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3,4,5,6-TETRASUBSTITUTED 2-PYRIDONE SYNTHESIS VIA NUCLEOPHILIC ADDITION OF ACTIVE METHINE COMPOUNDS TO DIALKYNYL IMINES DIRECTED TO THE SYNTHESIS OF (-)-A58365A

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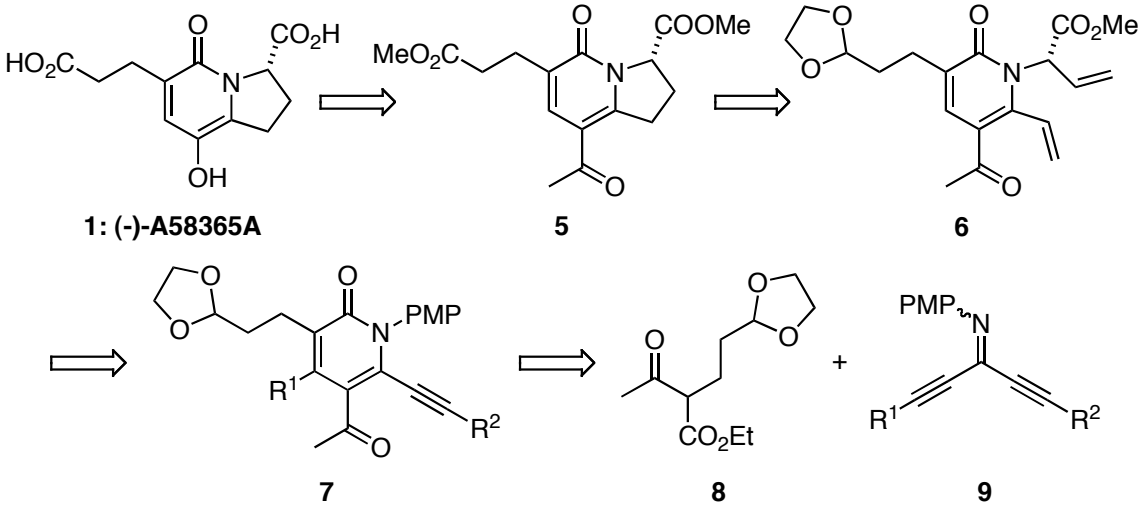
Abstract–3,4,5,6-Tetrasubstituted-2-pyridone synthesis via nucleophilic addition of active methine compounds to dialkynyl imines directed to the synthesis of (-)-A58365A has been developed. The reaction of active methine compounds such as malonic esters or β-keto esters to dialkynyl imines provided 3,4,5,6-tetrasubstituted-2-pyridones in moderate to good yields.

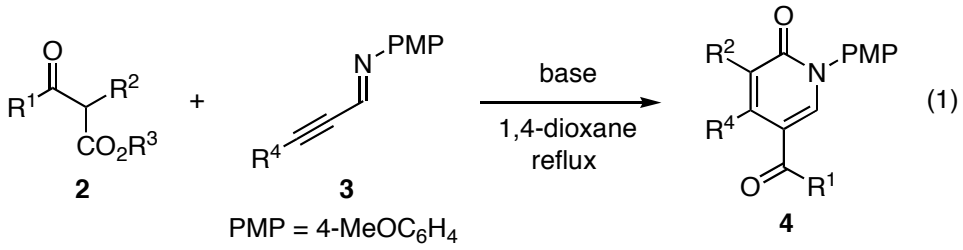
There are many biologically active compounds containing a 2-pyridone structure.[1] (-)-A58365A (**1**) having a 2-pyridone structure is one of them, which was obtained from a fermentation broth of the bacterium *Streptomyces chromofucus* in the Eli Lilly laboratories and found to be an angiotensin-converting enzyme inhibitors at nanomolar concentrations (Scheme 1).[2]



