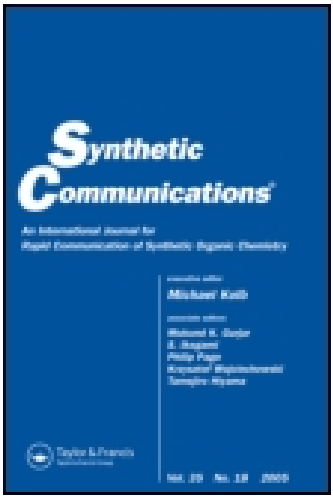

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 22 Dec 2008.

To cite this article: V. S. Prasada Rao Lingam, Ramanatham Vinodkumar, Khagga Mukkanti, Abraham Thomas & Balasubramanian Gopalan (2008) Tetra-n-butylammonium Fluoride-Catalyzed Eschenmoser-Claisen [3,3]-Sigmatropic Rearrangement, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:2, 332-341, DOI: 10.1080/00397910802374075

To link to this article: http://dx.doi.org/10.1080/00397910802374075

Synthetic Communications®, 39: 332–341, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802374075

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Tetra-*n*-butylammonium Fluoride–Catalyzed Eschenmoser–Claisen [3,3]-Sigmatropic Rearrangement

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Abstract: Condensation of dibenzofuran and dibenzothiophene carboxaldehydes with various aryl acetic acids followed by esterification of the acid intermediate afforded the 2,3-diaryl acrylates in good overall yields. Reduction of the esters with diisobutylaluminium hydride afforded the allylic alcohols, which underwent a smooth Eschenmoser–Claisen [3,3]-sigmatropic rearrangement on exposure to *N*,*N*-dimethylacetamide dimethylacetal in the presence of tetra *n*-butylammonium fluoride as catalyst to give 3,4-diaryl γ,δ-unstaturated amides in excellent yields.

Keywords: Acrylic acids, allylic alcohols, Eschenmoser–Claisen rearrangement, tetra-*n*-butylammonium fluoride trihydrate, γ,δ-unstaturated amides

INTRODUCTION

Dibenzo[*b*,*d*]furan and dibenzo[*b*,*d*]thiophene derivatives have been shown to exhibit a wide range of biological activities and therefore hold considerable potential as therapeutic agents. For example, some

Received March 9, 2008.
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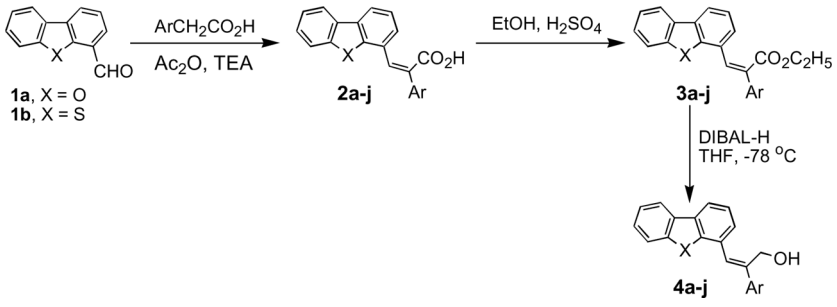
derivatives have been reported as anti-methicillin-resistant *Staphylococcus aureeus* (MRSA) agents,[1] endothelin-converting enzyme-1 inhibitors,[2] and DNA-dependent protein kinase (DNK-PK) inhibitors.[3] Recently our group has reported a similar series of compounds as phosphodiesterase IV (PDE-IV) inhibitors.[4,5] In continuation of our work on dibenzo[*b*,*d*]furan and dibenzo[*b*,*d*]thiophene derivates, we have been interested in the synthesis of γ,δ-unstaturated amides with dibenzo[*b,d*]-furan and dibenzo[*b,d*]thiophene as substituents. In this regard, our literature survey revealed that Eschenmoser–Claisen [3,3]-sigmatropic rearrangement[6] of allylic alcohols is an important and useful approach for the synthesis of γ,δ-unstaturated amides. The reaction normally involves coupling of an allyl alcohol or alkoxide with *N*,*N*-dimethylacetamidedimethyl acetal[7–9] or *N,N*-diakylalkoxymethylene imminium salts[10,11] followed by [3,3]-sigmatropic rearrangement of the allyl vinyl ether intermediate, resulting in the formation of a new carbon–carbon bond. The reaction generally requires prolonged reaction time and harsh temperature conditions, which limit the scope of this method. We have also observed that the rearrangement is not reported on allylic alcohols with bulky substituents on the olefin. We have been interested in the modification of this method using an appropriate catalyst to suit our need for the synthesis of γ,δ-unstaturated amides with two bulky aryl substituents. The present article describes our efforts in this direction.

