Pergamon

Tetrahedron Letters 41 (2000) 1147–1150

TETRAHEDRON LETTERS

A practical and efficient intramolecular Michael addition of ureas to α,β-unsaturated esters

Zhili Xin,* Zhonghua Pei, Tom von Geldem and Michael Jirousek

Abbott Laboratories, Metabolic Disease Research, 100 Abbott Park Road, Abbott Park, IL 60064-6098, USA

Received 11 October 1999; accepted 29 November 1999

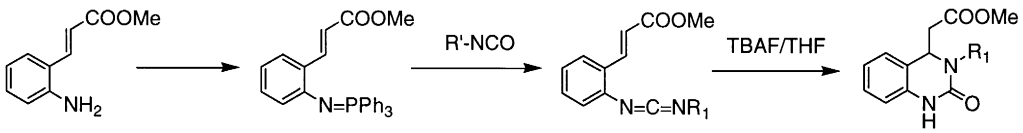
Abstract

A mild and efficient method is described for the synthesis of dihydroquinazoline derivatives via intramolecular *hetero*-Michael addition of ureas to ortho-substituted α,β-unsaturated esters in the presence of NaOH in THF with high chemical yield.

Keywords: cyclization; Michael addition; ureas; dihydroquinazolines.

Michael addition is a powerful method for the formation of carbon–carbon bonds under various conditions.[1] However, undesirable side reactions such as *retro*-Michael addition, auto-condensation and polymerization often limit the utility of heteroatom–carbon bond formation in the Michael reaction. There are a number of examples of *N*-conjugated Michael addition, for example, reactions involving amine,[2] lactam,[3] thiolactam,[4] carbodiimide[5] and guanidine nucleophiles.[6] Most of these reactions suffer from harsh reaction conditions and/or poor chemical yields. *Retro*-Michael reaction can be a major problem for *N*-conjugated additions in some cases.[3]

Dihydroquinazoline derivatives are an important class of hererocyclic compounds in pharmaceutical discovery research.[7] Although Molina's carbodiimide approach provide this class of compounds in moderate chemical yield,[5] the reaction conditions (carbodiimide:TBAF (tetrabutylammonium fluoride)=1:4) make it difficult to perform on a large-scale (Scheme 1). It has been noted that a major side-product was a urea resulting from hydrolysis of the carbodiimide.[5] This urea cannot be converted to the corresponding desired dihydroquinazoline derivative under Molina's reaction conditions.

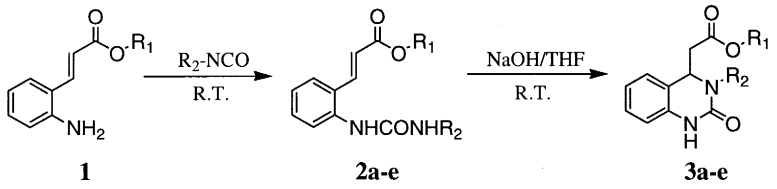


Scheme 1.

* Corresponding author. Tel: 1 847 935 7307; fax: 1 847 9381674; e-mail: zhili.xin@abbott.com (Z. Xin)

0040-4039/00/$ - see front matter
PII: S0040-4039(99)02283-2

We report here a direct conversion of urea to dihydroquinazoline derivative via intra-molecular Michael addition of a ureido–nitrogen anion to an α,β-unsaturated ester. These reactions are mediated by aqueous sodium hydroxide (NaOH) in tetrahydrofuran (THF), with high chemical yields under mild conditions (Scheme 2). This practical and efficient approach provides easy access to this type of heterocyclic compound, and is particularly amenable to scale up.



Scheme 2.

Aniline **1** reacted with isocyanates at room temperature to give the desired ureas **2a–e**, which were practically pure and were used in the following step without further purification. By treatment with aqueous NaOH in THF at room temperature, ureas **2a–e** underwent intramolecular Michael addition to an *ortho* substituted α,β-unsaturated ester affording dihydroquinazoline derivatives **3a–e**. Yields are generally quite high (> 90%). (Table 1).