Scheme 1. Synthetic Plan for the Synthesis of (-)-A58365A

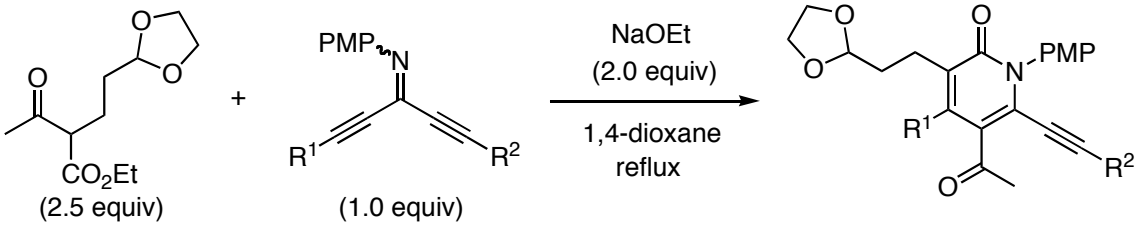
This paper is dedicated to Professor Satoshi Omura on the occasion of his 70th birthday.

This property makes it of potential value as a lead compound for the design of drugs to control blood pressure. In connection with the synthesis of (-)-A58365A (**1**), the development of the synthetic methods of functionalized 2-pyridone is important as a result of the large number of biologically active compounds containing a 2-pyridone structure and also as dienes in Diels-Alder cycloadditions.[3-5] We have already reported 5-alkoxycarbonyl-2-pyridone and 5-acetyl-2-pyridone (**4**) synthesis via the nucleophilic addition of malonic esters or β-keto esters (**2**), respectively, to alkynyl imines (**3**) derived from 2-alkynals (Eq. 1).[6]



On the basis of these results, we planed a synthesis of (-)-A58365A (**1**) as shown in Scheme 1.[7] Padwa group has already reported the total synthesis of (-)-A58365A via 2-pyridone intermediate (**5**),[7b] and therefore, the preparation of the 2-pyridone (**5**) provides a formal synthesis of (**1**). 2-Pyridone intermediate (**5**) would be obtained from (**6**) via olefin metathesis. The 2-pyridone (**7**) would be synthesized using our 2-pyridone synthesis via nucleophilic addition of β-keto ester (**8**)[8] to dialkynyl imine (**9**).

Table 1. 2-Pyridone (**7**) Synthesis via Nucleophilic Addition of (**8**) to (**9**)



9a: $R^1 = R^2 = H$
9b: R^1 =TMS, R^2 = TBDMS
9c: R^1 =H, R^2 = TBDMS

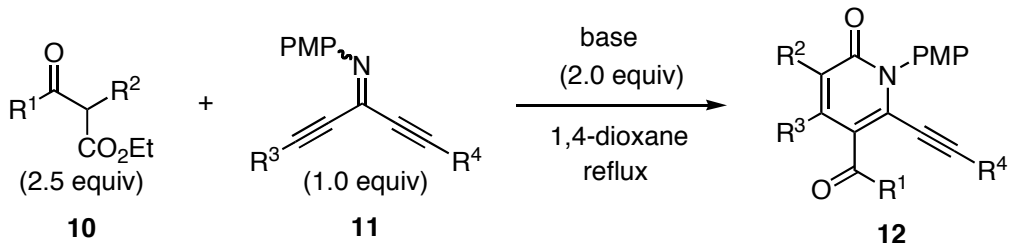
7a: $R^1 = R^2 = H$
7b: R^1 =TMS, R^2 = TBDMS
7c: R^1 =H, R^2 = TBDMS

