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A practical and expedient synthesis of 2-heterocycle (C–N bond) substituted 4-oxo-4-arylbutanoates

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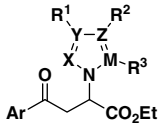
Dedicated to Professor E. J. Corey and Professor Richard C. Larock

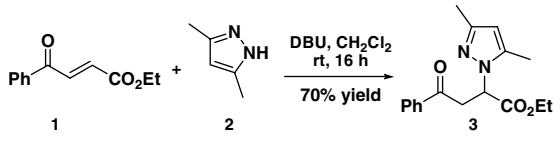
Abstract—A practical and expedient synthesis of the titled compounds is described. Using the same simple procedure (DBU was reacted with the mixture of an alkynol and a nitrogen heterocycle in CH_2Cl_2 at rt for 16 h), a wide variety of diverse NH-containing nucleophiles such as pyrazoles, indazoles, indoles, imidazoles and benzoimidazole, oxazolidinone and benzooxazolone, triazoles, phthalimides, and *N*-formyl anilines, have been reacted with 4-aryl-4-hydroxy-alkynyl esters to afford good yields of desired products. This reaction proceeded by the DBU catalyzed redox isomerization of ethyl 4-aryl-4-hydroxybut-2-ynoate to (*E*)-ethyl 4-aryl-4-oxobut-2-enoate, followed by the DBU catalyzed aza-Michael reactions with the isomerized product in one-pot.

The importance of nitrogen containing heterocyclic compounds in medicine can be very well appreciated by looking at the structures of many marketed drugs.[1] It is important that general methods to synthesize or to modify such compounds are developed. One such reaction is the aza-Michael reaction of NH-containing heterocycles and unsaturated aldehydes, ketones, esters, and others. There are many very recent reports on this reaction focused on using different reagents to catalyze or mediate this reaction,[2] or under some specific conditions.[3] Asymmetric version of this reaction has been rare,[4] although the asymmetric aza-Michael reaction of amines (NHR^1R^2; R^1, R^2 = alkyl, aryl, OBn, H) have been well developed.[5] Despite these many interesting and useful developments, no single method has found success with a variety of diverse NH-containing heterocycles (pyrazoles, indazoles, imidazole, benzoimidazole, indoles, oxazolidinone, and benzooxazolone, triazoles, phthalimides, etc.).

As part of a medicinal chemistry project, we needed to make 2–heterocycle (C–N bond) substituted 4-oxo-4-arylbutanoates as shown below. There are several reports of 2-heterocycle (C–N bond) substituted 4-oxo-4-arylbutanoic acids, useful for their antibacterial activity, made by the reaction of 4-oxo-4-arylbutenoic acids with heterocycles, such as pyrazoles,[6] anilines,[7] imidazoles



and 1,2,4-triazoles.[8] Encouraged by these reports, alkenoate **1** was reacted with pyrazole **2** in CH_2Cl_2 at rt for 16 h with different bases, such as DABCO, DBU, pyridine, and Et_3N. To my delight, when DBU was used as the base, **3** was formed in 70% yield, while DABCO, pyridine and Et_3N all gave incomplete conversion and lower yields.



(1)

Although **1** was commercially available, other aryl substituted examples have to be made in several steps.[9] In 1949, Nineham and Raphael[10] reported the first example of base catalyzed redox isomerization of

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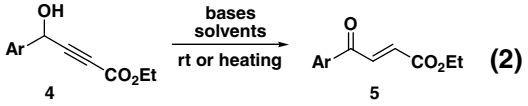
4-aryl-4-hydroxy-2,3-alkynyl esters **4** to *trans*-4-aryl-4-oxobut-2-enoate **5** [Et_3N (neat), rt, 16 h, then distillation. Ar = Ph, 94% yield]. In the beginning of 2006, Koide and Sonye[11] described a DABCO (10–20 mol %) catalyzed redox isomerization in DMSO (rt, 4 h, Ar = Ph, 72% yield). Since alkynols **4** are more readily accessible than alkenoates **5**, by the reaction of ethyl propionate with aromatic aldehydes,[12] I was interested in the direct reaction of alkynols **4** with NH-containing heterocycles to form compounds like **3**.