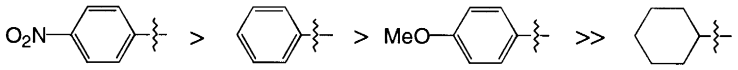
Table 1
Intramolecular *N*-conjugate addition of ureas to α,β-unsaturated esters

Entry	Ureas	R_1	R_2	NaOH (equiv)	ReactionTime	Products	Yield[a] (%)
1	**2a**	t-Butyl	C_6H_5	1.0	10 min	**3a**	91
				0.1	30 min		90
2	**2b**	t-Butyl	p-MeO-C_6H_4	1.0	1 h	**3b**	89
3	**2c**	t-Butyl	p-NO_2-C_6H_4	1.0	3 min	**3c**	92
4	**2d**	t-Butyl	Cyclohexyl	1.0	72 h	**3d**	62[b]
				0.1	72 h		trace
5	**2e**	Ethyl	C_6H_5	1.0	10 min	**3e**	90
				0.1	10 min		91
6	**2f**	t-Butyl	o-COOMe-C_6H_4	1.0	3 min	**3f**	96
				0.1	12 h		98
7	**2g**	Ethyl	o-COOMe-C_6H_4	1.0	3 min	**3g**	100
				0.1	12 h		99

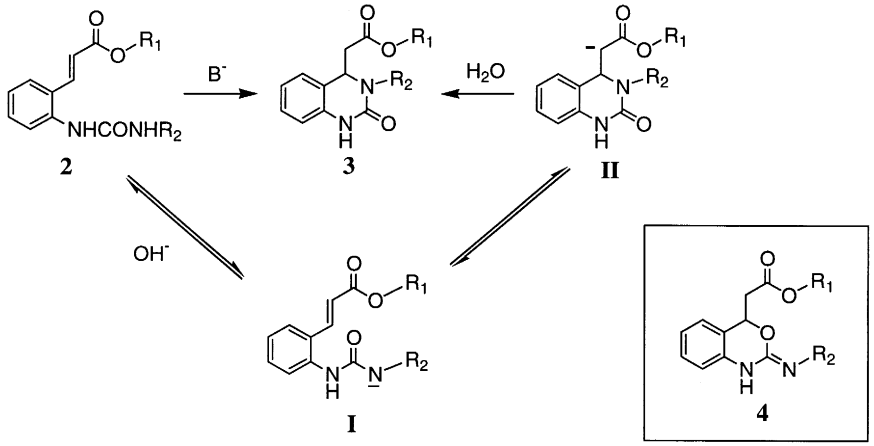
[a] All products gave satisfactory NMR, IR, MS and CHN microanalysis.
[b] Part of starting material was recovered.

Table 1 illustrates the influence of substitution pattern on the course of the cyclization. Cyclohexyl urea **2d** reacted sluggishly under standard conditions (entry 4) while aryl substituted urea gave almost quantitative yield within a few minutes. Although steric hindrance of the cyclohexyl over phenyl group[6]

may explain the results, subsequent studies suggest that the differences in reactivity may be due to electronic factors. *N*-Substitution with electron-withdrawing groups facilitated the reaction rate (entry 3), while electron-releasing groups decreased the reactivity (entry 2). It is interesting to note that although electron-withdrawing groups favor ureido–anion formation, the nucleophilicity of the *N*-anion is reduced due to favorable stabilization gained by electron-withdrawing group. On the other hand, electron-releasing groups should increase the nucleophilicity of the ureido–nitrogen anion for the Michael addition to the α,β-unsaturated ester, but the formation of the ureido–anion is more difficult. The dissociation of *N*-aromatic substituted acetamide proton is greatly affected by the σ value of the substituents with a ρ value around 4.1,[8] which implies that the aromatic substituent also plays an important role in the dissociation of ureido proton. The results indicate that the rate determining step is the deprotonation step, not the N–C bond formation step.

