Nanoporous Aluminosilicate Mediated Synthesis of 2- and 2,2-substituted 2,3-Dihydroquinazolin-4(*1H*)-ones

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Abstract: Nanoporous silicate materials, made by an operationally simple evaporation-induced self-assembly (EISA) approach, efficiently catalyze the formation of 2-substituted 2,3-dihydroquinazolin-4(*1H*)-ones from aldehydes and dimethyl acetals. This methodology can be extended to encompass the reaction of ketones and ketals to provide facile access to 2,2-disubstituted and spiro dihydroquinazolin-4(*1H*)-ones in high yields and short reaction times.

Keywords: Heterogeneous catalysis; dihydroquinazolinones; cyclocondensation; nanoporous aluminosilicates

Introduction

The development of new strategies which have improved efficiency, and which minimize environmental impact, is a central tenet of modern-day synthetic chemistry and numerous novel approaches have been developed in recent years in what has become a vibrant and diverse research area. [1,2] These strategies encompass every facet of synthetic chemistry including the development of tandem or telescoped reaction protocols which improve efficiency by reducing the number of work-up, isolation and purification steps, [3–6] the use of solvent-free strategies or strategies employing solvents with an improved environmental profile, [7–10] the development of on-water processes [11–12] or the use of microwave or ultrasonic conditions. [13–16] Perhaps the most successful and active area of research has been in the development of new catalytic entities, and in particular the development of heterogeneous materials, that display novel reactivity profiles and properties. [17–19] Heterogeneous catalysis is ideally suited to the requirements of sustainable chemistry given that there is ample opportunity to modify and fine-tune catalyst properties to optimise product selectivity and yields while presenting the added benefits of operational simplicity and catalyst isolation and re-use. It is not surprising that heterogeneous materials displaying catalytic activity have been applied to the synthesis of targets of current interest within sustainable chemistry, such as the development of biofuels and fuel additives, with significant success. [20–22] An additional area of current interest is the development of strategies for the synthesis of heterocyclic compounds, and especially those identified as novel pharmacophores. One such example is the synthesis of the dihydroquinazolinone moiety which is a highly versatile privileged scaffold in drug discovery displaying a rich array of biological activities and it is not surprising that the synthesis of this class of compound has attracted considerable recent attention (**Figure 1**). [23–25]

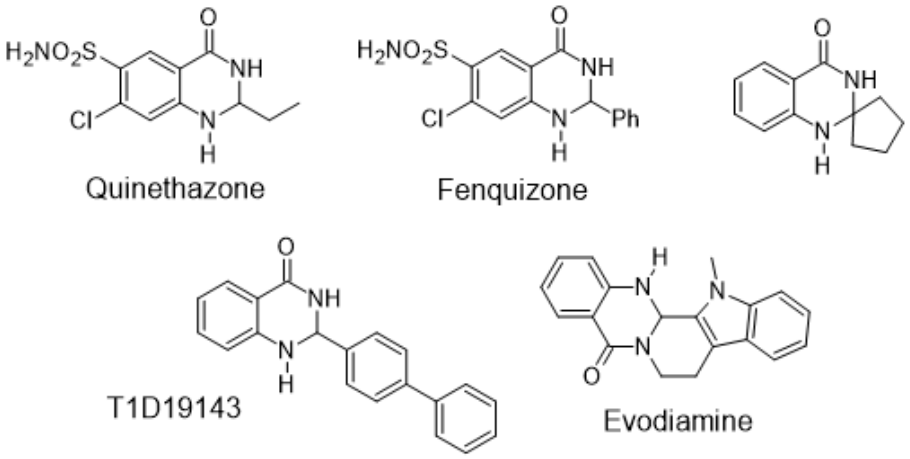
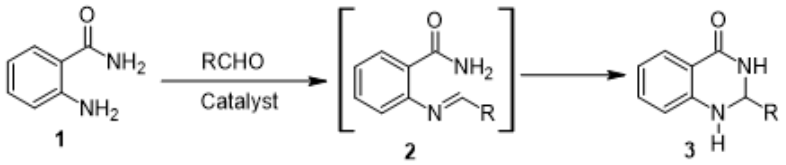