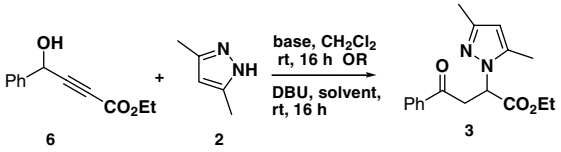


4 5 (2)

To find the best conditions for this direct transformation, the reaction of alkynol **6** and pyrazole **2** was used as a model reaction. Different bases and solvents were screened and the results are summarized in Table 1. Although DBU, Cy_2NMe, Et_3N, DABCO, DMAP, and Cs_2CO_3 all gave complete conversion, only DBU afforded **3** in a good isolated yield (73%) in CH_2Cl_2. When pyridine or K_2CO_3 was used as the base, <20% of conversion was observed. Various solvents were then evaluated with DBU as base. PhMe, THF, EtOAc all afforded **3** in ca. 55% yield, while acetone gave **3** in 31% yield and MeOH produced no product.

As a result of these studies, a general procedure was determined to be as follows: DBU (1.1 mmol) was added drop-wise at rt to a mixture of alkynol **4** (1.0 mmol) and a NH-containing heterocycle (2.0 mmol) in CH_2Cl_2 (5 mL or 10 mL, depending on the solubility of the NH-containing heterocycle in CH_2Cl_2). The mixture was stirred at rt for 16 h and then directly poured onto a silica gel column eluting with EtOAc/hexanes to afford the desired products.

Table 1. The base and solvent optimization of reaction **6** and **2** to form **3**[a]



6 2 3

Entry	Base (CH_2Cl_2 as solvent)	Solvent (DBU as solvent)	Conversion (%)	Yield[b] (%)
1	DBU	CH_2Cl_2	100	73
2	Cy_2NMe	CH_2Cl_2	100	10
3	Et_3N	CH_2Cl_2	100	20
4	DBACO	CH_2Cl_2	100	0[c]
5	DMAP	CH_2Cl_2	100	0[c]
6	Pyridine	CH_2Cl_2	<20[d]	0[c]
7	K_2CO_3	CH_2Cl_2	<20[d]	0[c]
8	Cs_2CO_3	CH_2Cl_2	100	20
9	DBU	PhMe	100	56
10	DBU	THF	100	58
11	DBU	Acetone	100	31
12	DBU	EtOAc	100	56
13	DBU	MeOH	100	0[c]

[a] A base was added to the solution of ethyl 4-hydroxy-4-phenylbut-2-ynoate (0.5 mmol) and 3,5-dimethyl-1H-pyrazole (1.0 mmol) in a solvent (2.5 mL) in a 10 mL of vial at rt and the mixture was stirred at rt for 16 h.

[b] Isolated yields after flash chromatography.

[c] No compound **3** was formed by TLC analysis.

[d] By ^1H NMR integration using anisole as the internal standard.

The products formed using this general procedure are summarized in Table 2. Pyrazoles with substituents of different electronic and steric properties could be used for this reaction. Compounds **7**, **9**, **10**, **11**, **13**, and **15** were all formed as the sole products, while **8a–b**, **14a–b**, and **16a–b** were all formed as a mixture of two regioisomers. This indicated that regioselectivity was controlled by both steric hindrance and substituent electronegativity. Alkynols **4** with different Ar substitution such as 4-H, 4-MeO and 4-MeO_2C could also be used in this reaction with roughly equal efficiency (**7** vs **13**, **15**). Indazoles closely followed the pattern of pyrazoles. Compounds **17** and **20** were formed as the sole products, while **18a–b** and **19a–b** were formed as a mixture of two isomers in the same ratio due to the presence of 7-Me in the indazole core.