Order of reactivity: 

We also noticed that for a reactive urea, a catalytic amount of NaOH (0.1equiv.) is sufficient to drive the reaction to completion within a short period of time. It does, however, require a full equivalent of base to gain a good chemical yield in a reasonable time for a non-reactive urea (entry 4). This observation also implies that formation of the ureido anion is a crucial step for the cyclization, which is proposed to occur through the mechanism indicated in Scheme 3.

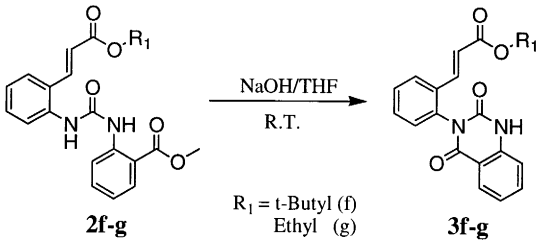


Scheme 3.

It is interesting to note that none of the alternative oxygen nucleophile Michael addition product **4** was isolated,[9] while this could be a problem in some other cases.[10] Whether this is due to a stereoelectronic factor or due to fast *retro*-addition of the oxygen–carbon linked intermediate is not clear at this time.

When a donor aromatic ring is substituted with an *ortho*-carboxylic ester, the competition between Michael addition of α,β-unsaturated ester moiety and cyclization onto the benzoic ester moiety favors the latter. Compounds **3f** and **3g** were obtained exclusively with the cinnamate moiety intact, when ureas **2f** and **2g** were treated with sodium hydroxide (Scheme 4). Since both cyclizations should be favored stereoelectronically,[11] a plausible explanation is that the relatively good reactivity of ester functionality towards the ureido–nitrogen anion drives the reaction toward the product **3**.

A typical procedure is as follows: To a solution of ethyl 2-aminocinnamate **1** (1.0 mmol, 191 mg) in diethyl ether (5 ml) was added phenyl isocyanate (1.0 mmol, 119 mg). The mixture was stirred at room temperature for 8 h. The precipitate was then filtered and washed with ether to give pure urea product **2e** (yield 82%). The urea derivative **2e** (0.1 mmol, 31 mg) was then dissolved in THF (1 ml), followed



Scheme 4.

by the addition of 1N aqueous NaOH (0.1 mmol (0.01 mmol for catalytic reactions)). The mixture was allowed to stir at room temperature for 10 min to complete the reaction. This was diluted with water and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and concentrated to obtain dihydroquinazoline derivative **3e** as a white solid (yield 91%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (t, J=7.1 Hz, 3H, CH_3), 2.54–2.75 (m, 2H, CH_2COO), 3.80–3.93 (m, 2H, $COOCH_2$), 5.26 (dd, J=4.9, 7.3 Hz, 1H, NCHPh), 6.88–6.96 (m, 2H), 7.14–7.30 (m, 3H), 7.41, 7.42 (s, 4H), 9.62 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 153.0, 140.7, 136.3, 129.3, 128.9, 127.5, 127.0, 125.9, 122.4, 121.4, 114.0, 60.8, 60.0, 40.0, 14.0; HRMS (FAB) $(M+H)^+$: calcd for $C_{18}H_{18}N_2O_3+H^+$: 311.1396; found: 311.1384. Anal. calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; found: C, 69.73; H, 5.82; N, 8.93. FTIR: 3198.6, 3060.8, 2984.0, 1726.2, 1673.4, 1600.8, 1497.9, 1416.5, 1275.4, 1145.4 cm^{-1}. Mp 139–140°C.

In summary, dihydroquinazoline compounds can be efficiently synthesized by intramolecular Michael addition of ureas to α,β-unsaturated esters under mild conditions.

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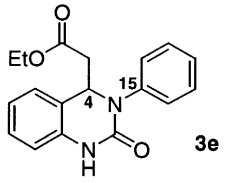
9. The structure of compound **3e** was unambiguously assigned by DQCOSY, HMQC and HMBC NMR experiments. In HMBC, H4 (δ=5.28 ppm) shows a long range ^{1}H–^{13}C correlation to C15 (δ=140.7 ppm) indicating that the phenyl group is attached to the N next to C7 as shown here:



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