Figure 1: Example of Biologically Active Quinazolinone Derivatives

While a number of interesting strategies have been developed to access dihydroquinazolinones, [26–33] the most direct and flexible approach is the condensation of carbonyl compounds with anthranilamide **1** under acid or basic conditions (**Scheme 1**). This approach, however, typically displays a less than ideal environmental profile and so has led to development of protocols employing heterogeneous alternatives which avoid the use of harsh conditions, toxic and corrosive reagents and problematic catalyst recovery and reuse. [28]



Scheme 1: Cyclocondensation Approach to Dihydroquinazolinones

Our interest in this area arose from the observation that in general, porous materials perform poorly in this transformation, with commonly available zeolites and mesoporous materials requiring significant modification to achieve acceptable yields under relatively harsh reaction conditions over extended reaction times. [34,35] Furthermore, and in common with most protocols employing either homogeneous or heterogeneous catalysts, their substrate scope is largely limited to aldehydes. We have

previously shown that moderately acidic nanoporous aluminosilicate materials, produced using an operationally simple evaporation-induced self-assembly (EISA) approach, display a significantly different reaction profile to more acidic zeolite materials efficiently promoting a range of acid catalyzed reactions. [36,37] We were intrigued as to how they would perform in this transformation and herein, we report the successful implementation of this strategy to provide facile access to 2-, 2,2- and spiro-dihydroquinazolinones from aldehydes, ketones and ketals under mild reaction conditions and short reaction times providing an operationally simple and general approach to the synthesis of dihydroquinazolinones.

Results and Discussion

We initially screened a small range of alumino- and borosilicate materials (**Table 1**) produced using our EISA methodology, [21,22,38] to assess their potential for the synthesis of dihydroquinazolinones using the reaction of benzaldehyde with anthranilamide **1** as a model reaction.

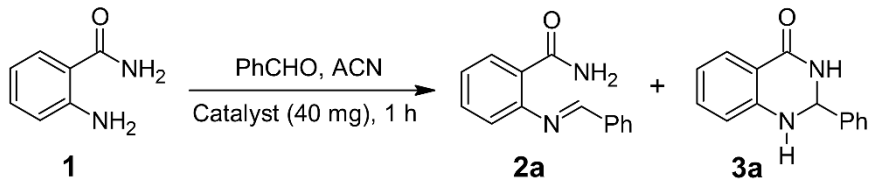
Table 1: Typical Catalyst Physicochemical Properties

Catalyst	Si/Metal Gel Composition	Si/Al[a]	BET Surface Area (m^2g^{-1})[b]	Acidity ($\mu mol\ g^{-1}$)[c]	Pore Width (nm)[d]
S-1-(3.42)	-	-	914	130	3.42
Al-13-(2.34)	13	14	614	440	2.34
Al-13-(3.18)	13	14	980	530	3.18
B-13-(2.34)	13	-	797	500	2.34
B-13-(3.54)	13	-	1095	590	3.54
ZSM-5-(30)	30	19	405	1450	0.82

[a] Determined by energy dispersive X-ray (EDX) analysis.
[b] Obtained by the Brunauer–Emmett–Teller (BET) method.
[c] Determined by NH_3 temperature programmed desorption (TPD) analysis.
[d] Determined by N_2 adsorption using the non-linear density function theory (NLDFT) method.

As expected, reactions of **1** in acetonitrile at room temperature employing either no catalyst or in the presence of the poorly acidic nanoporous silicate material (S-1-(3.42)) produced no dihydroquinazolinone products, and in these cases only the imine intermediate **2a was** observed in crude reaction mixtures (**Table 2,** entries 1 and 2). Gratifyingly, employing low catalyst loadings either the aluminosilicate (Al-13-(3.18)) or borosilicate (B-13-(3.54)) materials provided significant quantities of the desired dihydroquinazolinone product **3a** (entries 3 and 4). The role of pore size was demonstrated by the reaction of the smaller pore materials Al-13-(2.34) and B-13-(2.34) (entries 5 and 6) which provided only low yields of product **3a** suggesting that access to the catalytic sites is a determining factor. This was further confirmed using the commercially available small pore zeolite ZSM-5-(30) which, in line with previous studies, provided low yields of the dihydroquinazolinone product (entry 7). [34]