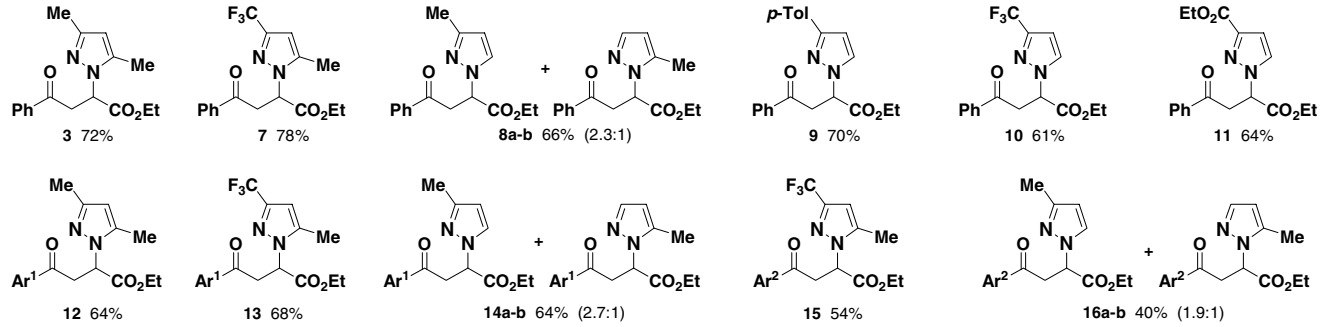
1,2,4-Triazole also reacted well, but 1,2,3-triazole and benzotriazole did not give any desired products nor isomerized product **5** despite 100% conversion (**21–23**), instead complex mixtures were formed in both cases. Electron rich indoles afforded no products, but electron-deficient indoles gave good yield of product probably due to the better stability of the nucleophiles after deprotonation (**24** vs **25**). It was very pleasing to find that benzoxazolone and oxazolidinone also afforded desired products in good yields (**26–28**) since they are normally considered poor nucleophiles.[2] When a chiral oxazolidinone was used, chiral induction was not observed (**27**). The low yield of **28** was because of the stability of benzooxaolone in the presence of strongly basic DBU. It was equally satisfying to see that strong basic and weak nucleophiles such as imidazole and benzoimidazole[2] could also be used in this reaction to afford the desired products, albeit in lower yields (**29–30**). Finally, acyl anilines, phthalimides and benzoimidazolones also reacted with alkynols **4** to afford products in good yields (**31–33**). However, aniline or 1-methylimidazolidin-2-one did not produce any desired product despite 100% conversion (**34–35**). In the former reaction, a complex mixture was formed and in the latter reaction, isomerized product **5** was formed in 52% yield.

The structures of applicable compounds were determined primarily by NMR analysis. The chemical shift of each proton and carbon was assigned by ^1H, ^{13}C, DEPT, COSY, and HMQC. The connectivity of key protons and carbons were determined by HMBC, thus the structures of compounds (Chart 1) with the assistance of 1D NOE. See Supplementary data for details.

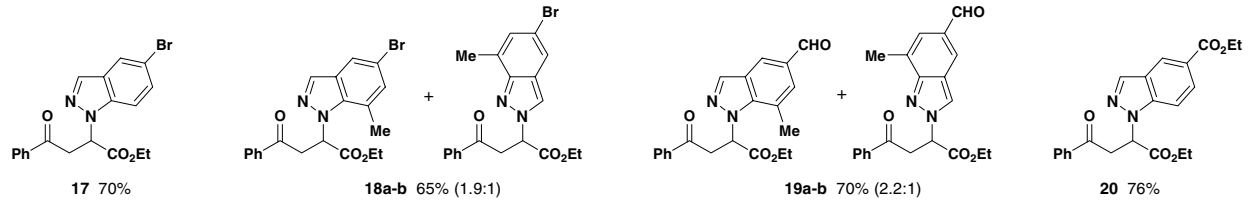
Since DBU was required as the base, the employment of acetyl containing nucleophiles such as 3-acetylpyrazole, AcNHPh, and indolin-2-one, resulted in the decomposition of the starting alkynols. Tetrazoles did not partici-

