Investigation into a Tetrahydroquinazoline Scaffold

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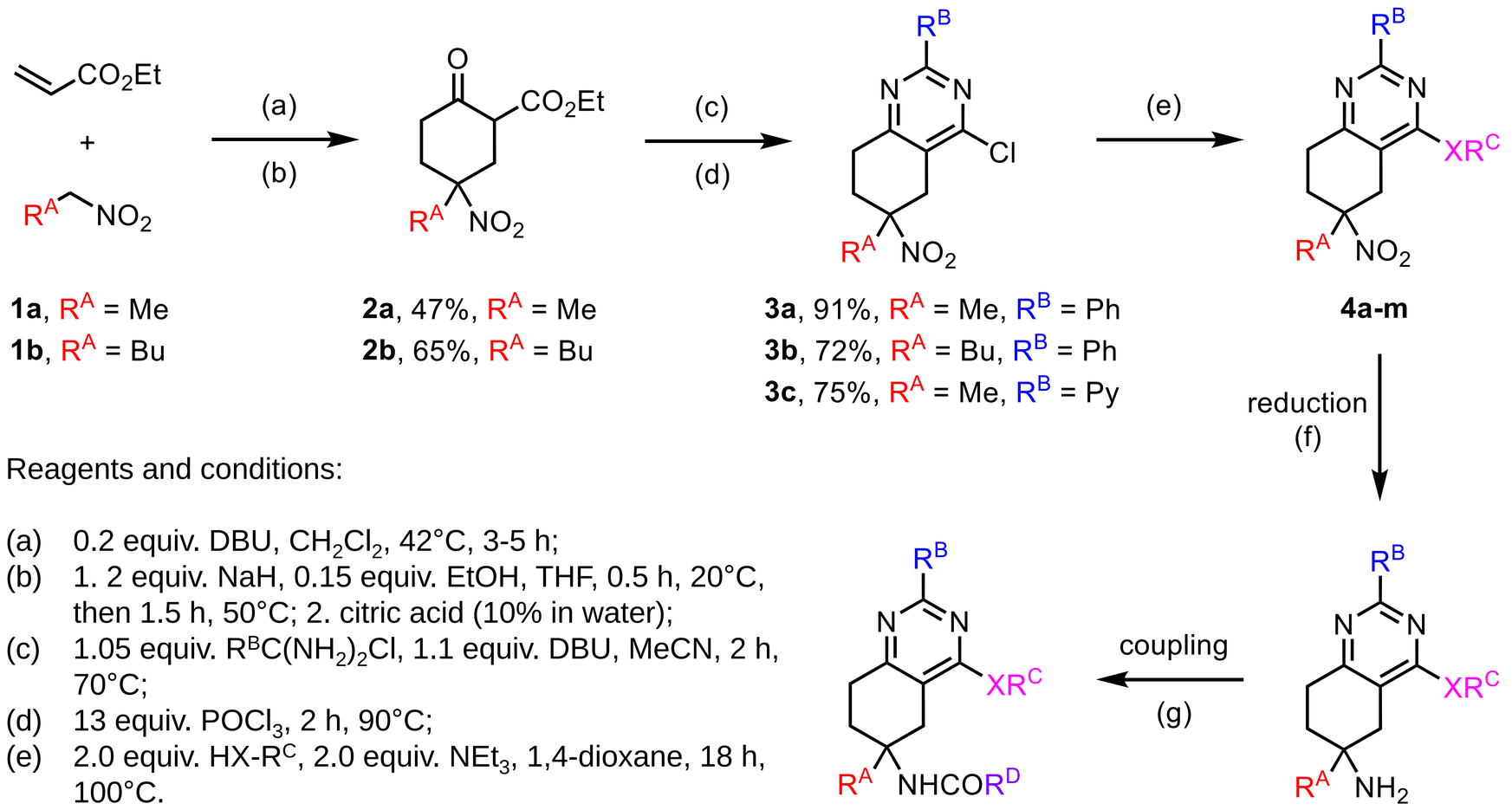
A new 5,6,7,8-tetrahydroquinazoline (i.e. 1,3-diazanaphthalene) scaffold with four points of diversification R^A–R^D was prepared. The seven-step sequence started from nitroalkanes $R^ACH_2NO_2$ (with R^A = Me, Bu), ethyl acrylate and amidines $R^BC(NH)NH_2$ (with R^B = Ph, 4-pyridyl). Residues R^C were introduced by nucleophilic substitution with alkyl amines R^CNH_2 (10 examples) or aryl thiols (two examples). Finally, the nitro group was reduced and the primary amino function amidated with various carboxylic acids R^ACO_2H.