Table 2: Catalyst Optimisation Studies[a]

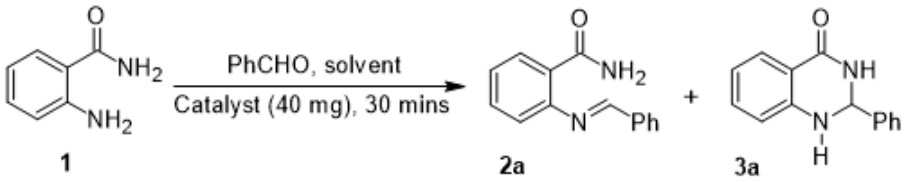


Entry	Catalyst	Ratio 2a:3a[b]	Conversion (%)[b]	Yield 3a (%)[b]
1	-	100:0	85	0
2	S-1-(3.42)	100:0	79	0
3	Al-13-(3.18)	50:50	67	34
4	B-13-(3.54)	60:40	72	30
5	Al-13-(2.34)	95:5	54	5
6	B-13-(2.34)	100:0	60	0
7	ZSM-5-(30)	50:50	53	7

[a] The specified catalyst (40 mg) was added to a stirred solution of **1** (1 mmol) and benzaldehyde (1 mmol) in acetonitrile (1 mL) at room temperature (20 ^{o}C) for 1 hour.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

With the observation that these materials displayed significant catalytic activity, we next undertook a series of experiments to optimise the reaction conditions. As expected, increasing the reaction temperature led to an increase in observed yields with both the larger pore alumino- or borosilicate materials, with the aluminosilicate material producing near quantitative conversion to **3a** in short reaction times under these conditions (**Table 3**; entries 1–3). Replacing acetonitrile with methanol produced similar results (entry 4) and it is noteworthy that in contrast to previous literature reports, the reaction also proceeded efficiently in relatively non-polar solvents such as chloroform (entry 5) or dimethyl carbonate (DMC) (entry 6). [39]

Table 3: Reaction Optimisation Studies[a]



1 2a 3a

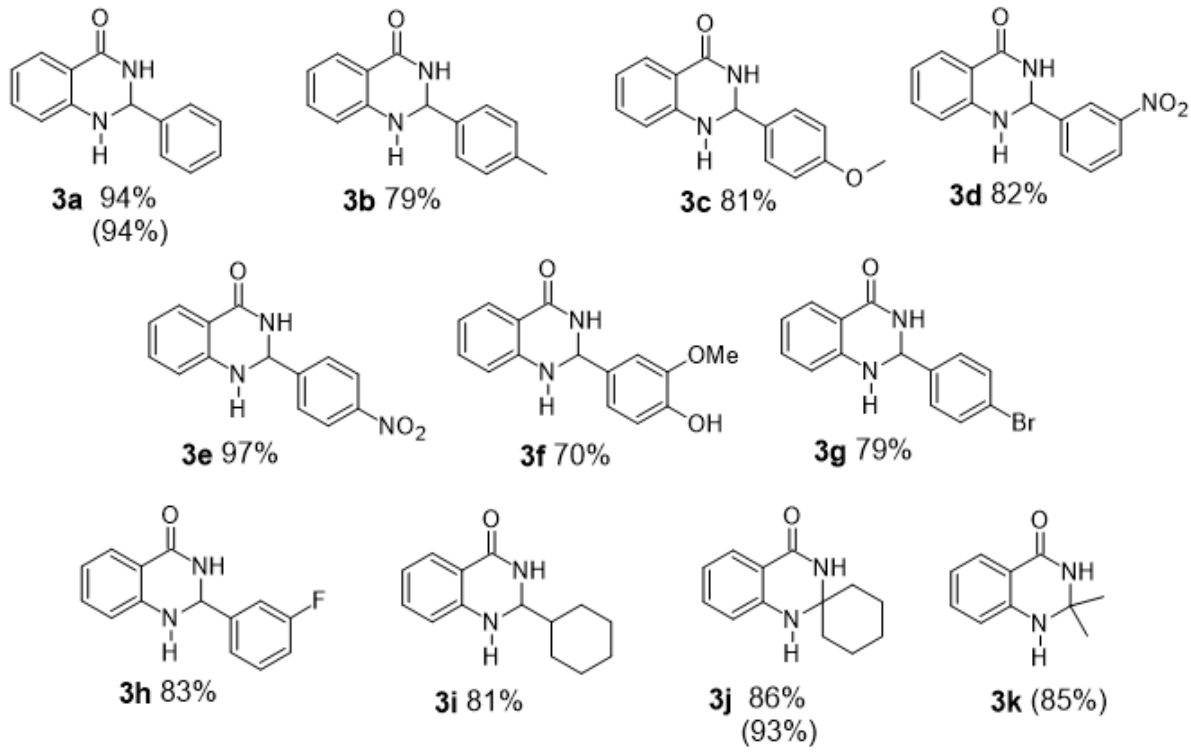
Entry	Catalyst	Temp (°C)[b]	Solvent	Ratio 2a:3a[c]	Conversion (%)[c]	Yield 3a (%)[c]
1	Al-13-(3.18)	rt	ACN	50:50	67	34[d]
2	Al-13-(3.18)	65	ACN	0:100	>95	>95
3	B-13-(3.54)	65	ACN	0:100	58	54
4	Al-13-(3.18)	65	MeOH	0:100	>95	>95
5	Al-13-(3.18)	65	$CHCl_3$	10:90	85	77
6	Al-13-(3.18)	65	DMC	0:100	93	93
7	Al-13-(3.18)	65	ACN	0:100	77	77[e]
8	Al-13-(3.18)	65	ACN	0:100	>95	>95[f]