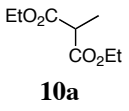
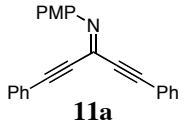
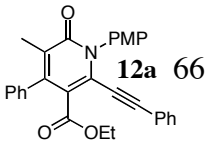
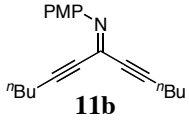
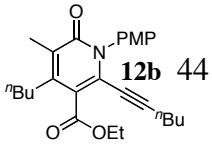
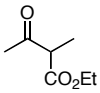
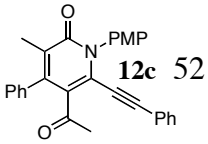
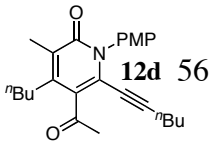
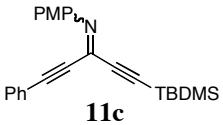
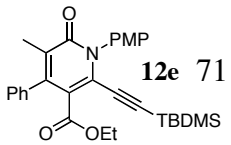
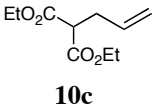
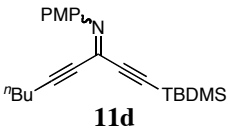
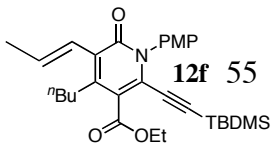
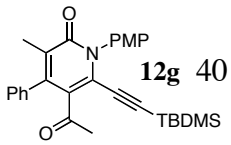
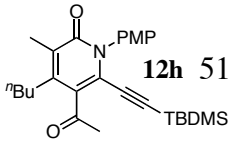
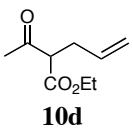
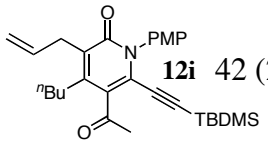
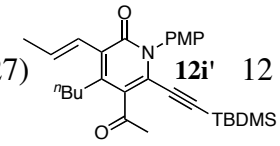
Entry	Imine	Time (h)	Product	Yield (%)
1	**9a**	5.5	**7a**	8
2	**9b**	23.5	**7b**	7
3	**9c**	2.5	**7c**	9
4[a]	**9c**	5.5	**7c**	51

[a] The imine (**9c**) was added dropwise using a syringe pump to the solution of β-keto ester sodium salt (**8**) in 1,4-dioxane under reflux.

We investigated the effect of the substituents R^1 and R^2 of dialkynyl imine (**9**) (Table 1).[9] When the reaction of β-keto ester (**8**) with imine (**9a**) was carried out in 1,4-dioxane in the presence of NaOEt under reflux, the desired 2-pyridone (**7a**) was obtained in 8% yield, because the imine (**9a**) decomposed under

Table 2. 2-Pyridone Synthesis Using Dialkynyl Imines



Entry	**10**	**11**	Base	Time (h)	**12**, %yield [a]
1	 **10a**	 **11a**	NaOEt	6	 **12a** 66
2	**10a**	 **11b**	NaOEt	9	 **12b** 44
3	 **10b**	**11a**	NaOEt	14	 **12c** 52
4	**10b**	**11b**	NaH	14	 **12d** 56
5	**10a**	 **11c**	NaH	1	 **12e** 71
6	 **10c**	 **11d**	NaH	21	 **12f** 55
7	**10b**	**11c**	NaOEt	7	 **12g** 40 (28)
8	**10b**	**11d**	NaOEt	12	 **12h** 51 (31)
9	 **10d**	**11d**	NaH	21	 **12i** 42 (27)  **12i'** 12

[a] Isolated yields. Yields of the recovered imines in parentheses.

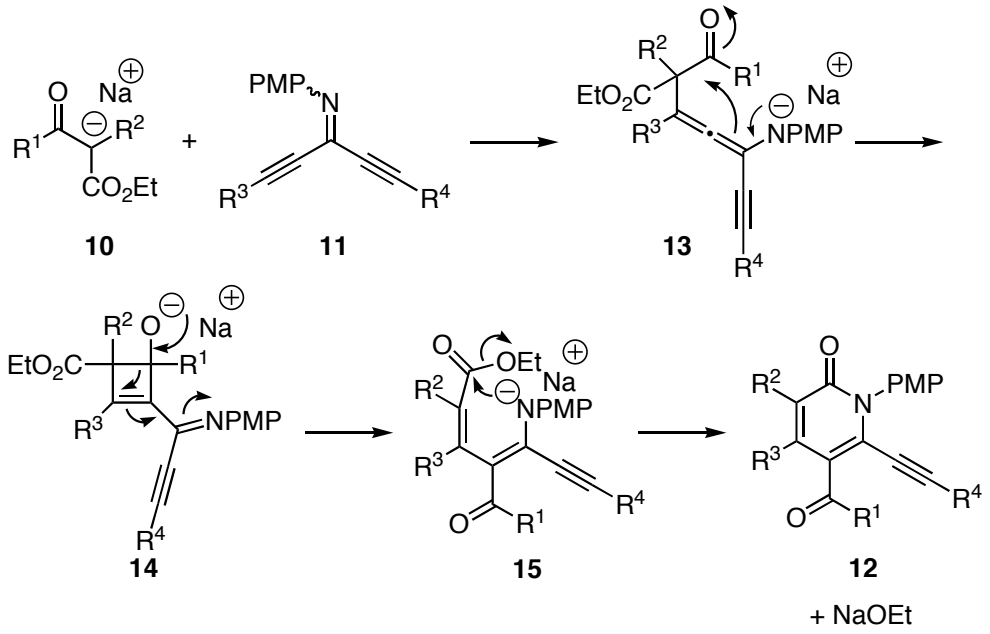
the reaction conditions (Entry 1). The reaction of imine (**9b**) gave the 2-pyridone (**7b**) in 7% yield along with the recovered imine (**9b**) in 84% yield since the initial 1,4-addition did not sufficiently proceed due to the steric bulk of the imine (**9b**). Use of imine (**9c**) afforded 2-pyridone (**7c**) in 9% yield (Entry 3). The reaction was very sensitive to the concentration of the imine (**9**). When the imine (**9c**) in 1,4-dioxane was added dropwise using a syringe pump to the solution of the sodium salt of β-keto ester (**8**) in 1,4-dioxane under reflux, 2-pyridone (**7c**) was obtained in 51% yield (Entry 4).