RESULTS AND DISCUSSION

The starting allyl alcohols **4a–j** required for the present study were prepared in three steps as shown in Scheme 1. Perkin reaction[12] of aldehydes **1a** and **1b** with various aryl acetic acids in the presence of triethylamine in refluxing acetic anhydride furnished the *trans*-2,3-diaryl acrylic acids **2a–j**. Esterification of **2a–j** with ethanol in the presence of



Scheme 1. Synthesis of 2,3-diaryl allyl alcohols.

catalytic amounts of sulfuric acid gave corresponding ethyl esters **3a–j**. Attempted reduction of esters **3a–j** with lithium aluminum hydride[13] and lithium borohydride[14] did not give the desired allyl alcohols, which suggests that the reaction does not give allyl alcohols by means of conjugate addition/elimination. The reduction was then attempted with diisobutylaluminum hydride[15] in dry THF at −78 °C resulted in the formation of desired allyl alcohols **4a–j**, and the results obtained are summarized in Table 1.

Table 1. Synthesis of acrylic acid **2a–j**, ethyl acrylates **3a–j**, and allyl alcohols **4a–j**

Entry	Starting material	Product	Time (h)	Yield (%)	Mp (°C)
1	**1a**, X = O	**2a**, X = O, Ar = phenyl	1.0	60	243–245
2	**1a**, X = O	**2b**, X = O, Ar = 2-bromophenyl	1.5	73	253–256
3	**1a**, X = O	**2c**, X = O, Ar = 2-iodophenyl	1.5	68	260–265
4	**1a**, X = O	**2d**, X = O, Ar = 4-chlorophenyl	1.0	62	250–253
5	**1a**, X = O	**2e**, X = O, Ar = 4-biphenyl	2.0	69	263–266
6	**1a**, X = O	**2f**, X = O, Ar = 1-naphthyl	2.0	57	246–248
7	**1b**, X = S	**2g**, X = S, Ar = phenyl	1.5	63	210–213
8	**1b**, X = S	**2h**, X = S, Ar = 4-chlorophenyl	1.5	67	231–233
9	**1b**, X = S	**2i**, X = S, Ar = 2-chlorophenyl	1.0	56	256–258
10	**1b**, X = S	**2j**, X = S, Ar = 1- thienyl	0.5	55	249–252
11	**2a**	**3a**, X = O, Ar = phenyl	24	97	121–123
12	**2b**	**3b**, X = O, Ar = 2-bromophenyl	18	93	93–96
13	**2c**	**3c**, X = O, Ar = 2-iodophenyl	18	92	90–92
14	**2d**	**3d**, X = O, Ar = 4-chlorophenyl	18	95	118–119
15	**2e**	**3e**, X = O, Ar = 4-biphenyl	24	95	154–156
16	**2f**	**3f**, X = O, Ar = 1-naphthyl	24	90	137–133
17	**2g**	**3g**, X = S, Ar = phenyl	18	92	118–120
18	**2h**	**3h**, X = S, Ar = 4-chlorophenyl	24	91	110–113
19	**2i**	**3i**, X = S, Ar = 2-chlorophenyl	18	93	123–126
20	**2j**	**3j**, X = S, Ar = 1- thienyl	18	90	67–69
21	**3a**	**4a**, X = O, Ar = phenyl	0.5	91	130–132
22	**3b**	**4b**, X = O, Ar = 2-bromophenyl	0.5	93	50–52
23	**3c**	**4c**, X = O, Ar = 2-iodophenyl	0.5	94	52–55
24	**3d**	**4d**, X = O, Ar = 4-chlorophenyl	0.5	92	161–163
25	**3e**	**4e**, X = O, Ar = 4-biphenyl	0.5	95	166–168
26	**3f**	**4f**, X = O, Ar = 1-naphthyl	0.5	85	101–103
27	**3g**	**4g**, X = S, Ar = phenyl	0.5	90	126–128
28	**3h**	**4h**, X = S, Ar = 4-chlorophenyl	0.5	92	138–140
29	**3i**	**4i**, X = S, Ar = 2-chlorophenyl	0.5	96	65–67
30	**3j**	**4j**, X = S, Ar = 1- thienyl	0.5	89	131–132