[a] The specified catalyst (40 mg) was added to a stirred solution of **1** (1 mmol) and benzaldehyde (1 mmol) in the specified solvent (1 mL) at the specified temperature for 30 minutes.
[b] Room temperature is 20 °C.
[c] Determined by quantitative ^{1}H NMR analysis of the crude reaction mixture.
[d] Reaction stirred for 1 hour.
[e] Reaction employing 20 mg of catalyst.
[f] Reaction employing recycled catalyst.

The reaction employing DMC is noteworthy as it is a solvent which has been advanced as an environmentally more acceptable alternative to halogenated solvents. [40,41] Significant quantities of **3a** were also observed employing reduced catalyst loadings of the aluminosilicate materials Al-13-(3.18) (entry 7). We have previously demonstrated that our aluminosilicate catalysts are fully recyclable and can be reused over multiple cycles without loss of activity requiring only washing to remove contaminants. [21,22,36–38] In line with these previous studies, we were gratified to observe that the use of recycled catalyst gave a similar reaction profile to the fresh material providing excellent conversion to the dihydroquinazolinone product (entry 8).

With effective conditions for the cyclocondensation reaction now in hand, we next demonstrated the scope of the reaction employing a range of carbonyl compounds (**Table 4**).

Table 4: Reaction Scope[a,b]



[a] Isolated yields of pure product.
[b] Yields in parenthesis relate to reactions employing acetal or ketal starting materials.

Gratifyingly, the reaction of a range of aldehydes and ketones provided excellent isolated yields of the corresponding 2-substituted, 2,2-disubstituted dihydroquinazolinone and spiroquninazolinone products in short reaction times. In all cases, the final reaction mixtures required only minimal work-up procedures to remove the catalyst which was achieved simply by dissolving the product followed by filtration. Removal of the solvent provided the dihyroquinazolinone products in near quantitative yields which were pure as determined by spectroscopic analysis.

To complete these studies, we next investigated the potential of employing acetals and ketals in place of aldehydes and ketones. The reaction of acetals as surrogates for carbonyl compounds is a surprisingly mature area and has been demonstrated to be a useful strategy in a number of areas including carbon-carbon bond formation, [42–45] and for C-O, C-S and C-N bonds [46-49] albeit one that has been comparatively under exploited. We have shown that acetals function as highly effective surrogates for carbonyl compounds [50,51] in reactions catalyzed by our nanoporous aluminosilicate materials and, in line with these studies, we were gratified to observe that corresponding acyclic dimethyl and diethyl acetals and ketals also provided excellent yields of these products.