The heterocycle quinazoline (i. e. benzo[*d*]pyrimidine, 1,3-diazanaphthalene) is a common structural motif in several natural products and pharmaceutically active ingredients.[1] For example, vasicine is an alkaloid from the Indian lungwort (*Justicia adhatoda*), which has antitussive properties and has been used against asthma and tuberculosis.[2]



1a, R^A = Me
1b, R^A = Bu

2a, 47%, R^A = Me
2b, 65%, R^A = Bu

3a, 91%, R^A = Me, R^B = Ph
3b, 72%, R^A = Bu, R^B = Ph
3c, 75%, R^A = Me, R^B = Py

4a-m

4a, 99%, $HX\text{-}R^C$ = H_2NHept
4b, 45%, $HX\text{-}R^C$ = H_2NCy
4c, 58%, $HX\text{-}R^C$ = H_2NiBu
4d, 79%, $HX\text{-}R^C$ = $H_2NCH_2CH_2OEt$
4e, 100%, $HX\text{-}R^C$ = $H_2NCH_2CH_2CO_2Et$
4f, 95%, $HX\text{-}R^C$ = $H_2NCH_2CH_2CH_2OH$
4g, 97%, $HX\text{-}R^C$ = $H_2NCH_2CH_2CH_2OAc$
4h, 100%, $HX\text{-}R^C$ = $H_2NCH_2CH_2NHBoc$
4i, 94%, $HX\text{-}R^C$ = $H_2NCH_2CH_2$(4-imidazolyl)
4j, 72%, $HX\text{-}R^C$ = $H_2NCH_2CH_2SH$
4k, 95%, $HX\text{-}R^C$ = $H_2NCH_2CH_2NMe_2$
4l, 100%, $HX\text{-}R^C$ = $HSpC_6H_4t$Bu
4m, 49%, $HX\text{-}R^C$ = HS(4-pyridyl)

5a-h

6a-f

Reagents and conditions:

(a) 0.2 equiv. DBU, CH_2Cl_2, 42°C, 3-5 h;
(b) 1. 2 equiv. NaH, 0.15 equiv. EtOH, THF, 0.5 h, 20°C, then 1.5 h, 50°C; 2. citric acid (10% in water);
(c) 1.05 equiv. $R^BC(NH_2)_2Cl$, 1.1 equiv. DBU, MeCN, 2 h, 70°C;
(d) 13 equiv. $POCl_3$, 2 h, 90°C;
(e) 2.0 equiv. $HX\text{-}R^C$, 2.0 equiv. NEt_3, 1,4-dioxane, 18 h, 100°C.

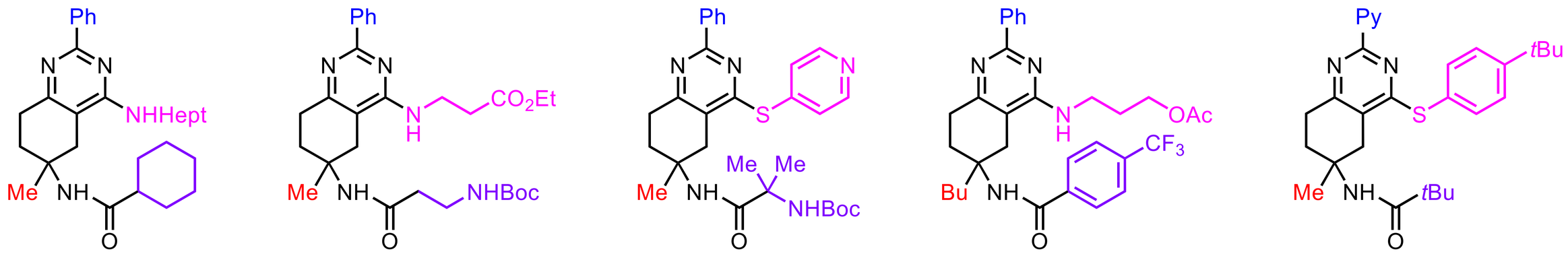
Table 1: Coupling (g), reagents and conditions.