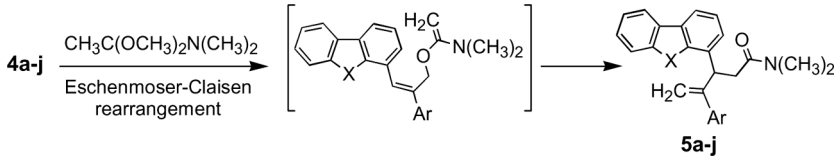
Having obtained the required alcohols **4a–j** for the synthesis of target molecules, we have then carried out the Eschenmoser–Claisen [3,3] rearrangement with tetra *n*-butylammonium fluoride trihydrate[16] (TBAF · $3H_2O$) as phase-transfer catalyst (PTC). The latter has been previously employed for several important synthetic transformations such as desilylation,[17] fluorination,[18] aldol condensation,[19] Michael addition,[20] Sonogashira reaction,[21] and alkylation.[22]

The reactions were initially carried out by refluxing allyl alcohol (**4a**) with *N*,*N*-dimethylacetamide dimethyl acetal (2.0 equiv) in the absence of any catalyst. The reactions in the absence of catalyst (Table 2, entries 1–3) gave poor to moderate yields of 3-dibenzo[*b*,*d*]furan-4-yl-*N*, *N*-dimethyl-4-phenylpent-4-enamide **5a** after prolonged reaction time. Then we attempted the reaction under Johnson–Claisen rearrangement conditions using excess (3.0 equiv) *N*,*N*-dimethylacetamidedimethyl acetal in refluxing toluene using propionic acid[23] or pivalic acid[24] as catalyst (entries 4 and 5). Under these conditions, total conversion of alcohol **4a** to less polar imino acetate intermediate was observed (by thin-layer chromatography, TLC), However, repeated attempts to isolate the intermediates at this stage were not successful because of the instability of the intermediate, and only moderate yield of the amide **5a** was achieved even after 48 h at reflux. Then, to assess the potential of TBAF for this rearrangement, a series of preliminary experiments was carried out. Initial studies with 10% catalyst in various polar and nonpolar solvents at reflux temperatures suggested that polar solvents are not useful for this rearrangement (entries 11 and 12). Complete conversion

Table 2. Eschenmoser–Claisen rearrangement of **4a** under various conditions

Entry	Catalyst	Mole (%)	Solvent[a]	Time (h)	5a yield (%)
1	—	—	Cyclohexane	72	5
2	—	—	Toluene	18	42
3	—	—	*o*-Xylene	18	51
4	$CH_3CH_2CO_2H$	10	Toluene	48	35
5	$(CH_3)_3CCO_2H$	10	Toluene	48	40
6	$(n\text{-}Bu)_4NF \cdot 3H_2O$	10	Cyclohexane	72	63
7	$(n\text{-}Bu)_4NF \cdot 3H_2O$	5	Toluene	5	81
8	$(n\text{-}Bu)_4NF \cdot 3H_2O$	10	Toluene	3	92
9	$(n\text{-}Bu)_4NF \cdot 3H_2O$	20	Toluene	3	92
10	$(n\text{-}Bu)_4NF \cdot 3H_2O$	10	*o*-Xylene	3	89
11	$(n\text{-}Bu)_4NF \cdot 3H_2O$	10	Tetrahydrofuran	48	15
12	$(n\text{-}Bu)_4NF \cdot 3H_2O$	10	1,4-Dioxane	48	30

[a]All reactions were carried out at reflux temperature of the solvents specified in the table.



Scheme 2. Synthesis of γ,δ-unsaturated amides.

was obtained in both toluene (bp 111 °C) and *o*-xylene (bp 145 °C) within 3 h. Increasing the temperature of reaction by using *o*-xylene resulted in reduction of reaction time by 20–30 min with no significant change in yield (entry 10). On the other hand, decrease in reaction temperature by using cyclohexane (bp 81 °C) required around 3 days for completion even with an excess (3.0 equiv) of *N*,*N*-dimethylacetamide dimethyl acetal (entry 6). Reactions with 5% catalyst (entry 7) required 5 h to complete the reaction, whereas 20% catalyst (entry 9) did not give any additional advantage, although yield was not compromised either case.