Conclusions

In conclusion, we have demonstrated that nanoporous aluminosilicate materials, produced using an operationally simple EISA approach, effectively catalyze the cyclocondensation reaction of aldehydes and acetals to anthranilamide to produce 2-substituted dihydroquinazolinone products in high yields and in short reaction times. The reaction profile can be extended to encompass the reaction of ketones and ketals to provide facile and high yielding access to both the corresponding 2,2-disubstituted and spirodihydroquinazolinone products. The reaction employs short reaction times and the products require minimal work-up and purification procedures.

Supplementary Material

Details of catalyst preparation and characterisation, experimental procedures and ^{1}H and ^{13}C spectroscopic data for isolated dihydroquinazolinone products are available.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1]. B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[2]. P. T. Anastas and T. Williamson. In Green Chemistry: Designing Chemistry for the Environment, ACS Symposium Series 626, P. T. Anastas and T. Williamson (Eds.), pp. 1-17, American Chemical Society, Washington, DC (1996).

[3]. Y. Hayashi, *Chem. Sci*. **2016**, *7*, 866–880.

[4]. B. M. Smith, A. E. Graham, *Tetrahedron Lett*. **2007**, *48*, 4891–4894.

[5]. B. M. Smith, A. E. Graham, *Tetrahedron Lett*. **2011**, *52*, 6281–6283.

[6]. A. E. Graham, R. J. K. Taylor, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1087–1089.

[7]. R. A. Sheldon, *Green Chem*. **2005**, *7*, 267–278.

[8]. D. J. Cott, K. J. Ziegler, V. P. Owens, J. D. Glennon, A. E. Graham, J. D. Holmes, *Green Chem*. **2005**, *7*, 105–110.

[9]. B. M. Smith, T. M. Kubczyk, A. E. Graham, *RSC Adv.* **2012**, *2*, 2702–2706.

[10]. B. M. Smith, T. M. Kubczyk, A. E. Graham, *Tetrahedron* **2012**, *68*, 7775–7781.

[11]. A. Chanda, V. V. Fokin, *Chem. Rev*. **2009**, *109*, 725–748.

[12]. M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou, B. H. Lipshutz, *Chem. Sci*. **2021**, *12*, 4237–4266.

[13]. D. Dallinger, C. O. Kappe, *Chem. Rev*. **2007**, *107*, 2563–2591.

[14]. R. S. Varma, *Green Chem*. **1999**, *1*, 43–55.

[15]. Microwaves in Drug Discovery and Development: Recent Advances, edited by J. Spencer and M. C. Bagley, Future Science, London, UK, 2014.

[16]. G. Chatel, J. S. Varma, *Green Chem*. **2019**, *21*, 6043–6050.

[17]. C. M. Friend, B. Xu, *Acc, Chem. Res*. **2017**, *50*, 517–521.

[18]. C. Lucarelli, A. Vaccari, *Green Chem*. **2011**, *13*, 1941–1949.

[19]. C. Descorme, P. Gallezot, C. Geantet, C. George, *ChemCatChem* **2012**, *4*, 1897–1906.

[20]. G. W. Huber, S. Iborra, A. Corma, *Chem. Rev*. **2006**, *106*, 4044–4098.

[21]. D. R. Chaffey, T. E. Davies, S. H. Taylor, A. E. Graham, *ACS Sustain. Chem. Eng*. **2018**, 6, 4996–5002.

[22]. D. R. Chaffey, T. Bere, T. E. Davies, D. C. Apperley, S. H. Taylor, A. E. Graham, *Appl. Catal. B* **2021**, *293*, 120219.

[23]. I. Khan, A. Ibrar, W. Ahmed, A. Saeed, *Eur. J. Med. Chem*. **2015**, *90*, 124–

[24]. P. S. Auti, G. George, A. T. Paul, *RSC Adv*. **2020**, *10*, 41353–41392.

[25]. R. Karan, P. Agarwal, M. Sinha, N. Mahato, *ChemEngineering* **2021**, *5*, 73.

[26]. C. S. Rajput, S. Srivastava, A. Kumar, A. Pathak, *Tetrahedron Lett*. **2021**, *65*, 152791.

[27]. T. dos Santos, C. Grundke, T. Lucas, L. Großmann, G. C. Clososki, T. Opatz, *Eur. J. Org. Chem*. **2020**, 6429–6432.