Table 2. The products with yields and regioselectivity produced by the general procedure

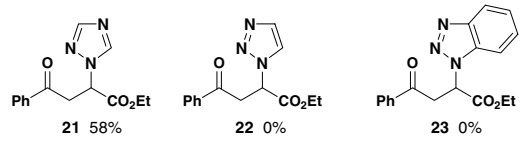
Pyrazoles:



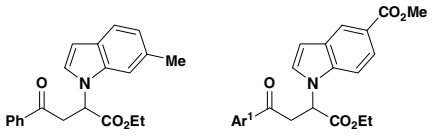
Indazoles:



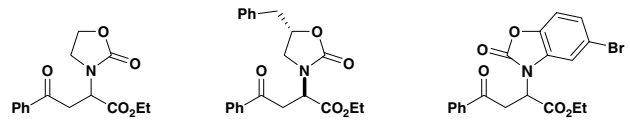
Triazoles:



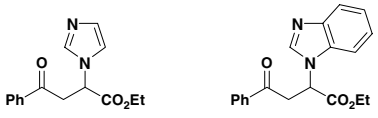
Indoles:



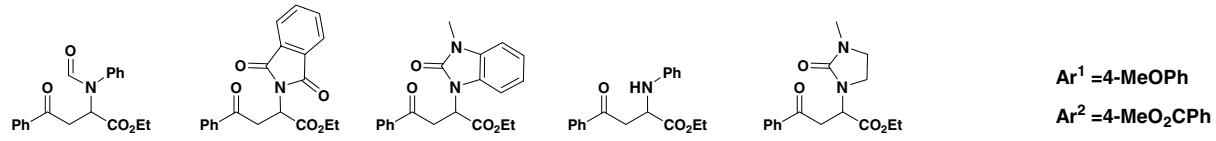
Benzooxazolone and oxazolidinone:



Imidazoles and Benzoimidazoles:



Acyl anilines, phthalimides, and benzoimidazolones



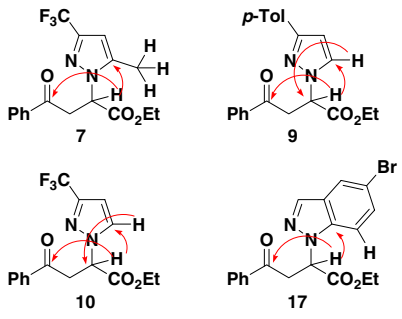
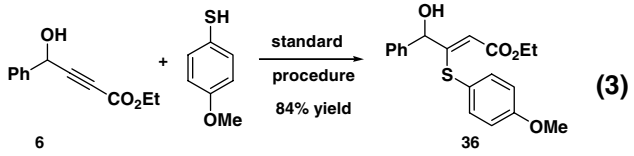


Chart 1. Structural determination of products by NMR (red arrows showed key hydrogen–carbon connectivity determined by HMBC).

pate in the reaction due to their strong acidity and the starting alkynol was recovered unchanged. When *N*-Boc-aniline or carbazole was used as a nucleophile, only the rearranged product **5** was formed in 65% and 70% isolated yields, respectively, conjugate addition did not proceed probably due to steric crowding around the nucleophile.

To further elucidate the mechanism of this reaction, 4-MeO–PhSH, a highly-reactive nucleophile, was coupled with alkynol **6** under the standard conditions, with formation of the direct conjugate addition product **36**. This suggests that addition of thiophenol to alkynol **6** was complete in 2 min before the addition of DBU which could not facilitate the isomerization process because

of the presence of β-ArS moiety.[13] When alkynol **6** was treated with DBU under the standard procedure but without any nucleophiles, isomerized product **5** was formed in 50% yield. This reaction provided easy access to this class of compounds exemplified by compound **36**, which was prepared previously via a much longer reaction sequence.[14]



(3)

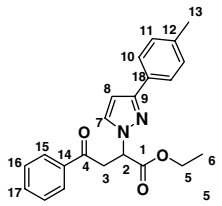
I believe that the reactions proceeded via two steps, redox isomerization followed by conjugate addition. DBU was required for the first step as well as the conjugate addition step. This one-pot process provided products more conveniently and in higher yields than the discrete two step process, probably due to the in situ formation of *trans*-4-aryl-4-oxobut-2-enoate, which is not very stable in the presence of DBU.

