j**

entry	thiazolium salt **1**	R	R^1	R^2	time[b] (h)	product **8**	yield[c] (%)
1	**1e**	CH_3	C_6H_5	H	5	**8a**	38 (63)
2	**1f**	C_2H_5	C_6H_5	H	5	**8b**	47 (78)
3	**1g**	*n*-C_4H_9	C_6H_5	H	5	**8c**	45 (75)
4	**1f**	C_2H_5	4-FC_6H_4	H	4	**8d**	51 (83)
5	**1g**	*n*-C_4H_9	4-FC_6H_4	H	4	**8e**	48 (78)
6	**1f**	C_2H_5	4-MeC_6H_4	H	6	**8f**	36 (59)
7	**1g**	*n*-C_4H_9	4-MeC_6H_4	H	6	**8g**	35 (55)
8	**1f**	C_2H_5	C_6H_5	Me	4	**8h**	52 (84)
9	**1g**	*n*-C_4H_9	C_6H_5	Me	4	**8i**	51 (82)
10	**1e**	CH_3	Me	H	30	**8j**	27(44)

[a] Reaction conditions: (1) NaH (1.2 mmol), **1** (1.0 mmol), CH_2Cl_2, −78 °C, 10−15 min; then the solution of aldehyde (0.5 mmol), DMAD (0.75 mmol), 2 h; then, warm to 0 °C for due time; (2) ice-cooled $NaHCO_3$ (aq). [b] Times refer to keeping at 0 °C. [c] Isolated yield; yield based on recovered aldehyde in parentheses.

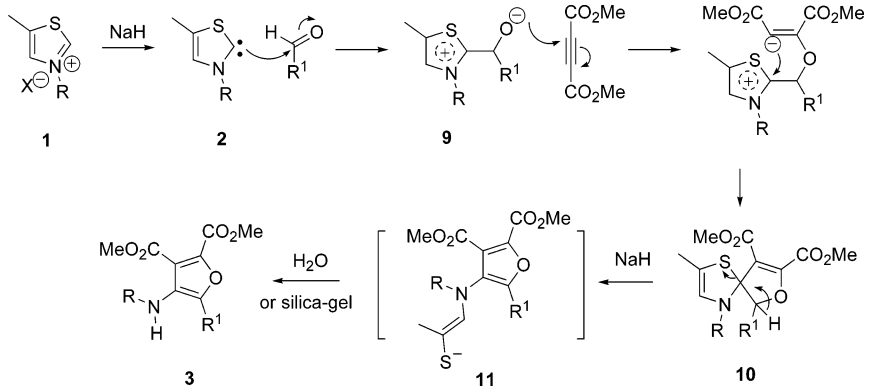
For the reaction of terephthalaldehyde with thiazolium salt **1f** and DMAD under the same conditions, a mixture of furan derivatives **6a** and **6b** was formed. To our satisfaction, when excess **1f** (4.0 equiv) was employed; the reaction proceeded so well that only **6b** was formed in 56% yield (Scheme 3).

Interestingly, even aliphatic aldehydes such as isobutyraldehyde on treatment with DMAD and **1f** furnished the corresponding furan derivative **7** in 42% yield (Scheme 4).

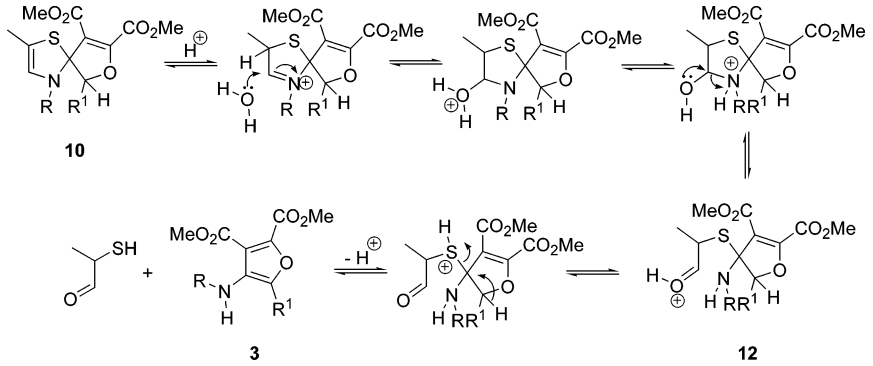
Recently, Bode[19a] and Glorius[19b] independently reported the nucleophile-catalyzed generation of homoeno-

(18) The attempt to use thiazolium salts derived from thiazole in the reaction was proved unsuccessful due to their very poor solubility in general nonprotic solvents.

SCHEME 5. Postulated Mechanism of the Thiazolium-Mediated Tandem Reaction



SCHEME 6. Another Plausible Pathway for the Hydrolysis of 10



lates from α,*β*-unsaturated aldehydes and their reaction with an electrophilic aldehyde, leading to a direct, stereoselective synthesis of *γ*-lactones. We were intrigued by these processes and turned our attention to α, *β*-unsaturated aldehydes to examine the chemoselectivity in the multicomponent reaction of these compounds with thiazole carbenes and DMAD (Table 3). Replacing arylaldehyde with cinnamaldehyde in the same reaction demonstrated that only the corresponding (*E*)-dimethyl 3-(methylamino)-2-styrylfuran-4,5-dicarboxylate **8a** was formed in 38% yield (entry 1, Table 3). The ^{1}H NMR spectrum was in good agreement with the assigned structure. Signals due to the methoxycarbonyl protons were discernible at *δ* 3.94 and 3.91. The olefinic protons provided two doublets centered at *δ* 6.99 (J = 16.0 Hz) and 7.13 (J = 16.0 Hz). The ^{13}C NMR spectrum showed characteristic peaks corresponding to the two carbonyls at *δ* 158.8 and 164.4.