[28]. M. Badolato, F. Aiello, N. Neamati, *RSC Adv*. **2018**, *8*, 20894–20921

[29]. S. Sahoo, S. Pal, *ChemistrySelect* **2023**, *8*, e20230029.

[30]. H. Hikawa, T. Nakayama, M. Takahashi, S. Kikkawa, I. Azumaya, *Adv. Synth. Catal*. **2021**, *363*, 4075–40.

[31]. B A. Dar1, A. K. Sahu1, P. Patidar1, J. Patial, P. Sharma, M. Sharma, B. Singh, *Am. J. Chem*. **2012**, *2*, 248–254.

[32]. B. Dam, R. A. Patil, Y.-R. Ma, A. K. Pal, *New J. Chem*. **2017**, *41*, 6553–6563.

[33]. H. R. Shaterian, A. R. Oveisi, M. Honarmand, *Synth. Commun*. **2009**, *40*, 1231–1242.

[34]. K. S. Gajula, N. Mameda, S. Kodumuri, D. Chevella, R. Banothu, V. Amrutham, B. I. Kutepov, N. Nama, *Synth. Commun*. **2019**, *48*, 2866–2876.

[35]. A. Lohdi, A. K. Dalai, K. C. Maheria, *J. Chem. Sci*. **2023**, *135*, 37.

[36]. T. E. Davies, S. A. Kondrat, E. Nowicka, J. J. Graham, D. C. Apperley, S. H. Taylor, A. E. Graham, *ACS Sustain. Chem. Eng*. **2016**, *4*, 835–843.

[37]. T. E. Davies, J. R. Kean, D. C. Apperley, S. H. Taylor, A. E. Graham, *ACS Sustain. Chem. Eng*. **2014**, *2*, 860–866.

[38]. L. A. Bailey, T. Bere, T. E. Davies, S. H. Taylor, A. E. Graham, *ACS Sustain. Chem. Eng*. **2022**, *10*, 13759–13764.

[39]. C. S. Rajput, S. Srivastava, A. Kumar, A. Pathak, *Tetrahedron Lett*. **2021**, *65*, 152791.

[40]. B. Schäffner, F. Schäffner, S. P. Verevkin, A. Börner, *Chem. Rev*. **2010**, *110*, 4554–4581.

[41]. G. Fiorani, A. Perosa, M. Selva, *Green Chem*. **2018**, *20*, 288–322.

[42]. C. W. Downey, M. W. Johnson, K. J. Tracy, *J. Org. Chem*. **2008**, *73*, 3299–3302.

[43]. L. Li, X. Ye, Y. Wu, L. Gao, Z. Song, Z. Yin, Y. Xu, *Org. Lett*. **2013**, *15*, 1068–1071.

[44]. A. Rodríguez-Gimeno, A. B. Cuenca, J. Gil-Tomás, M. Medio-Simón, A. Olmos, G. Asensio, *J. Org. Chem.* **2014**, *79*, 8263–8270.

[45]. N. Sagawa, H. Moriya, S. Hosokawa, *Org. Lett.* **2017**, *19*, 250–253.

[46]. L. A. Bailey, T. Bere, T. E. Davies, S. H. Taylor, A. E. Graham, *ACS Sustain. Chem. Eng*. **2022**, *10*, 13759–13764.

[47]. L. Yip, T. M. Kubcyzk, T. E. Davies, S. H. Taylor, D. C. Apperley, A. E. Graham, *Cat. Sci. Tech*. **2012**, *2*, 2258–2263,

[48]. A. E. Graham, *Synth. Commun*. **1999**, *29*, 697–703.

[49]. M. C. Carreño, J. M. Cuerva, M. Ribagorda, A. M. Echavarren, *Angew. Chem. Int. Ed*. **1999**, *38*, 1449–1452.

[50]. T. E. Davies, S. H. Taylor, A. E. Graham, *ACS Omega* **2018**, *3*, 15482–15491.

[51]. T. M. Kubczyk, S. M. Williams, J. R. Kean, T. E. Davies, S. H. Taylor, A. E. Graham, *Green Chem*. **2011**, *13*, 2320–2325.