In conclusion, a practical and expedient synthesis of 2-heterocycle (C–N bond) substituted 4-oxo-4-arylbutanoates was described. The simplicity of the procedure and its applicability to a wide variety of diverse NH-containing heterocycles are key features of this procedure. Because two equivalents of heterocycles was used in the reaction and there was <20% of conversion when pyridine was used as the base, this general procedure shall find wider applications in reactions involving more complex starting materials, such as 4-heteroaryl-4-hydroxy-2,3-alkynyl esters, whose products could be of interest as potential drug targets.

Experimental

General procedure for the formation of 2-heterocycle (C–N bond) substituted 4-oxo-4-arylbutanoates. Preparation of 9

1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU, 0.164 mL, 1.100 mmol) was added drop-wise at rt to the solution of ethyl 4-hydroxy-4-phenylbut-2-ynoate (0.204 g, 1 mmol) and 3-*p*-tolyl-1*H*-pyrazole (0.316 g, 2.000 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 16 h and it was poured onto a silica gel column. Flash chromatography eluenting with EA/hexanes (1:7) afforded ethyl 2-(3-phenyl-2-(3-*p*-tolyl-1*H*-pyrazol-1-yl)oxiran-2-yl)acetate (0.254 g, 0.700 mmol, 70% yield) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.98–8.02 (m, 2H, H15), 7.66 (d, $J = 7.93$ Hz, 2H, H10), 7.61 (d, $J = 2.44$ Hz, 1H, H7), 7.57 (t, $J = 7.32$ Hz, 1H, H17), 7.46 (t, $J = 7.78$ Hz, 2H, H16), 7.17 (d, $J = 7.90$ Hz, 2H, H11), 6.53 (d, $J = 2.44$ Hz, 1H, H8), 5.63 (t, $J = 6.41$ Hz, 1H, H2), 4.23 (q, $J = 7.12$ Hz, 2H, H5), 4.07 (dd, $J = 18.0$, 6.41 Hz, 1H, H3), 3.96 (dd, $J = 18.0$, 6.72 Hz, 1H, H3), 2.35 (s, 3H, H13), 1.22 (t, $J = 7.17$ Hz, 3H, H6). ^{13}C NMR



9

(126 MHz, $CDCl_3$) δ ppm 196.43 (C4), 169.21 (C1), 152.26 (C9), 137.47 (C12), 136.39 (C14), 133.64 (C17), 131.82 (C7), 130.78 (C18), 129.27 (C16), 128.76 (C11), 128.33 (C15), 125.77 (C10), 103.13 (C8), 62.15 (C5), 60.01 (C2), 40.59 (C3), 21.31 (C13), 14.09 (C6). LRMS 363.18 (MH^+), calcd for $C_{22}H_{22}N_2O_3$ 362.16.

Acknowledgements

I thank Drs. John Macor and Gene Dubowchik for their constant support during the course of this study and their critical reading of the manuscript and Dr. Yingzi Wang for assistance in 2D NMR analysis of compound **9**.

Supplementary data

^{1}H, ^{13}C NMR (data and spectra) and LRMS data for all compounds, structural determinations (by COSY, DEPT, HMQC, HMBC, and 1D NOE) of all applicable compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.101.

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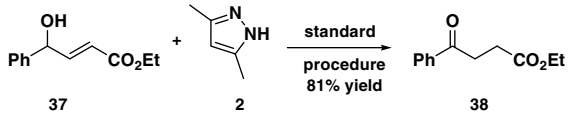
13. When alkenol **37** was reacted with pyrazole **2** under the standard procedure, ketone **38** was formed in 81% yield, via DBU mediated isomerization followed by tautermization of the resulting enol.



37 2 38

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