After these preliminary screening experiments and arriving at the appropriate conditions for the reaction of **4a** to obtain **5a**, the methodology was extended to different allyl alcohols **4b–j** to obtain corresponding amides **5b–j** (Scheme 2), thus establishing the generality of the present method, and the details are summarized in Table 3.

CONCLUSION

We have successfully demonstrated the use of tetra-*n*-butylammonium fluoride trihydrate as a very powerful catalyst for Eschenmoser–Claisen

Table 3. TBAF · $3H_2O$-catalyzed Eschenmoser–Claisen rearrangement of **4a–j** to obtain **5a–j**

Entry	Allyl alcohols	Yield (%)	Time (h)	Mp (°C)
1	**4a**	91	3.0	120–123
2	**4b**	95	3.5	48–51
3	**4c**	93	3.5	56–59
4	**4d**	96	3.5	43–45
5	**4e**	91	5.0	76–78
6	**4f**	95	5.0	53–55
7	**4g**	97	3.0	130–134
8	**4h**	97	4.0	50–53
9	**4i**	90	3.5	39–41
10	**4j**	95	3.0	148–150

[3,3]-sigmatropic rearrangement of hindered allylic alcohols **4a–j**, providing γ,δ-unstaturated amides **5a–5j** in excellent yields. The advantage of the present method is its operational simplicity, which proceeds with catalytic amounts of the TBAF · $3H_2O$ under mild conditions. This feature, combined with the short reaction times and easy workup procedures, makes this method an attractive choice over the existing procedure for Eschenmoser–Claisen rearrangement. Further, the method tolerates bulky aromatic substituents at 2 and 3 positions of the allyl alcohols. We hope that the present method will find wide and useful application for practicing chemists in the field.

EXPERIMENTAL

Typical Procedure for the Preparation of Acrylic Acids: Synthesis of (2*Z*)-3-Dibenzo[*b*,*d*]furan-4-yl-2-phenyl Acrylic Acid (2a)

Triethylamine (7.80 ml, 77.082 mmol) was added to a solution of dibenzofuran-1-carboxaldehyde **1a** (10 g, 50.968 mmol) and phenyl acetic acid (7.61 g, 55.971 mmol) in acetic anhydride (25 ml), and the mixture was stirred under reflux for 1.0 h under nitrogen atmosphere. Water (25 ml) was added to the hot reaction mixture, and the mixture was slowly (30 min) allowed to cool to room temperature. The product precipitated out was collected by filtration, washed with water (2 × 25 ml), and dried in an air oven. The material was crystallized from ethyl acetate to give 9.61 g (60%) of (2*Z*)-3-dibenzo[*b*,*d*]furan-4-yl-2-phenylacrylic acid as a white solid; IR (KBr) 3359 (br) 3050, 2951, 1677, 1606, 1416, 1288, 1182, 1117, 835 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.78 (d, $J = 7.5$ Hz, 1H), 7.09 (t, $J = 7.8$ Hz, 1H), 7.22–7.24 (m, 2H), 7.35–7.37 (m, 3H), 7.42 (t, $J = 7.8$ Hz, 1H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.75 (d, $J = 7.2$ Hz, 1H), 8.04 (d, $J = 7.8$ Hz, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 8.25 (s, 1H), 12.97 (br s, 1H, exchangeable with D_2O); MS m/z (+ cESI): 315.11 $(M+H)^+$. Anal. calcd. for $C_{21}H_{14}O_3$ (%): C, 80.24; H, 4.49. Found C, 80.35; H, 4.56.

Typical Procedure for the Preparation of Acrylates: Synthesis of Ethyl (2*Z*)-3-Dibenzo[*b*,*d*]furan-4-yl-2-phenylacrylate (3a)

Conc. sulfuric acid (0.5 ml, 0.1 mmol) was added to a stirred solution of (2*Z*)-3-dibenzo[*b*,*d*]furan-4-yl-2-phenylacrylic acid (9.3 g, 29.586 mmol) in ethanol (50 ml), and the mixture was refluxed for 18 h under nitrogen atmosphere. The ethanol was evaporated under reduced pressure, and the residue obtained was diluted with ethyl acetate (50 ml) and water (50 ml). The layers were separated, and the aqueous layer was extracted