Next, we investigated the scope of substrates in a 3,4,5,6-tetrasubstituted-2-pyridone (**12**) synthesis via nucleophilic addition of active methine compounds (**10**) to dialkynyl imines (**11**). The results are summarized in Table 2.

First, we examined the reaction of a symmetrical dialkynyl imine with an active methine compound. The reaction of dialkynyl imine (**11a**) with the sodium salt of diethyl methylmalonate (**10a**) proceeded smoothly in 1,4-dioxane under reflux for 6 h to give the desired 2-pyridone (**12a**) in 66% yield (Entry 1).[10] In the case of ethyl 2-methyl-3-oxobutanoate (**10b**), 2-pyridone (**12c**) was obtained in 52% yield (Entry 3). Not only an aromatic group but also an aliphatic counterpart as a substituent of imine (**11**) worked well (Entries 2 and 4). Next, we examined the reaction of an unsymmetrical dialkynyl imine.[9] The 1,4-addition reaction of the sodium salt of diethyl methylmalonate (**10a**) to unsymmetrical dialkynyl imine (**11c**) proceeded regioselectively to give only 2-pyridone (**12e**) in 71% yield where the less hindered sp carbon reacted preferentially (Entry 5). Even increasing the steric bulk of the nucleophile as in the case with diethyl allylmalonate (**10c**), 2-pyridone (**12f**) possessing a double bond isomerized internally was obtained in 55% yield (Entry 6). The use of ethyl 2-allyl-3-oxobutanoate (**10d**) gave 2-pyridone (**12i**) in 42% yield accompanied by 2-pyridone (**12i'**) in 12% yield (Entry 9).

We propose a plausible reaction mechanism as shown in Scheme 2. Methalloallenamine (**13**) would be generated via a regioselective 1,4-addtion reaction of the sodium salt of active methine compound (**10**) to dialkynyl imine (**11**) and undergoes an intramolecular cyclization to give cyclobutenoxide intermediate (**14**). The cyclobutenoxide intermediate (**14**) would be transformed into metalloenamine (**15**) via a ring-opening reaction, and the subsequent cyclization would give 3,4,5,6-tetrasubstituted 2-pyridone (**12**).

In summary, we have found a 3,4,5,6-tetrasubstituted-2-pyridone synthesis via nucleophilic addition of active methine compounds to dialkynyl imines. Numerous methods for the synthesis of 2-pyridones have been reported. However, the present 2-pyridone synthesis is an attractive alternative method because substituted malonic esters, β-keto esters (**10**), and dialkynyl imines (**11**) are readily available, respectively and alkynyl groups in 2-pyridones can also be easily transformed into alkenyl and alkyl groups. The synthesis of (-)-A58365A from 2-pyridone (**7c**) is now in progress.