product	educt	conditions	yield
5a	**6a**	1.05 equiv. Ac_2O, 0.05 equiv. DMAP, 1.5 NEt_3, CH_2Cl_2, 0°C→23°C, 90 min	82%
5b	**6a**	1.5 equiv. $CyCO_2H$, 1.5 equiv. iPr_2NEt, 1.1 equiv. HATU, CH_2Cl_2, 40°C, 18 h	85%
5c	**6a**	1.5 equiv. *N*-Boc-β-Ala, 1.5 equiv. iPr_2NEt, 1.1 equiv. HATU, CH_2Cl_2, 40°C, 18 h	87%
5d	**6b**	1.5 equiv. *N*-Boc-β-Ala, 1.5 equiv. iPr_2NEt, 1.1 equiv. HATU, CH_2Cl_2, 40°C, 18 h	78%
5e	**6c**	1.5 equiv. *N*-Boc-Aib, 1.5 equiv. iPr_2NEt, 1.1 equiv. HATU, CH_2Cl_2, 40°C, 18 h	62%
5f	**6d**	1.5 equiv. 4-$CF_3C_6H_4CO_2H$, 1.5 equiv. iPr_2NEt, 1.1 equiv. HATU, CH_2Cl_2, 40°C, 18 h	93%
5g	**6e**	1.5 equiv. 2,4-$F_2C_6H_3CO_2H$, 1.5 equiv. iPr_2NEt, 1.1 equiv. HATU, CH_2Cl_2, 40°C, 18 h	99%
5h	**6f**	1.2 equiv. *t*BuCOCl, 0.05 equiv. DMAP, 1.3 equiv. NEt_3, CH_2Cl_2, 40°C, 1 h	82%

Table 2: Reduction (f), reagents and conditions.

product	R^A	R^B	XR^C	conditions	yield
6a	Ph	Me	NHHept	9 bar H_2, cat. Pd-C, 50°C, 24 h	99%
6b	Ph	Me	$NHCH_2CH_2CO_2Et$	9 bar H_2, cat. Pd-C, 40°C, 18 h	99%
6c	Ph	Me	S(4-pyridyl)	5 equiv. $HSiCl_3$, 7 equiv. NEt_3, 0°C→23°C, 3 h	45%
6d	Ph	Bu	$NHCH_2CH_2CH_2OAc$	9 bar H_2, cat. Pd-C, 40°C, 20 h	91%
6e	4-pyridyl	Me	NHHept	7 equiv. In (powder), NH_4Cl, H_2O, EtOH, 80°C, 24 h	97%
6f	4-pyridyl	Me	S(4-C_6H_4tBu)	9 bar H_2, cat. Pd-C, 30°C, 7 d	65%

Selected final products



5b **5d** **5e** **5f** **5h**

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[2] J. M. Grange, N. S. C. Snell, *J. Ethnopharmacol.* **1996**, *50*, 49–53.
[3] a) D. Wachtendorf, M. Schmidtmann, J. Christoffers, *Org. Lett.* **2020**, *22*, 6420–6423; b) B. Schäfer, M. Schmidtmann, J. Christoffers, *Eur. J. Org. Chem.* **2018**, 4490–4497; c) I. Geibel, J. Christoffers, *Eur. J. Org. Chem.* **2016**, 918–920.