Encouraged by these results, other α, *β*-unsaturated aldehydes were also examined under similar conditions. As disclosed in Table 3, a prolonged reaction time was required to get a reasonable yield of furan derivatives **8**, and about 20−40% of unreacted enals were recovered after the reaction. Furthermore, no product resulting from the conjugated addition on the enal was observed in the reaction process.

Based on the experiment results, we ascertain the whole tandem reaction sequence pivots on the nucleophilicity of thiazole carbenes, and a possible mechanism for the present reaction is shown in Scheme 5. The thiazol-2-ylidene **2** would be formed in situ by the deprotonation of the thiazolium salt **1** at its most acidic position[20] and then reacted with the aldehyde to form the zwitterion **9**. The latter **9** underwent an oxa-Michael addition to DMAD, followed by intramolecular annulation to give spirocycle intermediate **10**. Afterward, ring opening of thiazole may proceed by cleavage of C−S bond to afford intermediate **11**.[21] It seems that a rearrangement to the formation of the aromatic furan provides the driving force for the C−S bond breaking. Several papers have mentioned this similar type of bond breaking between carbon and heteroatoms in the heterocyclic system.[22] Finally, the unstable intermediate **11** was hydrolyzed to furnish furan derivative **3**.

Another plausible pathway for the formation of **3** is based on the acid-catalyzed hydrolysis of **10** during silica gel chromatographic separation (Scheme 6). Thus, enamine hydrolysis of spiro compound **10** under acid condition afforded amine **12**. The latter underwent a rearrangement to give furan **3** via the cleavage of C−S bond.

Conclusion

In conclusion, we have developed a facile and effective synthesis of highly substituted 3-amino furan derivatives

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via a novel multicomponent reaction of thiazole carbenes, aldehydes and DMAD in moderate to good yields. It is ascertained the whole tandem reaction sequence pivots on the nucleophilicity of thiazole carbenes, and the solubility of thiazolium precursors has an enormous effect on the reactions. Moreover, an improved overall economy of the process could be achieved using 4-methylthiazolium salts **1e**−**h** as carbene precursors. Furthermore, aromatic aldehydes, α, β-unsaturated aldehydes, and some aliphatic aldehydes could complete the reaction smoothly. It is conceivable that the novel multicomponent reactions described herein will find application in the synthesis of heterocyclic compounds and in natural product synthesis.

Experimental Section

General Procedure for the Reaction of Thiazolium Salts (1e−g), α,β-Unsaturated Aldehydes, and DMAD. To a suspension of NaH (1.2 mmol) in anhydrous CH_2Cl_2 (3 mL) was added thiazolium salt (**1e**−**g**) (1.0 mmol) in dry CH_2Cl_2 (2 mL) at −78 °C. After 10−15 min, a solution of aldehyde (0.5 mmol) and DMAD (0.75 mmol) in CH_2Cl_2 (2 mL) was added over 10 min and then stirred at this temperature for 2 h. The reaction temperature was then raised slowly to 0 °C within 1 h and kept at 0 °C for an additional several hours. On completion of the reaction, the reaction mixture was carefully poured onto a solution of ice-cooled $NaHCO_3$ (satd solution, 50 mL) and then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was washed with brine (2 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was purified by column chromatography using appropriate hexanes−ethyl acetate solvent mixture to afford the products **8a**−**j**.

(*E*)-Dimethyl 3-(methylamino)-2-styrylfuran-4,5-dicarboxylate (8a): pale yellow viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, 2H, J = 8.0 Hz), 7.34 (t, 2H, J = 7.75 Hz), 7.23 (t, 1H, J = 7.75 Hz), 7.13 (d, 1H, J = 16.0 Hz), 6.99 (d, 1H, J = 16.0 Hz), 3.94 (s, 3H), 3.91 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 158.8, 141.9, 138.7, 137.4, 135.6, 129.0, 127.8, 126.4, 126.3, 115.4, 114.9, 52.7, 52.5, 34.2; IR (film) ν 3406, 2952, 1731, 1703, 1593, 1439, 1323, 1225, 927, 751 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}NO_5$ ($[M + H]^+$) 316.1179, found 316.1178.

Preparation of 6b. To a suspension of NaH (3.0 mmol) in anhydrous CH_2Cl_2 (3 mL) was added thiazolium salt **1f** (2.0 mmol) in dry CH_2Cl_2 (2 mL) at −78 °C. After 10−15 min, a solution of aldehyde (0.5 mmol) and DMAD (0.75 mmol) in CH_2Cl_2 (2 mL) was added over 10 min and then stirred at this temperature for 2 h. The reaction temperature was then raised slowly to 0 °C within 1 h and kept at 0 °C for an additional several hours. On completion of the reaction, the reaction mixture was carefully poured onto a solution of ice-cooled $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was purified by column chromatography to afford the product **6b**.

Dimethyl 3-(ethylamino)-2-{4-[3-(ethylamino)-4,5-bis(methoxycarbonyl)-2-furyl]phenyl}-4,5-furandicarboxylate (6b): pale yellow crystalline solid; mp 158−160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 4H), 3.96−3.95 (m, 14H), 2.99 (q, 4H, J = 7.0 Hz), 1.14 (t, 6H, J = 6.75 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 158.6, 142.5, 141.1, 134.1, 129.2, 125.8, 119.8, 52.6, 52.6, 43.1, 15.8; IR (KBr) ν 3352, 2958, 1729, 1700, 1609, 1556, 1444, 1306, 1232, 1138, 967, 831 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{28}N_2O_{10}$ ($[M + H]^+$) 529.1817, found 529.1822.

Supporting Information Available: Characterization data for 3-aminofuran derivatives and thiazolium salts **1d**−**h** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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