Scheme 2. Plausible Reaction Mechanism

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. For recent examples, see: a) M.-L. Bennasar, E. Zulaica, C. Juan, Y. Alonso, and J. Bosch, *J. Org. Chem.*, 2002, **67**, 7465. b) P. Fossa, G. Menozzi, P. Dorigo, M. Floreani, and L. Mosti, *Bioorg. Med. Chem.*, 2003, **11**, 4749.
2. A. H. Hunt, J. S. Mynderse, S. K. Samlaska, D. S. Fukuda, G. M. Maciak, H. A. Kirst, J. L. Occolowitz, J. K. Swartzendruber, and N. D. Jones, *J. Antibiot.,* 1988, **41**, 771, and references therein.
3. K. Afarinkia, V. Vinader, T. D. Nelson, and G. H. Posner, *Tetrahedron*, 1992, **48**, 9111.
4. For reviews, see: (a) A. McKillop and A. J. Boulton, 'Comprehensive Heterocyclic Chemistry,' Vol. 2, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, New York, 1984, Part 2A, p 67. (b) G. Jones, 'Comprehensive Heterocyclic Chemistry,' Vol. 2, ed. by A. R. Katritzky, C. W. Rees, Pergamon Press, New York, 1984, Part 2A, p 395.
5. For recent examples of the synthesis of functionalized 2-pyridones, see: (a) N. Nishiwaki, H. Morimura, K. Matsushima, M. Tamura, and M. Ariga, *Heterocycles*, 2003, **61**, 19. (b) W. Li, Y. Chen, and Y. Lam, *Tetrahedron Lett.*, 2004, **45**, 6545. (c) S. Wang, J. Pan, Y. Hu, and H. Hu,

Synthesis, 2005, 753.

6. (a) I. Hachiya, K. Ogura, and M. Shimizu, *Org. Lett.*, 2002, **4**, 2755. (b) I. Hachiya, K. Ogura, and M. Shimizu, *Synthesis*, 2004, 1349. We also reported the synthesis of bicyclic compounds containing a 2-pyridone structure by addition of malonic esters to alkynylpyridines pyrimidine, and thiazoles. See: (c) I. Hachiya, M. Atarashi, and M. Shimizu, *Heterocycles*, 2006, **67**, 523.
7. For some syntheses, see: (a) F. G. Fang and S. Danishefsky, *Tetrahedron Lett.*, 1989, **30**, 3621. (b) A. Padwa, S. M. Sheehan, and C. S. Straub, *J. Org. Chem.*, 1999, **64**, 8648. (c) A. Reichelt, S. K. Bur, and S. F. Martin, *Tetrahedron*, 2002, **58**, 6323, and references therein.
8. R. Grigg, J. Markandu, S. Surendrakumar, M. Thornton-Pett, and W. J. Warnock, *Tetrahedron*, 1992, **48**, 10399.
9. Unsymmetrical imines were geometrical mixtures of C=N bond.
10. A typical experimental procedure of the reaction of dialkynyl imines with active methine compounds: To NaOEt (27.2 mg, 0.400 mmol) was added a solution of diethyl methylmalonate (**10a**) (87.1 mg, 0.500 mmol) in 1,4-dioxane (2.0 mL) and a solution of dialkynyl imine (**11a**) (67.1 mg, 0.200 mmol) in 1,4-dioxane (2.0 mL) at room temperature. The reaction mixture was stirred under reflux for 6 h and then cooled to room temperature. Brine (10 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were dried over sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (*n*-Hex/EtOAc = 1/1, as an eluent) to give 3,4,5,6-tetrasubstituted-2-pyridone (**12a**) (61.0 mg, 66%) as a light yellow solid. Mp 153.5-155.5 °C (white mica-like crystals, *n*-Hex-EtOAc). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.38-7.47 (m, 3H), 7.20-7.36 (m, 7H), 7.01-7.08 (m, 4H), 3.96 (q, *J* = 7.3 Hz, 2H), 3.87 (s, 3H), 2.02 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 166.2, 162.6, 159.7, 146.8, 137.3, 132.1, 131.5, 129.5, 129.3, 129.2, 128.3, 128.3, 128.1, 128.1, 127.9, 121.1, 119.4, 114.4, 101.8, 81.2, 61.4, 55.5, 14.7, 13.6. IR (KBr): 3051, 2986, 2953, 2934, 2838, 2211, 1725, 1653, 1608, 1590, 1511, 1465, 1442, 1389, 1369, 1320, 1298, 1250, 1172, 1156, 1107, 1075, 1026, 1011, 832, 799, 764, 702, 691 cm^{-1}. MS (ESI) m/z: 464 $(M+H)^+$.