with ethyl acetate (25 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (50 ml) and water (50 ml). The ethyl acetate solution was dried over anhydrous sodium sulfate. The solid obtained after evaporation of the solvent was crystallized from ethyl acetate and hexane to 9.8 g (97%) white solid; IR (KBr) 3047, 2985, 1707, 1450, 1417, 1236, 1190, 1027, 843 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.26 (t, $J = 6.9$ Hz, 3H), 4.26 (q, $J = 6.9$ Hz, 2H), 6.77 (d, $J = 7.8$ Hz, 1H), 7.09 (t, $J = 7.8$ Hz, 1H), 7.22–7.25 (m, 2H), 7.35–7.37 (m, 3H), 7.41 (dt, $J = 0.6$, 7.8 Hz, 1H), 7.55 (dt, $J = 1.2$, 6.3 Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 8.05 (dd, $J = 1.2$, 6.6 Hz, 1H), 8.13 (dd, $J = 0.9$, 6.9 Hz, 1H), 8.24 (s, 1H); MS m/z (+cESI): 343.22 $(M+H)^+$. Anal. calcd. for $C_{23}H_{18}O_3$(%): C, 80.68; H, 5.30. Found C, 80.77; H, 5.39.

Typical Procedure for Ester Reduction: Synthesis of (2*Z*)-3-Dibenzo[*b*,*d*]furan-4-yl-2-phenylprop-2-en-1-ol (4a)

To a stirred and cooled (−78 °C) solution of ester **3a** (9.7 g, 28.331 mmol) in dry THF (60 ml), a 20% toluene solution of diisobutylaluminium hydride (50.4 ml, 70.826 mmol) was added, and the mixture was stirred at this temperature for 30 min. The reaction mixture was then quenched with water (20 ml) and diluted with EtOAc (50 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (25 ml). The combined organic layers were washed with water (3 × 50 ml) followed by brine (20 ml). The solution was dried over anhydrous sodium sulfate. The solvent was evaporated to give 8.45 g (99%) of **4a** as a white solid. IR (KBr) 3244, 3051, 2945, 1451, 1418, 1186, 1029 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.35 (d, $J = 4.5$ Hz, 2H), 5.44 (t, $J = 3.6$ Hz, 1H, exchangeable with D_2O), 6.79 (d, $J = 7.2$ Hz, 1H), 7.03 (t, $J = 7.8$ Hz, 1H), 7.13 (s, 1H), 7.21 (d, $J = 8.1$ Hz, 2H), 7.29–7.32 (m, 3H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.88 (d, $J = 7.5$ Hz, 1H), 8.10 (d, $J = 7.2$ Hz, 1H); MS m/z (-cESI): 299.32 $(M-H)^-$. Anal. calcd. for $C_{21}H_{16}O_2$(%): C, 83.98; H, 5.37; Found C, 84.08; H, 5.45.

Typical Procedure for Eschenmoser–Claisen [3,3]-sigmatropic Rearrangement: Synthesis of 3-Dibenzo[*b*,*d*]furan-4-yl-*N*,*N*-dimethyl-4-phenylpent-4-enamide (5a)

To a stirred solution of compound **4a** (500 mg, 1.664 mmol) in toluene, *N*,*N*-dimethylacetamide dimethyl acetal (333 mg, 2.500 mmol) and TBAF · $3H_2O$ (52.69 mg, 0.116 mmol) were added, and the mixture was refluxed for 3 h under nitrogen atmosphere. The reaction mixture was

then cooled to room temperature and diluted with ethyl acetate (50 ml). The organic layer was washed with water (3×50 ml) and brine (10 ml) and dried over anhydrous sodium sulfate. The residue obtained after evaporation of the solvent was purified by silica-gel column chromatography using a mixture of ethyl acetate–petroleum ether as eluent to give 560 mg (91%) of **5a** as a white solid; IR (KBr) 3054, 2920, 1634, 1493, 1449, 1419, 1399, 1183, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85 (s, 3H), 2.93 (s, 3H), 3.03–3.10 (m, 2H), 5.11 (s, 1H), 5.25 (br s, 1H), 5.45 (s, 1H), 7.20–7.38 (m, 6H), 7.44–7.55 (m, 3H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.78 (d, $J = 6.9$ Hz, 1H), 7.91 (d, J = 6.9 Hz, 1H); MS m/z (+cESI): 370.46 $(M + H)^+$. Anal. calcd. for $C_{25}H_{23}NO_2$(%): C, 81.27; H, 6.27; N, 3.79. Found C, 81.18; H, 6.35; N, 3.85.

ACKNOWLEDGMENTS

The authors thank Glenmark Pharmaceuticals Limited for granting permission to carry out the present research work.

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